RĪGAS TEHNISKĀ
UNIVERSITĀTE

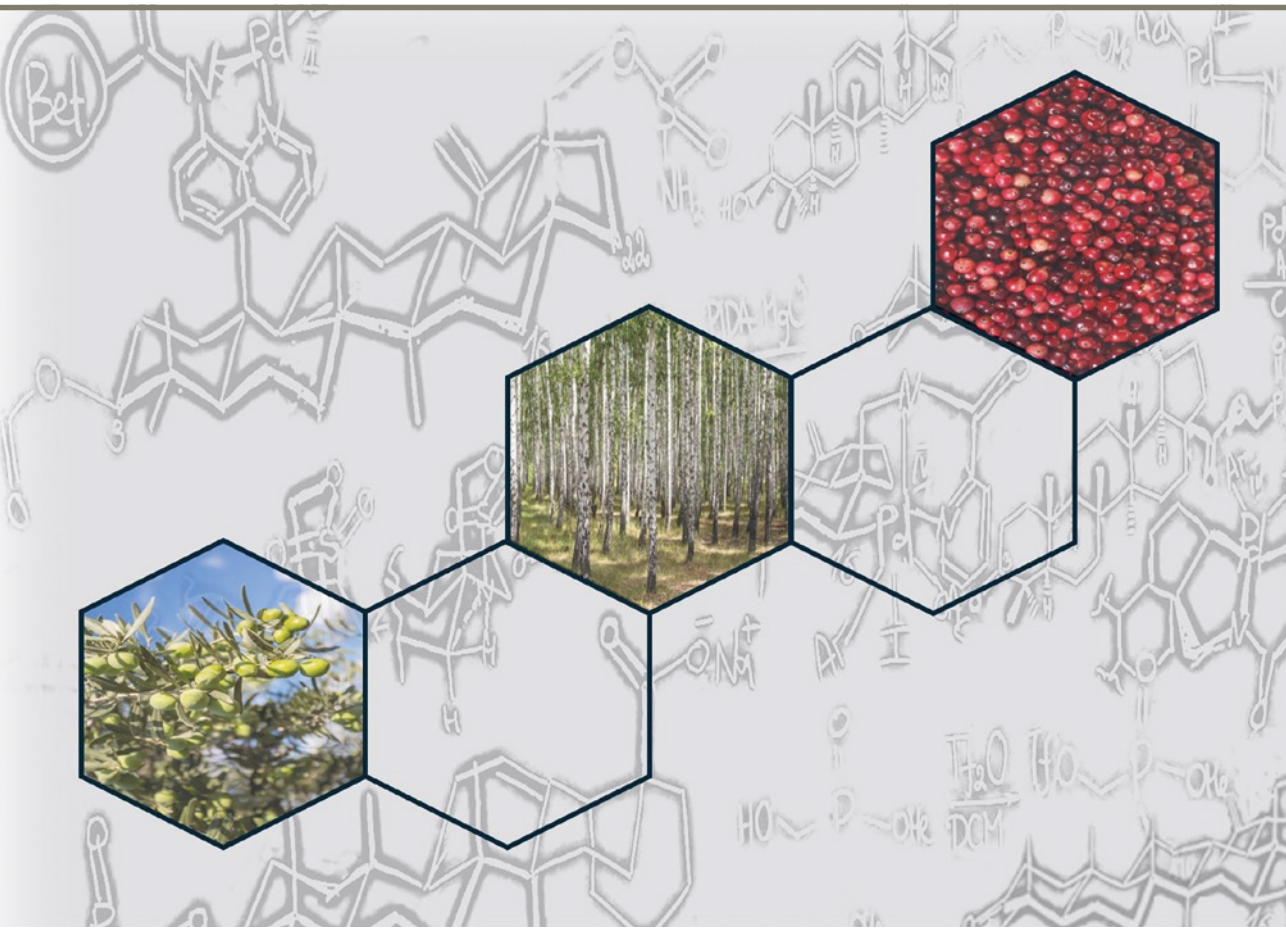
**Vladislavs Kroškins**

# PENTACIKLISKO TRITERPENOĪDU C-H FUNKCIONALIZĒŠANA UN ŪDENĪ ŠĶĪSTOŠU ATVASINĀJUMU SINTĒZE

Promocijas darbs

# C-H FUNCTIONALIZATION AND SYNTHESIS OF WATER-SOLUBLE PENTACYCLIC TRITERPENOIDS

Doctoral Thesis



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**RĪGAS TEHNISKĀ UNIVERSITĀTE**

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Zinātniskais vadītājs / Scientific supervisor

Profesors *Dr. chem.* / Professor Dr. chem.

MĀRIS TURKS

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APSTIPRINĀJUMS

Apstiprinu, ka esmu izstrādājis šo promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē zinātnes doktora (*Ph. D.*) grāda iegūšanai. Promocijas darbs zinātniskā grāda iegūšanai nav iesniegts nevienā citā universitātē.

Vladislavs Kroškins …….

(paraksts)

Datums …..……...……...

Promocijas darbs sagatavots kā tematiski vienotu zinātnisko publikāciju kopa ar kopsavilkumu latviešu un angļu valodā. Promocijas darbs apkopo trīs oriģinālpublikācijas *SCI* žurnālos, vienu apskatrakstu, vienu patentu un nepublicētus rezultātus.

# SATURS/CONTENTS

2. pielikums / Appendix 2. Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Turks, M. Water-soluble triterpenoid phosphonates and synthesis method thereof. LV15836 B1, 20.03.2025.

3. pielikums / Appendix 3. C(3)-Phosphonate derivatives of pentacyclic triterpenoids (unpublished results).

4. pielikums / Appendix 4. Kroškins, V., Turks, M. Recent investigations in synthesis of oxathiazinanes by sulfamate estercyclization (microreview). *Chem. Heterocycl. Comp*. **2023**, *59*, 637–639.

5. pielikums / Appendix 5. Kroškins, V., Lugiņina, J., Lācis, R., Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M. Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids. *ACS Omega.* **2025**, *10*, 27992–28019.

6. pielikums / Appendix 6. Kroškins, V., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M. Site-selective C-H amination of lupane type triterpenoids. *Eur. J. Org. Chem*. **2025**, 2500340.

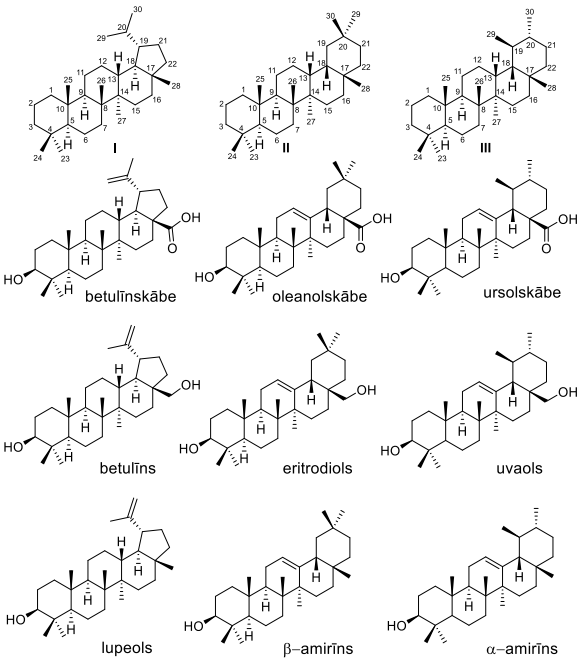
# LIETOTO SAĪSINĀJUMU SARAKSTS

| | |
|---|---|
| Ac | acetil- |
| *t*-Am | *t*-amil- |
| Ar | aril- |
| Bn | benzil- |
| Boc | *t*-butoksikarbonil- |
| brsm | balstoties uz atgūto izejvielu |
| BQ | benzohinons |
| *t*-Bu | *t*-butil- |
| Cbz | benziloksikarbonil- |
| CMD | saskaņotā metalēšana |
| deprotonēšana | |
| cod | ciklooktadiēns |
| Cp | ciklopentadienil- |
| DCM | dihlormetāns |
| DCE | dihloretāns |
| DG | virzošā grupa |
| DMAP | 4-dimetilaminopiridīns |
| DMSO | dimetilsulfoksīds |
| DIBAL-H | diizobutilalumīnija hidrīds |
| DMF | *N*,*N*-dimetilformamīds |
| EAG | elektronakceptora grupa |
| EDG | elektrondonora grupa |
| EDTA | etilēndiamīntetraetiķskābe |
| Esp | α,α,α′,α′-tetrametil-1,3-benzoldipropionskābe |
| Eq | ekvivalents |
| h | stunda |
| HAT | ūdeņraža atoma pārnese |
| HATU | *O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N*′,*N*′-tetrametiluronija heksafluorfosfāts |
| HFIP | heksafluor-2-propanols |
| IT | istabas temperatūra |
| LDA | litija diizopropilamīds |
| Nbe | norbornēns |
| NMP | *N*-metil-2-pirolidons |
| KMR | kodolu magnētiskā rezonanse |
| OP | oksidējošā pievienošanās |
| Pc | ftalocianīns |
| PCC | piridīnija hlorhromāts |
| PCT | pentacikliskais triterpenoīds |
| pfb | perfluorbutirāts |
| PG | aizsarggrupa |
| Ph | fenil- |
| phe | fenilalanīns |
| PIDA | (diacetoksijod)benzols |
| Piv | pivaloil- |
| phen | fenantrolīns |
| Phs | fenilsulfamoil- |
| PMB | 4-metoksibenzil- |
| PPTS | piridīnija p-tollilsulfonāts |
| *i*-Pr | *i*-propil- |
| Py | piridīns |
| RE | reducējošā eliminešanās |
| Tf | trifluormetānsulfonil- |
| TFA | trifluoretiķskābe |
| THF | tetrahidrofurāns |
| TM | pārejas metāls |
| TMS | trimetilsilil- |
| Troc | 2,2,2-trihloretoksikarbonil- |

# PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

## Tēmas aktualitāte

Pentacikliskie triterpenoīdi (PCT) ir plaši izplatīta sekundāro metabolītu grupa, kam piemīt plašs bioloģisko īpašību klāsts.[1, 2, 3, 4] PCT var iedalīt trīs galvenajās klasēs: lupāna tipa terpenoīdi **I** (betulīnskābe, betulīns un lupeols), oleanāna tipa terpenoīdi **II** (oleanolskābe, eritrodiols un β-amirīns) un ursāna tipa terpenoīdi **III** (ursolskābe, uvaols un α-amirīns) (1. att.).[5]




1. attēls. Lupāna **I**, oleanāna **II** un ursāna **III** klašu pentaciklisko triterpenoīdu izplatītākie pārstāvji.

Aptuveni ceturtā daļa no mūsdienu zāļvielām ir dabasvielas vai to pussintētiskie atvasinājumi. Savukārt pretvēža un pretinfekcijas terapijas jomā dabasvielas, dabasvielu atvasinājumi, kā arī dabasvielu mimētiķi un savienojumi ar dabasvielu tipa farmakoforiem kopā aizņem pat vairāk nekā pusi no pēdējos 40 gados radītajām zālēm.[6] Pazemināts toksicitātes profils normālās[7] šūnās apvienojumā ar plašu pieejamību dabā un relatīvi vienkāršu izdalīšanas procesu ir veicinājis PCT un to pussintētisko atvasinājumu kā iespējamu zāļvielu izpēti. To vidū daudzsološākie PCT lietojumi ir pretvēža un pretvīrusu zāļu jomās.[8, 9, 10, 11, 12] Citas PCT un to sintētisko atvasinājumu lietošanas jomas ietver arī antibakteriālu[13] un pretsēnīšu[14] līdzekļu izstrādi, kā arī pretdiabēta[15] un pretiekaisuma[16] zāļu meklējumus.

Papildus medicīniskajiem lietojumiem PCT var veiksmīgi izmantot arī kosmetoloģijā. Kosmētikas nozarē bērza tāss ekstrakts ir atzīts par vērtīgu dabasvielu maisījumu. Plašu betulīnu saturošu produktu klāstu var atrast pazīstamu zīmolu produkcijā gan ādas, gan matu kopšanai. Vairāki pētījumi ir pierādījuši betulīna un tā atvasinājumu spēju dziedēt apdegumus un citas ādas brūces.[17] Turklāt, pateicoties labvēlīgai betulīna ietekmei uz kolagēna ražošanu, betulīns un to saturoši produkti tiek izmantoti gan ikdienas ādas kopšanas krēmos, gan pretcelulīta līdzekļos.[18, 19]

Pentaciklisko triterpenoīdu unikālie molekulārie karkasi, kam piemīt augsts bioloģiskais potenciāls, rada ievērojamas sintētiskas problēmas. Stabilā policikliskā arhitektūra un augstā C-H saišu piesātinājuma pakāpe bieži ierobežo dažādu ķīmisko transformāciju lietojumu. Tradicionāli derivatizācijas pētījumi ir balstīti reaģētspējīgās perifērijā esošās funkcionālajās grupās, kas ir spirta un karbonskābes funkcionalitātes pie C(3) un C(28), kā arī betulīna gadījumā dubultsaite C(20)=C(29) un alilpozīcija pie C(30).[20] Lai gan iegūtās modifikācijas ir devušas daudzus vērtīgus atvasinājumus, tās izmanto tikai mazu daļu no visa molekulārā karkasa, atstājot lielāko daļu no oglekļa skeleta plašā potenciāla praktiski neizmantotu.

Pēdējās desmitgadēs pārejas metālu katalizētu C-H funkcionalizēšanas metožu attīstība ir pavērusi jaunas iespējas inertu C($sp^3$)-H saišu tiešai un selektīvai transformācijai.[21] Šī stratēģija piedāvā iespēju iegūt jaunus atvasinājumus no neaktivētām C($sp^3$)-H sistēmām, tādējādi nodrošinot efektīvu vēlīno funkcionalizēšanu. Neskatoties uz šo metožu plašo lietojumu citās sarežģītās molekulārās sistēmās, C-H funkcionalizēšanas izmantošanas piemēri triterpenoīdu ķīmijā ir bijuši pārsteidzoši ierobežotā daudzumā. Taču tieši sarežģītas dabasvielas kalpo kā ideāli modeļi, lai demonstrētu sintētisko metodoloģiju vispārīgumu un efektivitāti, pateicoties to strukturālajai daudzveidībai un funkcionālajai sarežģītībai. PCT molekulas var kalpot kā testa platforma, kas ļauj izvērtēt C($sp^3$)-H funkcionalizēšanas metožu selektivitāti, pielāgojamību un potenciālu lietojumu plašākā bioloģiski nozīmīgu savienojumu klāstā.

Promocijas darbs apkopo pētījumus, kuru mērķis ir paplašināt PCT molekulāro karkasu funkcionalizēšanas iespējas, izmantojot inovatīvas C-H funkcionalizācijas stratēģijas un heteroatomu saturošu funkcionalitāšu stratēģisku ieviešanu PCT struktūrās (2. att.). Darba gaitā ir izstrādātas un optimizētas divas galvenās katalītiskās metodes – palādija katalizēta C-H arilēšana/azetidinēšana un rodija katalizēta C-H aminēšana iepriekš neapskatītu pozīciju aktivēšanai triterpenoīdu policikliskajās struktūrās.

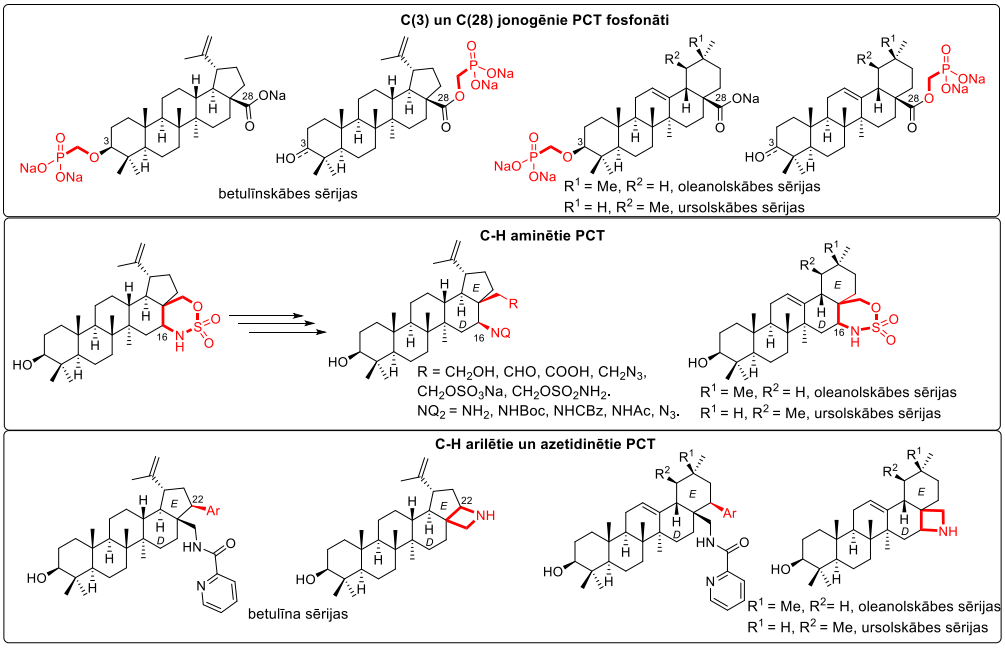
Pirmā izstrādātā pieeja ietver palādija katalizētu triterpenoīdu pikolīnamīdu C($sp^3$)-H arilēšanu un azetidinēšanu. Šeit pikolīnamīda virzošā grupa, kas piesaistīta pie konformacionāli elastīga C(28) linkera, ļāva veikt reģioselektīvu arilēšanu pie C(22). Savukārt reakcijās ar elektrondeficītiem jodarēniem tika iegūti annelēti pentaciklisko triterpenoīdu-azetidīna analogi. PCT C-H arilēšanas protokols būtiski paplašina PCT ķīmisko daudzveidību un ievieš jaunu slāpekli saturošu atvasinājumu, kuru bioloģisko aktivitāšu profils tiks pētīts nākotnē, klasi.

Otrā izstrādātā pieeja ietver rodija katalizētu betulīna sulfamāta esteru iekšmolekulāru C-H aminēšanu, kas dod triterpenoīdu-1,2,3-oksatiazināna konjugātus ar augstu reģioselektivitāti C(16) pozīcijā. Virzošās grupas ievadīšana pie C(28) dod iespēju piekļūt reaģētspējīgam starpproduktam

pie tuvumā esošās neaktivētās metilēngrupas, ļaujot kontrolēti veidoties jaunai C-N saitei. Iegūtie produkti pēc tam tika pārveidoti par 16-amino- un 16-azidoatvasinājumiem, kas ir unikāli, sintētiski vērtīgi atvasinājumi PCT ķīmijā. Secīgas C-H funkcionalizēšanas iespēja pie betulīna C(22) vēl vairāk izceļ šīs metodes potenciālu PCT molekulārā skeleta dekorēšanai.

Papildus minētajām C-H funkcionalizēšanas stratēģijām tika veikti pētījumi, kas koncentrējās uz PCT šķīdības uzlabošanu, ievadot jonogēnās fosfonātu grupas (2. att.). Ievadot metilēnfosfonātus pie C(3) un/vai C(28), lietojot vienkāršas alkilēšanas stratēģiju, tika sintezēta virkne mono- un bisfosfonātu esteru/ēteru un to nātrija sāļu. Šie savienojumi uzrādīja lielisku šķīdību ūdenī – īpašību, kas parasti nebija novērota dabā sastopamajiem PCT. Lai gan šī darba kontekstā tikai fosfonātu sērijai ir raksturīga šķīdības uzlabošana, tā parāda strukturālo modifikāciju lietderību terpenoīdu zāļvielu problēmu risināšanā.

Rezumējot – promocijas darbs ir veltīts jaunām un efektīvām metodoloģijām PCT karkasa funkcionalizēšanai. Aktivējot ķīmiski inertas pozīcijas, piemēram, C(16)-H un C(22)-H, tiek nodrošināta piekļuve iepriekš nezināmiem strukturāliem motīviem. Izstrādātais sintētisko metožu kopums nākotnē nodrošinās strukturāli jaunus būvblokus triterpenoīdos balstītu farmakoloģiski aktīvu savienojumu un/vai kosmētikas līdzekļu izstrādei, kas nodrošinās arī padziļinātus triterpenoīdu struktūras un aktivitātes attiecību pētījumus.




2. attēls. Promocijas darbā izstrādātās sintētiskās pieejas, kas ļauj veikt pentaciklisko triterpenoīdu (PCT) šķīdību uzlabojošas modifikācijas un selektīvu C-H funkcionalizēšanu.

## Pētījuma mērķi un uzdevumi

Promocijas darba mērķi ir:

- sintētisko metožu izstrāde pentaciklisko triterpenoīdu D/E ciklos C-H funkcionalizēto atvasinājumu iegūšanai;
- sintētisko metožu izstrāde jonogēno pentaciklisko triterpenoīdu fosfonātu ar paaugstinātu šķīdību ūdenī ieguvei.

Lai sasniegtu mērķi, tika definēti vairāki uzdevumi.

- Izstrādāt PCT C(28) fosfonātu konjugātu sintēzes metodes, izmantojot estera saiti, un PCT C(3) fosfonātu konjugātu sintēzes, izmantojot ētera saiti, un novērtēt iegūto produktu šķīdību ūdenī.
- Izstrādāt PCT C($sp^3$)-H arilēšanas un hetarilēšanas metodes terpenoīdu D/E ciklos. Veikt C($sp^3$)-H deiterēšanas eksperimentus, kā arī izdalīt uz analizēt iespējamos C($sp^3$)-H arilēšanas reakcijas piemaisījumus, lai izprastu mehānismu un reģioselektivitāti nosakošos aspektus.
- Veikt dažādu C(16) un C(22) PCT-(het)arilatvasinājumu sintēzi, pārbaudot lietojamo arilhalogenīdu klāstu.
- Izstrādāt C($sp^3$)-H aminēšanas metodi C-N saišu veidošanai betulīna D/E ciklos. Parādīt iegūto aminobetulīna atvasinājumu sintētisko lietojumu, izstrādājot C($sp^3$)-H aminēšanas produktu tālākas funkcionalizēšanas iespējas.

## Zinātniskā novitāte un galvenie rezultāti

Promocijas darbā ir izstrādātas sintēzes metodes jaunām pentaciklisko triterpenoīdu pārvērtībām, kas dod vairākas līdz šim nepieejamas savienojumu bibliotēkas. Nozīmīgākie sasniegumi ir šādi.

- Izstrādāts betulīnskābes, oleanolskābes un ursolskābes jauna tipa jonogēno fosfonātu atvasinājumu dizains. Izstrādāta mērogojama, ērta sintēzes procedūra, kas piemērota PCT atvasinājumu ieguvei. Visi jonogēnie PCT fosfonāti uzrāda augstu šķīdību ūdenī līdz pat 26 mg/mL pie pH 8,5. Tie ir hidrolītiski stabili un ar zemu citotoksicitāti pret osteoblastu prekursoru šūnu līniju MC3T3-E1, tādējādi paverot daudzsološas iespējas iegūto savienojumu turpmākai izpētei medicīnas ķīmijas jomā.
- Pirmo reizi izstrādāta sintētiska procedūra pentaciklisko triterpenoīdu reģioselektīvai palādija katalizētai C-H arilēšanai un azetidinēšanai. Šī metodoloģija uzskatāmi demonstrē pikolinamīda virzošās grupas efektīvu lietojumu PCT selektīvai funkcionalizēšanai. Optimizētie C-H arilēšanas reakcijas apstākļi nodrošina vēlamo C($sp^3$)-H arilēšanas un heteroarilēšanas produktu iegūšanu ar

C(22)/C(16) selektivitāti no 9 : 1 lupāna (betulīna) rindā līdz pat 19 : 1 oleanāna un ursāna rindās. Savukārt, aizstājot EDG saturošus jodarēnus ar EAG saturošiem jodarēniem, tika panākta C-N saites veidošanās PCT molekulārajā skeletā, iegūstot betulīna atvasinātu annelētu C(22)-azetidīnu un oleanāna atvasinātu annelētu C(16)-azetidīnu.

- Izstrādāta jauna katalītiska metode reģioselektīvai C-H aminēšanai betulīna molekulārajā skeletā, izmantojot rodija katalizatoru. Ieteiktais 28-*O*-sulfamāta esteris darbojas kā nitrēna prekursors, kas intramolekulāri ar augstu selektivitāti C(16) pozīcijā virza nitrēna iespiešanos un noved pie annelētas 1,2,3-oksatiazīnān-2,2-diona struktūras veidošanās. Izstrādātas arī secīgas funkcionalizēšanas metodes, kas ļauj iegūt tādus savienojumus kā 16-aminobetulīns, 16-azidobetulīns, 16-aminobetulīnskābe un 16-aminobetulonskābe. Papildus tam atrasts, ka 16-aminobetulīna atvasinājumos iespējama atkārtota C-H aminēšana, bet šoreiz ar C(22)-selektivitāti. Tas dod iespēju sintezēt 16,22-diaminobetulīna prekursorus. Iegūtie produkti piedāvā modulāras iespējas tālākai funkcionalizēšanai un jaunu pussintētisko triterpenoīdu kombinatoro bibliotēku veidošanai ar potenciālu lietojumu medicīnas ķīmijā.

Kopumā ņemot, šajā promocijas darbā ieteiktais savienojumu dizains un to iegūšanai izstrādātās sintēzes metodes nodrošina preparatīvu piekļuvi jauniem strukturāliem motīviem, kas iepriekš pentaciklisko triterpenoīdu ķīmijā nebija pieejami, tādējādi paverot jaunas iespējas PCT atvasinājumu medicīnas ķīmijas pētījumiem.

## Darba struktūra un apjoms

Promocijas darbs ir sagatavots kā tematiski vienotu zinātnisku publikāciju kopa, kas veltīta jonogēno fosfonātu un C-H funkcionalizēto pentaciklisko triterpenoīdu atvasinājumu sintēzei un to bioloģisko un sintētisko lietojumu izpētei. Promocijas darbs ietver trīs oriģinālpublikācijas *SCI* žurnālos, viena patenta, viena apskatraksta un nepublicētus rezultātus.

## Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti publicēti trīs zinātniskajos oriģinālrakstos un vienā patentā. Promocijas darba izstrādes laikā sagatavots viens apskatraksts. Pētījumu rezultāti prezentēti 13 konferencēs.

**Zinātniskās publikācijas**

**1)** **Kroškins, V**., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M. Site-selective C-H amination of lupane type triterpenoids. *Eur. J. Org. Chem*. **2025**, 2500340.

**2)** **Kroškins, V**., Lugiņina, J., Lācis, R., Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M. Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids. *ACS Omega.* **2025**, *10*, 27992–28019.

**3)** Lugiņina, J., **Kroškins, V**., Lācis, R., Fedorovska, E., Demir, Ö., Dubnika, A., Loca, D., Turks, M. Synthesis and preliminary cytotoxicity evaluation of water soluble pentacyclic triterpenoid phosphonates. *Sci. Rep*. **2024,** *14*, 28031.

**4)** **Kroškins, V**., Turks, M. Recent investigations in synthesis of oxathiazinanes by sulfamate estercyclization (microreview). *Chem. Heterocycl. Comp*. **2023**, *59*, 637–639.

**Iegūtie patenti**

Lugiņina, J., **Kroškins, V**., Lācis, R., Fedorovska, E., Turks, M. Ūdenī šķīstoši triterpenoīdu fosfonāti un to sintēzes metode. LV15836 B1, 20.03.2025.

**Konfernces, kurās prezentēti pētījumu rezultāti**

1) **Kroškins, V**., Lugiņina, J., Loča, D., Dubņika, A. Water Soluble Phosphonate Derivatives of Pentacyclic Triterpenoids. In *Balticum Organicum Syntheticum 2024*: *Abstract Book,* Latvia, Riga, 7–10 July, 2024. Riga: 2024, p. 80.

2) **Kroškins, V**., Lugiņina, J., Turks, M. Regioselective C-H Amination of Lupane-Type Triterpenoids. In *Balticum Organicum Syntheticum 2024*: *Abstract Book,* Latvia, Riga, 7–10 July, 2024. Riga: 2024, p. 81.

3) **Kroškins, V**., Lugiņina, J., Turks, M. Site Selective C-H Amination of Lupane Type Triterpenoids. In *24th Tetrahedron Symposium: Abstract Book*, France, Montpellier, 18–21 June, 2024. Montpellier, p. 242.

4) Kumpiņš, V., **Kroškins, V**., Lugiņina, J., Turks, M. Site Selective C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *24th Tetrahedron Symposium: Abstract Book*, France, Montpellier, 18–21 June, 2024. Montpellier, p. 243.

5) **Kroškins, V**., Lācis, R., Lugiņina, J., Turks, M. Palladium-Catalyzed C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *International Symposium on Synthesis and Catalysis 2023: Abstract Book*, Portugal, Evora, 5–9 September, 2023. Evora: 2023, p. 204.

6) **Kroškins, V**., Lācis, R., Lugiņina, J., Loča, D., Turks, M. Synthesis of Phosphonate Derivatives of Pentacyclic Triterpenoids. In *International Symposium on Synthesis and Catalysis 2023: Abstract Book*, Portugal, Evora, 5–9 September, 2023. Evora: 2023, p. 227.

7) **Kroškins, V**. C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *13th Paul Walden Symposium on Organic Chemistry: Program and Abstract Book*, Latvia, Riga, 14–15 September, 2023. Riga: 2023, p. 46.

8) **Kroškins, V**., Lugiņina, J., Turks, M. C-H Arylation of Pentacyclic Triterpenoids. In *81st International Scientific Conference of the University of Latvia 2023. Chemistry Section and Section of Institute of Chemical Physics: Book of Abstracts.*, Latvia, Riga, March 17, 2023. Riga: University of Latvia Press, 2023, p. 11.

9) Lugiņina, J., **Kroškins, V**., Lācis, R., Loča, D., Turks, M. Pentaciklisko triterpenoīdu fosfonātu atvasinājumu sintēze. In *Konference "Inovāciju fonds – nozaru pētījumu programma: viedie materiāli, fotonika un biomedicīna"*, Latvia, Riga, November 18, 2023. Riga: 2023, p. 1–2.

10) **Kroškins, V**., Lugiņina, J., Turks, M. Rh Catalyzed C-H Amination of Pentacyclic Triterpenoids. In: *Materials Science and Applied Chemistry 2022: Programme and Abstracts*, Latvia, Riga, October 21, 2022. Riga: 2022, p. 5.

11) **Kroškins, V**., Lugiņina, J., Jankovičs, K. C-H Activation of Lupane Type Triterpenoids. In: *80th International Scientific Conference of the University of Latvia 2022. Chemistry Section: Book of Abstracts*, Latvia, Riga, February 11, 2023. Riga: University of Latvia Press, 2022, p. 75.

12) Lugiņina, J., **Kroškins, V**., Mishnev, A., Turks, M. Palladium-Catalyzed C-H Activation of Triterpenoids. In: *Balticum Organicum Syntheticum 2022: Program and Abstract Book*, Lithuania, Vilnius, 3–6 July, 2022. Vilnius: 2022, p.115.

13) **Kroškins, V**., Lugiņina, J., Turks, M. C-H Amination of Pentacyclic Triterpenoids. In: *Balticum Organicum Syntheticum 2022: Program and Abstract Book*, Lithuania, Vilnius, 3–6 July, 2022. Vilnius: 2022, p.115.

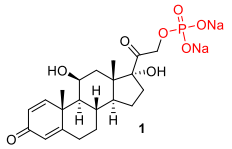
# GALVENIE PROMOCIJAS DARBA REZULTĀTI

## 1. Jonogēno pentaciklisko triterpenoīdu fosfonātu sintēze un lietojums

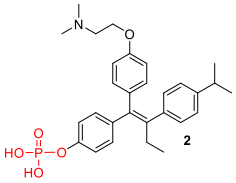
Daudzas dabasvielas uzrāda ievērojamu bioloģisko aktivitāti gan *in vitro* eksperimentos, gan preklīniskajos dzīvnieku modeļos. Tomēr to efektivitāte cilvēku klīniskajos pētījumos bieži vien dod nekonsekventus rezultātus. Atšķirīgo rezultātu iemesls starp laboratorijas pētījumiem vai pētījumiem dzīvnieku līmenī un lietojumu uz cilvēkiem ir bieži sastopama dabasvielu ierobežotā biopieejamība, ko savukārt iespaido dabasvielu molekulu paaugstinātā lipofilitāte. Hidrofobitātes un lipofilitātes jēdzieni tiek plaši izmantoti attiecībā uz organisko savienojumu sorbciju no ūdens vides.[22] Hidrofobais efekts raksturo nepolāru savienojumu tieksmi pret neūdens vidi ūdens vides vietā. Tomēr absolūta lipofilitātes nomākšana var izraisīt aktīvo farmaceitisko vielu pasīvā transporta pārtraukšanu caur organisma membrānām un pēc zāļu saistīšanās ar receptoriem. Tā rezultātā tradicionālās zāles parasti tiek izstrādātas, koncentrējoties uz labas biopieejamības un vēlamu farmakokinētisko īpašību nodrošināšanu, ko sasniegt vienlaikus ir visnotaļ sarežģīti.[23]

Viena no visizplatītākajām stratēģijām fizikāli ķīmisko, biofarmaceitisko vai farmakokinētisko īpašību uzlabošanai savienojumiem ar augstu farmakoloģisko potenciālu ir priekšzāļu izstrāde. Priekšzāles ir farmakoloģiski aktīvo molekulu ķīmiski modificētas formas, kurām jāpārveidojas *in vivo*, lai atbrīvotu aktīvo sākotnējo molekulu. Jāatzīmē, ka priekšzāļu metodi var izmantot, lai palielinātu hidrofobu nepolāru savienojumu šķīdību ūdenī un biopieejamību, ievadot polāras jonogēnas funkcionalitātes, un, pretēji, lai uzlabotu polāru hidrofilu molekulu lipofilitāti un caurlaidību, aizsargājot polārās funkcionalitātes ar nepolārām grupām.[24] Tādējādi prednizolona fosfāta esteris **1** ir reprezentatīvs steroīdo zāļu jomas priekšzāļu piemērs ar uzlabotu šķīdību ūdenī (3. att.). Vēl viens piemērs ir miproksifēna fosfāta esteris **2**, kam ir ievērojami uzlabota šķīdība ūdenī, salīdzinot ar nemodificētu miproksifēnu.

- Biokonversiju veic sārmainā fosfatāze
- Fosfāta šķīdība ļāva izstrādāt šķidro zāļu formu

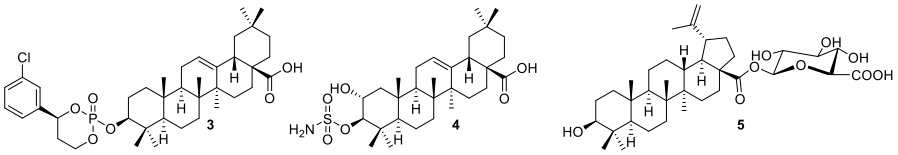



- Biokonversiju veic sārmainā fosfatāze
- Šķīdība ūdenī pie pH 7,4 palielinājās ~1000 reizes




3. attēls. Prednizolona un miproksifēna ūdenī šķīstošās priekšzāles.

Pentaciklisko triterpenoīdu steroīdiem līdzīgo struktūru paaugstināta lipofilitāte ir bieži sastopams ierobežojums šo savienojumu klašu pārstāvju medicīnas ķīmijas pētījumos un iespējamam tālākam terapeitiskam lietojumam. Lai uzlabotu triterpenoīdu šķīdību ūdenī, ir izstrādātas priekšzāļu stratēģijas. Triterpenoīdu fosfāti un sulfāti, kā arī to aminoskābju, hidrofīlu polimēru vai ogļhidrātu konjugāti (4. att.) ir plaši izmantoti, lai uzlabotu šķīdību ūdenī un perorālo biopieejamību.[25]



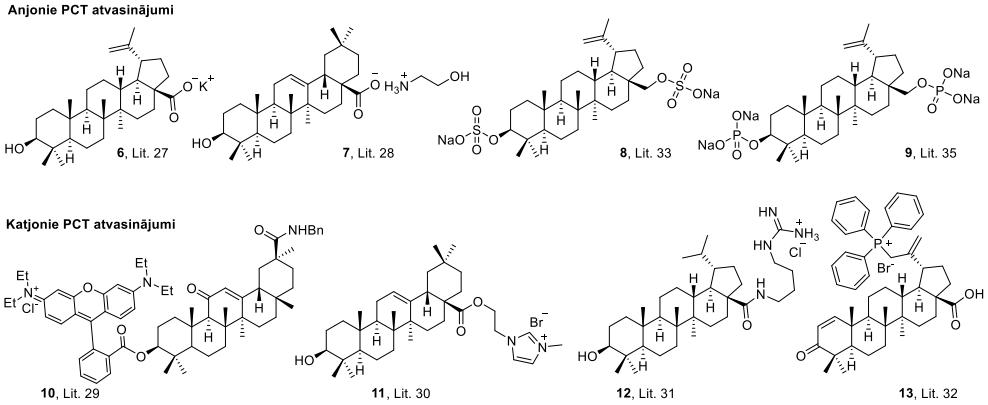
4. attēls. Oleanolskābes fosfāta prekursora **3** un ūdenī šķīstošo PCT atvasinājumu **4**, **5** piemēri.

Šķīdību ūdenī var uzlabot, arī ievadot stabilas polāras jonogēnas funkcionalitātes, nodrošinot bioloģiski aktīvo savienojumu sāls formas.[26] Ja zāļu viela ir skābe vai bāze, tad to sāļiem parasti ir augstāka šķīdība ūdenī nekā atbilstošajām nejonizētām formām. Protams, jaunu funkcionālo grupu ieviešana, kā arī jauna pretjona klātbūtne molekulā var ietekmēt modificētā savienojuma saistīšanos ar olbaltumvielām, bioloģisko sadalījumu un metabolismu.

Pašas triterpēnskābes var viegli pārveidot atbilstošos sāļos, veicot vienkāršu neitralizācijas reakciju ar dažādām neorganiskām un organiskām bāzēm. Piemēram, nātrija vai kālija betulinātu **6** var iegūt, apstrādājot betulīnskābi ar NaOH un KOH etanola šķīdumu. Tomēr šo sāļu šķīdības testi deva neskaidrus rezultātus koloīdu veidošanās dēļ koncentrācijās virs 0,02 mg/g.[27] Organiskais pretjons, kā tas ir holīna oleanolāta **7** gadījumā, uzrāda vislabāko šķīdību (81,7 µg/mL) kuņģa sulai pietuvinātā vidē (NaCl un nātrija dodecilsulfāta ūdens šķīdums, kura pH ar HCl šķīdumu ir noregulēts līdz 1,2).[28]

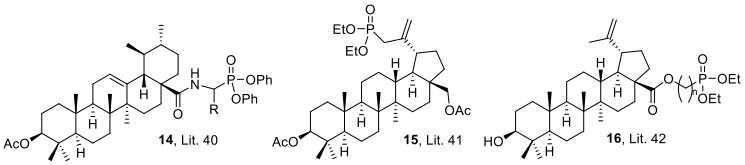
Pēdējās desmitgades laikā, veicot dažādas funkcionālo grupu pārvērtības PCT struktūrā pie C(3), C(28) un dubultsaitē, ir sintezēti daudzi katjonie PCT atvasinājumi (5. att.). Izmantojot dažāda veida saites, pentaciklisko triterpenoīdu karksasi ir atvasināti ar atšķirīgus pretjonus saturošiem amonija **10**[29], imidazolija **11**[30] un guanidīnija **12**[31] fragmentiem. Analoģiski dažādiem bioloģiskiem mērķiem ir iegūti C(28), C(30) un C(2) PCT trifenilfosfonija sāļi.[32] Diemžēl ziņojumu par šo katjono PCT konjugātu šķīdības datiem nav.

Līdz šim zināmie pussintētiskie PCT analogu anjonie atvasinājumi (5. att.) galvenokārt ietver sulfātu un fosfātu atvasinājumus, ko var iegūt, sulfatējot[33, 34] vai fosforilējot[35, 36, 37] C(3)-OH vai/un C(28)-OH grupas. Monofosforilēto un difosforilēto PCT molekulu izmainītais telpiskais izkārtojums un elektroniskā vide piešķir daudzveidīgas bioloģiskās īpašības, ko apliecināja vairāki pētījumi. Tomēr visaptveroši dati par šo savienojumu šķīdību ūdenī vēl nav publicēti.




5. attēls. Iepriekš publicēto jonogēno PCT atvasinājumu piemēri.

Fosfātu grupas aizstāšana ar izostērisko fosfonātu grupu var ievērojami samazināt fosfātiem raksturīgo zemo hidrolītisko stabilitāti. Šī pieeja ir pierādījusi fosfonātu atvasinājumu nozīmi kā stabilu bioloģiski aktīvu savienojumu klasi, kas vislielāko lietojumu līdz šim ir radusi nukleotīdu atvasinājumu kā pretvīrusu zāļu vidū.[38, 39] Ir publicēti arī daži piemēri par fosfonātu atvasinājumiem PCT ķīmijā. Fosfonāta daļas ievadīšana triterpenoīda karkasā līdz šim ir veikta ar amīda **14**[40] saiti vai C-C **15**[41] saiti (6. att.). Pirms promocijās darbā atspoguļoto pētījumu sākšanas bija aprakstīts tikai viens piemērs par PCT fosfonātu atvasinājumu **16**,[42] kurā fosfonāta grupa ir saistīta ar estersaiti pie C(28) (6. att.). Tomēr sintētiskās metodes par PCT fosfonātu pārveidošanu fosfonskābēs vai to sāļos, kā arī šādi iegūtu fosfonātu sāļu šķīdības dati nav pieejami.

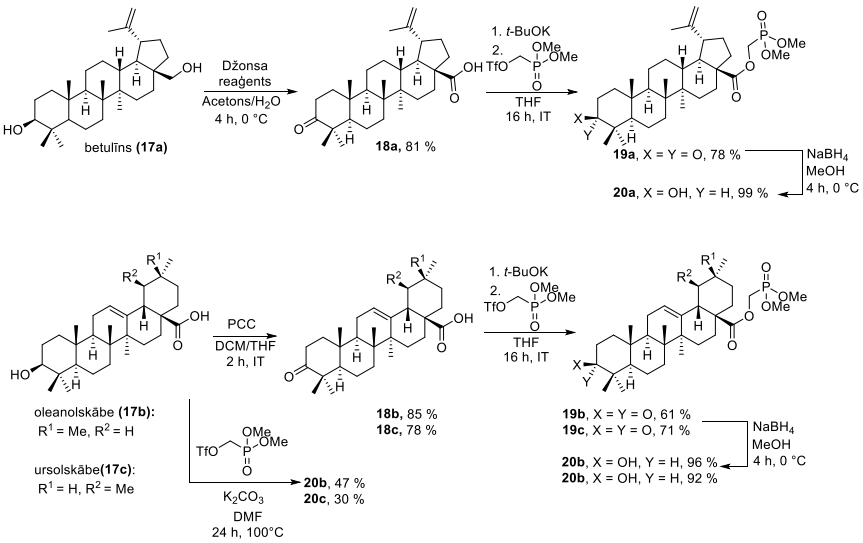



6. attēls. Iepriekš publicētie PCT fosfonātu konjugāti.

Promocijas darbā ir izstrādāti jaunu pentaciklisko triterpenoīdu fosfonātu atvasinājumu ar vispārīgo struktūru C(17)-COO-$CH_2$-*P*, C(3)-O-$CH_2$-*P* un C(3/28)-O-$CH_2$-*P* dizains un sintēzes metode. Tajā fosfonāta fragmenta ievadīšanai, izmantojot estera vai ētera saiti, ir izvēlēts vienkāršākais iespējamais -$CH_2$- tiltiņš. Jāuzsver, ka iepriekš publicētie triterpenoīdu C(28) esteri uzrāda augstu stabilitāti skābā un bāziskā vidē.[43] Savukārt izstrādātā metode dod iespēju viegli iegūt šādus no triterpenoīdiem atvasinātus fosfonātu esterus. Tos ir arī viegli pārvērst sāls formā, un tiem piemīt uzlabota šķīdība ūdenī. Sākotnēji tika mēģināts ievadīt vēlamo fosfonāta fragmentu, veicot 3-okso-PCT karbonskābju esterifikācijas reakciju ar dimetil(hidroksimetil)fosfonātu, taču netika atrasti pietiekami efektīvi reakcijas apstākļi. Problēma tika atrisināta, attālinot reakcijas centru par vienu atomu no C(17) kvaternārā centra, tādējādi pārvarot triterpenoīdu skeleta stēriskos

traucējumus. Šim nolūkam tika nolemts pāriet no nukleofīla reakcijas ar aktivētu karbonskābes fukciju uz karboksilāta alkilēšanas reakciju ar elektrofīlu komponenti.

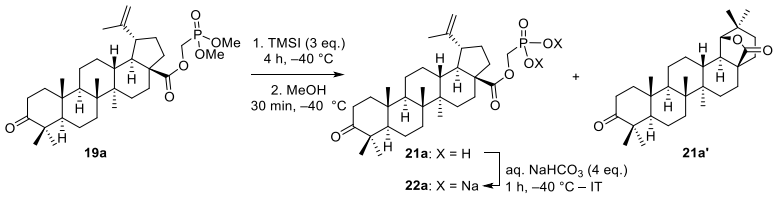
*t*-BuOK bija piemērots 3-oksotriterpēnskābju **18a-c** veiksmīgai deprotonēšanai, un pēc sekojošas alkilēšanas ar (dimetoksifosforil)metiltrifluormetānsulfonātu bezūdens THF vidē ar labu iznākumu tika iegūti vēlamie esteri **19a-c** (1. shēma). Izmantotais triflāts ir viegli iegūstams no iepriekš minētā spirta.[44] Līdzīga pieeja, izmantojot (dimetoksifosforil)metiltrifluormetānsulfonātu kombinācijā ar 3-hidroksitriterpēnskābēm **17b**,**c**, nodrošināja savienojumus **20b**,**c** (process **17b**,**c** → **20b**,**c**, 2. shēma), bet ar zemākiem iznākumiem blakusproduktu veidošanās dēļ. Lai uzlabotu ķīmisko selektivitāti starp mērķa C(17)-COOH un nevēlamo C(3)-OH alkilēšanu transformācijā **17b**,**c** → **20b**,**c**, tika izmantots $K_2CO_3$ kā vājāka bāze. Šādos apstākļos tika novērota arī nevēlama transesterifikācija starp C(17)-COOH un alkilēšanas reaģenta fosfonskābes metilestera daļu, veidojot C(17)-COOMe blakusproduktu kopā ar $TfOCH_2P(O)(OH)(OMe)$. PCT fosfonātu **19a-c** diastereoselektīvā C(3) reducēšana tika atzīta par optimālāku, nodrošinot selektīvākas transformācijas un piekļuvi C(3)-OH fosfonātu atvasinājumiem **20a-20c**.




1. shēma. PCT fosfonātu **19a-c** un **20a-c** sintēze.

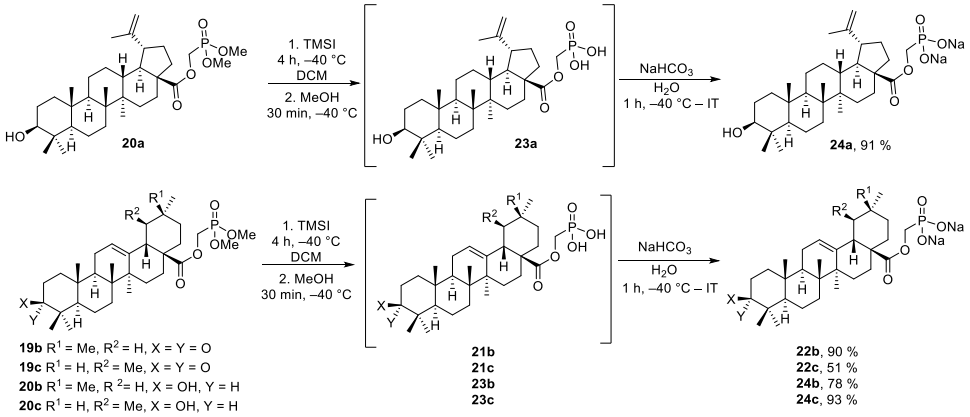
Tālāk pētījām iegūto fosfonātu **19a-c** un **20a-c** transformāciju par nātrija fosfonātiem **22a-c** un **24a-c**, izmantojot demetilēšanu trimetilsililjodīda (TMSI) klātienē, kam sekoja izveidoto fosfonskābju **21a-c** un **23a-c** pārveidošana atbilstošajos nātrija sāļos. Kā modeļvielu lietojot betulonskābes fosfonātu **19a**, tika atklāts, ka demetilēšanai nepieciešamā temperatūra ir –40 °C (2. shēma). Augstākā temperatūrā tika novērota iepriekš izveidotās estersaites šķelšanās un betulonskābes dubultsaites katjonā pārgrupēšanās.[45] Tika atklāts, ka starpprodukta O-TMS-

fosfonātu metanolīze un sekojoša HI neitralizācija kopā ar fosfonskābes dinātrija sāls veidošanos, pievienojot nātrija bikarbonāta ūdens šķīdumu, arī ir jāveic pazeminātā temperatūrā.




2. shēma. Savienojuma **19a** demetilēšana.

Izstrādātie demetilēšanas apstākļi tika veiksmīgi izmantoti visām pārējām savienojumu sērijām, kas sastāv no betulīnskābes atvasinājuma **20a** ar brīvu C(3)-OH grupu, no 3-oksooleanolskābes un ursolskābes atvasinātiem fosfonātiem **20b,c** un to atbilstošajiem C(3)-OH atvasinājumiem **21b,c**, iegūstot mērķa produktus **22a-c** un **24a-c** ar labiem līdz izciliem iznākumiem (2., 3. shēma).

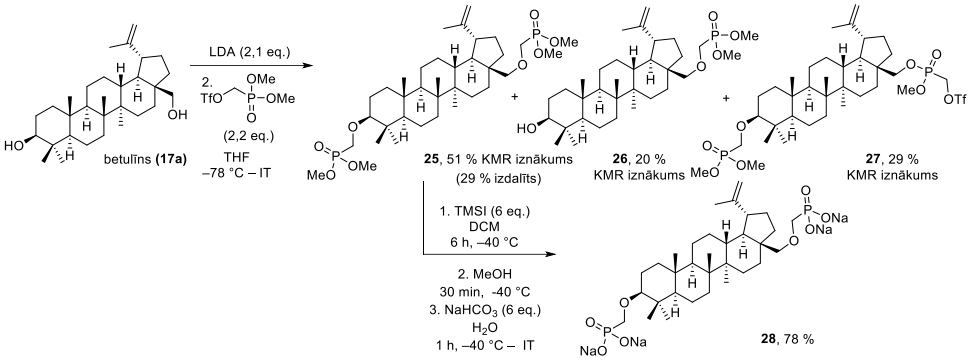



3. shēma. No triterpēnskābēm atvasinātu nātrija fosfonātu **22b,c** un **24a-c** sintēze.

Iegūtie produkti **22a-c** un **24a-c** uzrādīja augstu hidrolītisko stabilitāti, un karboksilāta estera saites šķelšanās netika novērota pat pēc karsēšanas divos dažādos bāziskos apstākļos: (1) 60 °C temperatūrā 1,5 M NaOH/MeOH šķīdumā 6 stundas; (2) 100 °C temperatūrā 4 ekvivalentu NaOH klātbūtnē $H_2O$ 24 stundas. Iegūtajiem jonogēnajiem PCT atvasinājumiem piemīt augsta šķīdība ūdenī, ko var labi parādīt, reģistrējot to $^1$H KMR spektrus $D_2O$ vidē.

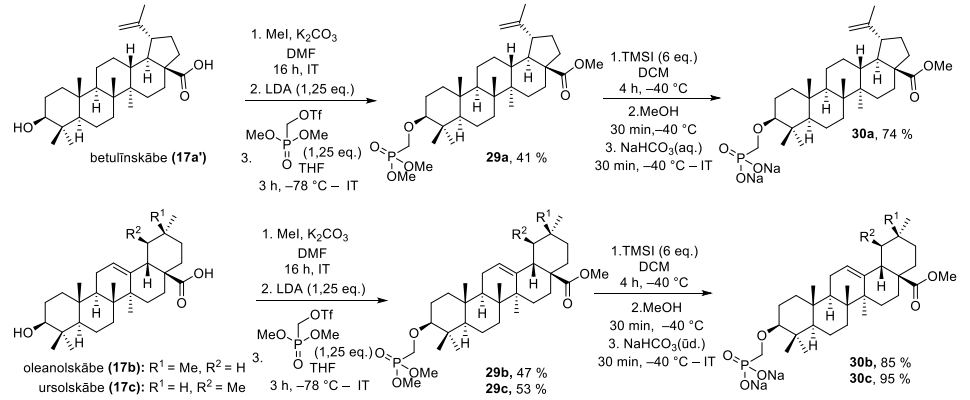
Tālāk tika pētīta fosfonāta funkcionalitātes ievadīšana PCT, izmantojot ētera saiti. Sākot ar betulīnu, visizplatītāko dabisko PCT-3,28-diolu, tika pārbaudīta abu hidroksilgrupu alkilēšanas iespējamība vienlaikus. Tādu spēcīgu bāzu kā NaH, *t*-BuOK, *n*-BuLi un MeMgBr izmantošana kombinācijā ar iepriekš lietoto (dimetoksifosforil)metiltriflātu vai tozilātu izrādījās neefektīva.

Visbeidzot tika atklāts, ka, apvienojot triflāta alkilēšanas reaģentu (2,2 eq.) un no LDA (2,1 eq.) iegūto betulīna litija dialkoksīdu, var iegūt mērķa produktu **25** ar 29 % iznākumu (4. shēma). Kopā ar vēlamo produktu **25**, tika izdalīts C(28)-O-monoalkilēšanas produkts **26** un C(28)-O-fosfonilēšanas produkts **27** attiecībā **25** : **26** : **27** 51 : 20 : 29 (KMR). Blakusprodukta **27** veidošanās rodas no alkoksīda uzbrukuma fosfora centram divu konkurējošu elektrofīlu reakcijas centru klātbūtnes dēļ (dimetoksifosforil)metiltrifluormetānsulfonātā. Iegūtais tetrametilbis-fosfonāts **25** tika veiksmīgi pārveidots par tetranātrija sāli **28** (78 %), izmantojot iepriekš izstrādātos demetilēšanas apstākļus.



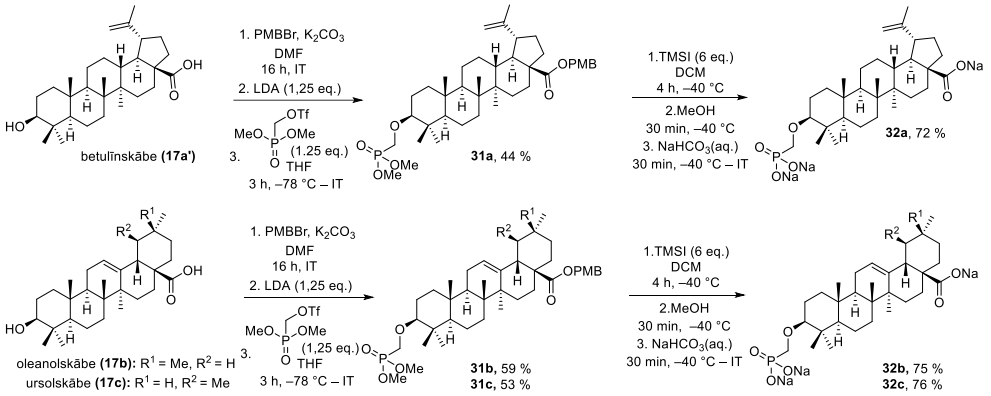

4. shēma. Bis-fosfonāta **28** sintēze.

Pēc tam tika sintezēti monofosfonātu PCT atvasinājumi pie C(3). Šim nolūkam betulīnskābes (**17a'**), oleanolskābes (**17b**) un ursolskābes (**17c**) karbonskābes funkcijas tika aizsargātas kā metilesteri. Iepriekš izstrādātās LDA/triflāta kombinācijas lietošana deva pieeju vēlamajiem C(3)-ēteriem ar vidējiem iznākumiem (5. shēma). Papildus mērķa produktiem pēc reakcijas tika novērota arī izejvielu klātbūtne un alkilējošā reaģenta degradācija.



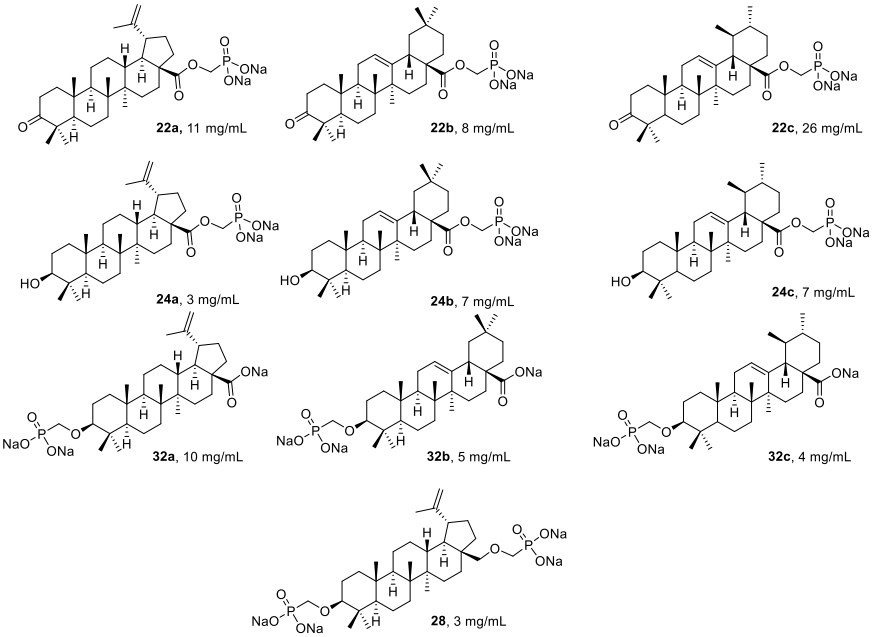

5. shēma. Metilaizsargātu PCT fosfonātu atvasinājumu **29a-c** sintēze un demetilēšana.

Tika sagaidīts, ka iepriekš izstrādātie TMSI apstākļi nodrošinās gan fosfonātu demetilēšanu, gan C(28) karbonskābes metilestera demetilēšanu, iegūstot vēlamos trinātrija sāļus. Tomēr C(28) metilesteri **29a-c** uzrādīja paaugstinātu stabilitāti, veidojot produktus **30a-c** (5. shēma). Alternatīvu apstākļu pārbaude metilesteru **29a-c** šķelšanai, piemēram, 6M KOH/EtOH attecē, LiI/DMF/DMSO attecē, izrādījās neefektīva. Tāpēc tika nolemts mainīt metilgrupu uz vieglāk nošķeļamo 4-metoksibenzilgrupu. Šoreiz C(28)O-PMB aizsargāto C(3) ēteru **31a-c** apstrāde ar TMSI, sekojoša metanolīze un neitralizācija ar $NaHCO_3$ deva mērķa PCT jonogēnos atvasinājumus **32a-c** ar labiem iznākumiem (6. shēma).




6. shēma. PMB aizsargātu PCT fosfonātu atvasinājumu **31a-c** sintēze un demetilēšana.

Visiem iegūtajiem jonogēnajiem PCT nātrija fosfonātiem tika veikti šķīdības testi ūdenī (7. att.). Precīzai šķīdības aprēķināšanai tika izmantota kvantitatīvā $^1$H-KMR pieeja $D_2O$ vidē, izmantojot kālija hidrogēnftalātu kā ārējo standartu. Fosfonātu bāziskās formas[46] tika nodrošinātas, uzmanīgi pievienojot NaOD, kvantitatīvās noteikšanas laikā uzturot pH 8,0–8,5, kas ir par 2–3 vienībām augstāks nekā fosfonskābes disāls pKa.[47] Kā paredzams, jaunizveidotajiem PCT fosfonātiem **22a-c**, **24a-c**, **32a-c** un **28** piemīt lieliska šķīdība ūdenī diapazonā no 3 mg/mL līdz 26 mg/mL (pH 8,08,5) (7. att.). Tā ir vismaz par divām kārtām augstāka nekā līdz šim publicētie dabisko triterpēnskābju šķīdības dati. Piemēram, oleanolskābes un betulīnskābes šķīdība ūdenī neitrālā pH ir < 0,1 μg/mL, un to var palielināt līdz 42,1 μg/mL betulīnskābei un 99,5 μg/mL oleanolskābei pie pH 11,8.[22] Arī dabiskajai ursolskābei ir līdzīgi zema šķīdība ūdenī,[20] ko var zināmā mērā palielināt ar dažādām modernām zāļu piegādes sistēmām.[18, 19] Fosfonskābes ir stiprākas skābes un vieglāk jonizējamas nekā karbonskābes. Šī īpašība palīdz palielināt šķīdību ūdenī, kā to pierāda šeit aprakstītie savienojumi.




7. attēls. PCT fosfonātu šķīdība deiterētā ūdenī ($D_2O$) pie pH 8,0 – 8,5.

Iegūto savienojumu citotoksiskā aktivitāte dažādās koncentrācijās (10–50 μM) tika noteikta cilvēka osteosarkomas šūnu līnijās MG-63 (ATCC, CRL-1427) un peles preosteoblastu šūnu līnijās MC3T3-E1 (ATCC, CRL-2593) sadarbībā ar *Dr. sc. ing.* A. Dubņiku un profesori D. Loču (RTU Biomateriālu un bioinženierijas institūts). Kā standartvielas citotoksicitātes testos tika lietotas arī dabiski sastopamās betulīnskābe (**17c'**), oleanolskābe (**17b**) un ursolskābe (**17c**), kā arī to 3-oksoanalogi **18a-c** un doksorubicīns. Tika konstatēts, ka izstrādātie ūdenī šķīstošie PCT fosfonātu atvasinājumi un dabiskās triterpēnskābes, tostarp to 3-oksoanalogi, neuzrāda toksicitāti MC3T3-E1 šūnās. Kā interesants izņēmums jāmin koncentrācijas atkarīga MC3T3-E1 šūnu dzīvotspējas samazināšanās oleanonskābes klātbūtnē (0,49 ± 0,12 relatīvā vielmaiņas aktivitāte pie 50 μM **18b**). Mazākā mērā ursonskābe ietekmēja MC3T3-E1 šūnu vielmaiņas aktivitāti (0,72 ± 0,09 relatīvā vielmaiņas aktivitāte pie 50 μM **18c**). Tomēr MG-63 šūnu līnija uzrādīja nedaudz zemāku vielmaiņas aktivitāti oleanonskābes fosfonāta **24b** klātbūtnē (0,73 ± 0,05 relatīvā vielmaiņas aktivitāte pie 50 μM **24b**) nekā oleanolskābes klātbūtnē (1,03 ± 0,18 **18b** gadījumā). Interesanti atzīmēt, ka ursolskābe (**17c**) un ursonskābe (**18c**) šūnu dzīvotspējas testos uzrādīja citotoksisku iedarbību pret MG-63 šūnu līniju (attiecīgi 0,28 ± 0,04 un 0,67 ± 0,04 relatīvā vielmaiņas aktivitāte pie 50 μM **17c** un **18c**).

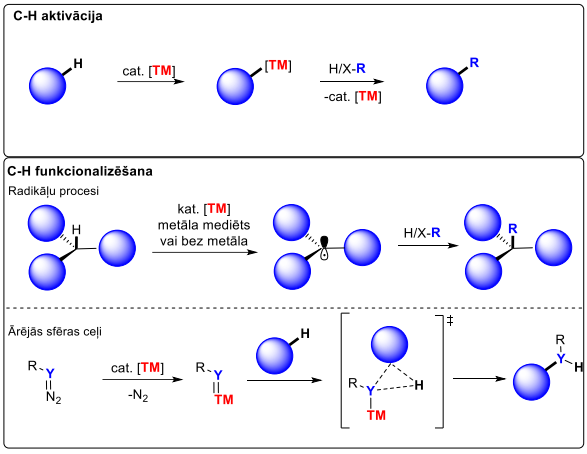
Kopsummā var secināt, ka ir iespējams izveidot pentaciklisko triterpenoīdu fosfonātu atvasinājumus, kur fosfonāta fragmenti ir saistīti pie triterpēna karkasa ar ētera vai estera tipa funkcionālajām grupām un ar īsāko iespējamo metilēntiltiņu. Fosfonāta demetilēšana ar TMSI tika

optimizēta, lai izvairītos no skābes izraisītām pārgrupēšanās blakusrekcijām. Iegūti ir gan ar estera saiti saistīti dinātrija fosfonāti no betulīnskābes, oleanolskābes un ursolskābes, ieskaitot to 3-oksoformas, gan ar ētera saiti saistīti fosfonskābju un terpēnkarbonskābju trinātrija sāļi. Sāļiem konstatēta augsta šķīdība ūdenī (3–26 mg/mL pie pH 8,0–8,5), kas noteikta ar kvantitatīvo KMR. To augstā šķīdība pieļauj pat savienienojumu KMR raksturošanu $D_2O$ šķīdumos. Sākotnējie citotoksicitātes testi liecina par zemu toksiskumu normālām šūnām, kas paver iespējas pētījumiem to izmantošanai pretvīrusu, pretmikrobu, antidiabētiskās un pretiekaisuma terapijās.

Par šiem pētījumiem plašāk var lasīt publikācijā Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E.; Demir, Ö., Dubnika, A., Loca, D., Turks. M. Synthesis and preliminary cytotoxicity evaluation of water soluble pentacyclic triterpenoid phosphonates. *Sci. Rep.* **2024**, *14*, 28031; (1. pielikums) patentā Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Turks, M. Ūdenī šķīstoši triterpenoīdu fosfonāti un to sintēzes metode. LV15836 B1, 20.03.2025. (2. pielikums); kā arī 3. pielikumā par PCT 3-*O*-metilfosfonātu sintēzi.

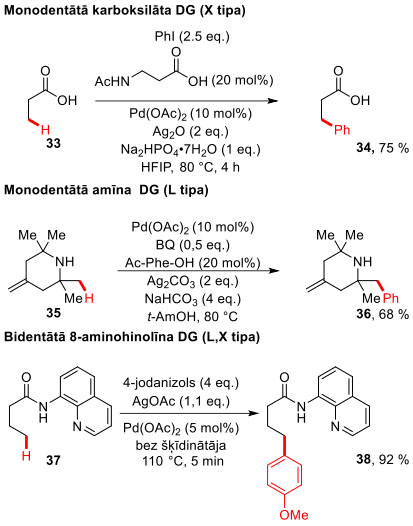
## 2. Pentaciklisko triterpenoīdu C-H fukcionalizēšana

Pārejas metālu katalītisko metožu attīstība ir radījusi virkni sasniegumu sintētiskajā organiskajā ķīmijā, ļaujot konstruēt arvien sarežģītākus savienojumus.[21] Pārejas metālu katalizēta C-H aktivācija, kas ietver iekšējās sfēras C-H saites šķelšanu, lai radītu oglekļa-metāla saiti, piedāvā ilgtspējīgu un ekonomisku pieeju organiskajā sintēzē. Termini C-H aktivācija un C-H funkcionalizēšana bieži tiek lietoti līdzvērtīgi, taču zināma atšķirība slēpjas mehānismā.[48] C-H aktivācija ietver mehānisma soļus, kuros C-H saite tiek šķelta, veidojot tiešu saiti starp oglekli un metālu (7. shēma). Turpretī C-H funkcionalizēšana ir plašāks termins, kas neprasa C-M saites veidošanos un ietver gan iekšējās sfēras, gan ārējās sfēras mehānismus. Ārējās sfēras C-H funkcionalizēšana parasti notiek, izmantojot radikāļu starpniecību, ūdeņraža atoma pārnesi (HAT) vai iespiešanos C-H saitē, kurā iesaistītas metāla karbenoīdu, okso- vai nitrenoīdu daļiņas, kā arī citus procesus.



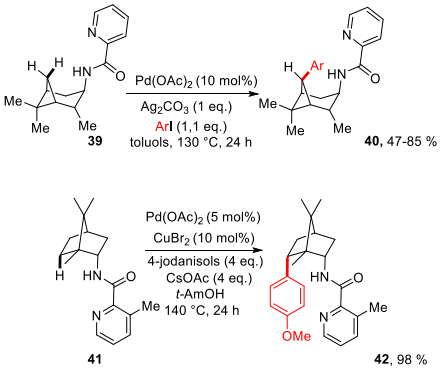

7. shēma. C-H aktivācija un C-H funkcionalizēšana.

Absolūtas ķīmiskās selektivitātes un reģioselektivitātes kontroles sasniegšana joprojām ir būtisks izaicinājums sintētiski piemērotām C-H aktivēšanas reakcijām. Reģioselektivitāti var regulēt ar substrāta elektroniskajām vai stēriskajām īpašībām, kā arī ar helātu palīdzību. Lai atvieglotu pēdējo, ir izstrādātas dažādas monodentātās un bidentātās virzošās grupas vai nu dabiski substrātā esošas (8. shēma: izejvielas **33**, **35**), vai arī apzināti ievadītas (8. shēma: izejviela **37**), lai nodrošinātu pārejas metālu katalizētu C-H aktivāciju.[49, 50, 51, 52]




8. shēma. C($sp^3$)-H aktivācija izmantojot dažāda veida virzošās grupas.

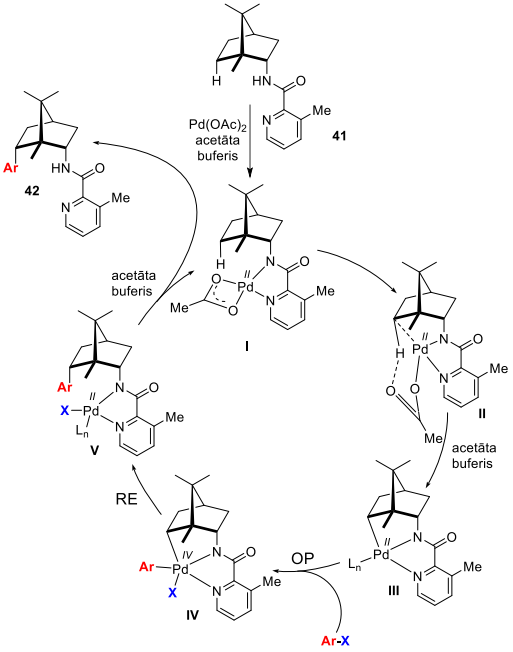
Pēdējo desmitgažu laikā ir ziņots par ievērojamiem dabasvielu C-H arilēšanas un sekojošas funkcionalizēšanas lietojumiem. Piemēram, pinamīnu **39**, kas satur pikolinamīda virzošo grupu, var selektīvi funkcionalizēt ar dažādi aizvietotiem aromātiskiem cikliem (9. shēma).[53] Savukārt Šeparda (*Shepard*) grupa ir aprakstījusi sintētisku protokolu 4-anizolilaizvietotāja iekļaušanai bornilamīna karkasā **41**, izmantojot dažādi aizvietotas virzošās piridilgrupas, starp kurām 2-metilpiridilgrupa nodrošināja vislabāko reģioselektivitāti.[54]




9. shēma. Dabisko terpēnu C-H arilēšana.

Tiek uzskatīts, ka palādija katalizētās C-H arilēšanas mehānisms sākas ar palādija koordinēšanos pie virzošās grupas un ligandu apmaiņu, veidojot kompleksu **I** (10. shēma). Pēc tam

C-H aktivācijas solis notiek, izmantojot saskaņotu metalēšanas-deprotonēšanas ceļu[55], kas ietver C-H saites koordinēšanos ar palādiju, veidojot palādija-oglekļa σ-kompleksu **II**. Aprēķinātais pārejas stāvoklis parāda, ka oglekļa-metāla saite sāk veidoties vienlaikus ar protona pārnesi uz karboksilāta grupu, kā rezultātā veidojas metāla komplekss **III**. Salīdzinot ar citiem iespējamiem procesiem, piemēram, C-H saites oksidējošo pievienošanos metālam, CMD process prasa ievērojami mazāk enerģijas.[56] Ariljodīda oksidējošā pievienošanās kompleksam **III** dod palādija(IV) intermediātu **IV**, un sekojoša C-C reducējošā eliminēšanās un ligandu apmaiņa rada palādija kompleksu **V**, kas atbrīvo mērķa arilēšanas produktu.

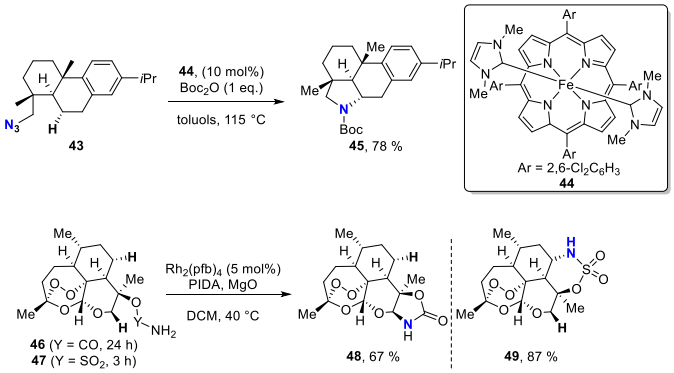



10. shēma. Palādija katalizētas C-H arilēšanas mehānisms.

Metālu piedevas, piemēram, vara(II) un sudraba(I) sāļi, bieži ir izšķirošas palādija katalizētās C-H aktivācijas reakcijās, palīdzot uzlabot reakcijas spēju, selektivitāti vai pat nodrošināt noteiktas pārvērtības, kas citādi nenotiktu efektīvi. Vara piedeva var atjaunot Pd(II) savienojumus, kas var reducēties līdz Pd(0) un apturēt Pd(II)/Pd(IV) katalītisko ciklu. Dažos gadījumos vara(II) sāļi tieši palīdz C-H saišu šķelšanā, darbojoties kā Luisa skābe, kas aktivizē substrātu, vai Brensteda bāze (īpaši ar acetāta ligandiem), kas palīdz deprotonēšanā (īpaši CMD procesā).[57] Ag(I) sāļu loma ir aprakstīta dažādos palādija katalizētos C-H aktivācijas procesos. Parasti sudraba piedevas var izmantot kā terminālo oksidētāju vai halogenīdu saistītāju, tomēr daudzi pētījumi par heterometālisku Pd-Ag katalīzi liecina, ka palādijs un sudrabs var darboties kopā visa katalītiskā cikla laikā. Dažos gadījumos sudraba karboksilāti var tieši aktivizēt (sašķelt) C-H saites arēnos,

veidojot arilsudraba(I) savienojumus. Šie arilsudraba starpprodukti pēc tam var pārnest arilgrupu uz palādija kompleksu, palīdzot veidot vēlamo produktu.[58]

Dažādu terpēnu dabasvielu aminoatvasinājumu sintēzei ir plaši lietota neaktivētu C-H saišu pārveidošana par C-N saitēm, izmantojot C-H funkcionalizēšanas metodi (11. shēma). Šajā gadījumā metāla-nitrenoīda daļiņas kalpo kā izšķirošs starpprodukts C-H saites šķelšanas procesā, kas rodas, pārnesot nitrēna grupu no aminēšanas aģenta uz metāla centru. Ar virzītu nitrēna iespiešanos ir panākta intramolekulāra aminēšana, izmantojot dažādas aminoskābes vai azīdu grupas, piemēram, sulfonamīdus, sulfamīdus, sulfamātus, karbamātus vai azīdus, sulfonilazīdus un karbonilazīdus. Piemēram, lēlamīna azidoatvasinājums **43** paaugstinātā temperatūrā un dzelzs katalizatora **44** klātienē tika izmantots kā nitrēna prekursors, iegūstot pirolidīna atvasinājumu **45** (11. shēma). No artemizīna atvasināts karbamāts **46** un sulfamāts **47** rodija katalizatora un PIDA klātienē tika attiecīgi ciklizēti par oksazolidinonu **48** un oksatiazinānu **49**, uzrādot viens otram pretēju nitrēna C-H iespiešanas reģioselektivitāti.

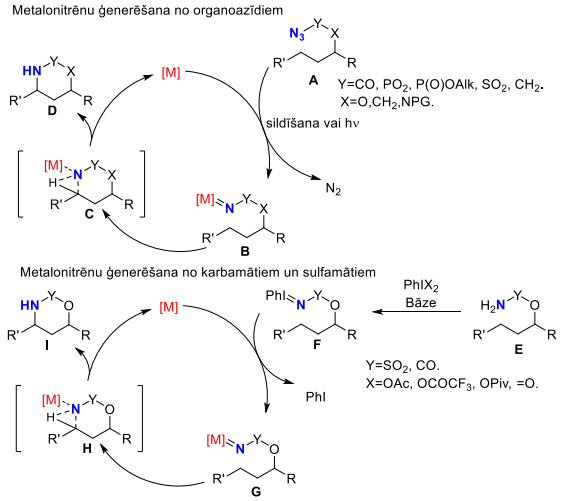



11. shēma. Lēlamīna azidoatvasinājuma **43**,[59] artemizīna karbamāta **46** un sulfamāta **47**[60] iekšmolekulārā C-H aminēšana.

Metalonitrēnu **B** var iegūt, apstarojot ar UV gaismu vai termiski sadalot organozīdus **A** piemērota pārejas metāla klātbūtnē (12. shēma). Arī karbamāti un sulfamāti kalpo kā efektīvi nitrēna prekursori hipervalentā joda reaģentu klātbūtnē, veidojot starpproduktus **F**, kas tālāk mijiedarbojas ar pārejas metāla katalizatoru un izveido vēlamo metalonitrēnu **G**. Iekšmolekulāras nitrēna iespiešanās reakcijas ir pieradījušas sevi kā spēcīgu paņēmienu dažādu *N*-heterociklu sintēzē, nodrošinot augstu ķīmisko un reģioselektivitāti. Tomēr sulfamāta un karbamāta ciklizācija var notikt arī pa radikāļu ceļu bez pārejas metālu starpniecības, kā Hofmana-Leflera-Freitāga reakcijas variācija vai arī kā π-selektīva Luisa skābes katalizēta amīnu pievienošana nepiesātinātām sistēmām.[61,62]

Par pēdējo gadu sasniegumiem oksatiazināna ciklu sintēzē no sulfamātu esteriem, ieskaitot nitrēna tipa intermediātu lietojumu, kādi tiks apskatīti arī šī darba 2.2. apakšnodaļā, var lasīt apskstrakstā: Kroškins, V., Turks, M. Recent investigations in synthesis of oxathiazinanes by

sulfamate ester cyclization (microreview). *Chem. Heterocycl. Comp*. **2023**, *59*, 637–639. (4. pielikums).



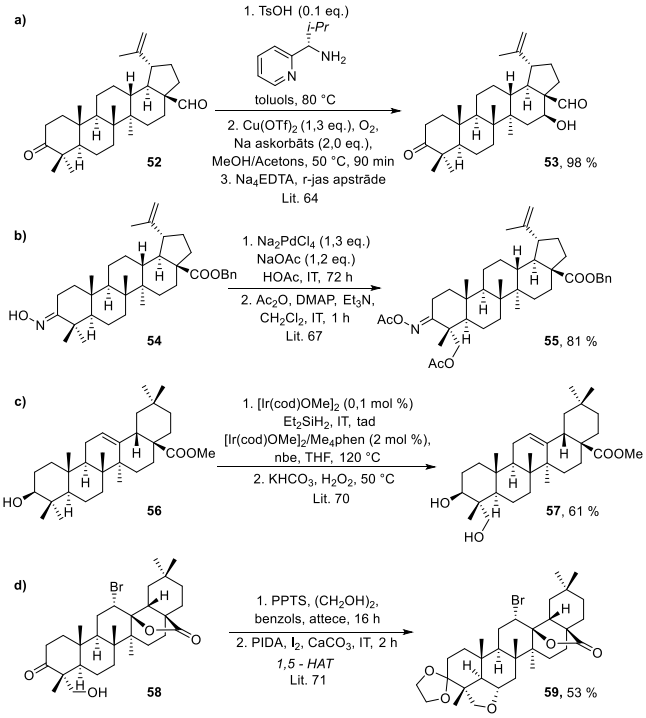

12. shēma. Metalonitrēnu ģenerēšanas mehānismi un sekojoša iespiešanās C-H saitē.

Starpmolekulārajai C-H iespiešanās pieejai nav nepieciešams sintētiski ievadīt virzošo grupu, tomēr, to lietojot, parasti tiek novērota zemāka selektivitāte. Piemēram, fenilsulfamāts ($PhsNH_2$) rodija katalizatora un $PhI(OPiv)_2$ klātbūtnē tika izmantots kā starpmolekulārs C-H aminēšanas reaģents, nodrošinot strukturāli sarežģītas dabavielas **50** C-N saites veidošanos ar 38 % iznākumu (13. shēma).[63]


13. shēma. Dabasvielas **50** iekšmolekulārā C-H aminēšana.

Lielākā daļa zināmo sintētisko pārvērtību pentaciklisko triterpenoīdu funcionalizēšanai ietver biogēno C(3) un C(28) C-O funkcionalitāšu un pieejamās dubultsaites izmantošanu.[24] Tomēr jāatzīmē, ka PCT terpenoīdā struktūra ir bagāta ar daudzām C($sp^3$)-H saitēm, ko teorētiski varētu funkcionalizēt, izmantojot pārejas metālu katalizētu C-H aktivācijas pieeju. Savukārt reakcijas spējas un reģioselektivitātes problēmas var apgrūtināt PCT ciklu tiešu funkcionalizēšanu. Priekšnoteikums šādu sarežģītu savienojumu reģioselektīvai derivatizācijai, aktivējot C-H saites, ir funkcionālu virzošo grupu klātbūtne struktūrā.

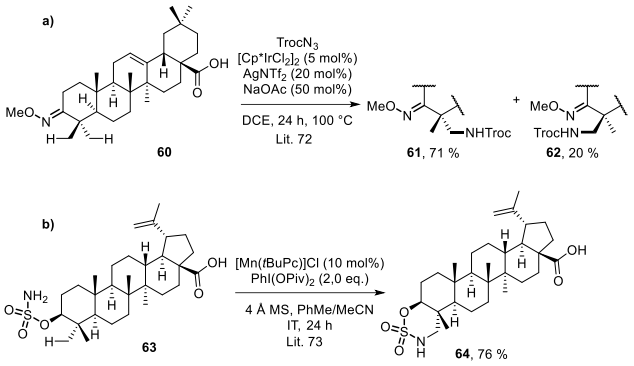
Literatūrā ir tikai daži C($sp^3$)-H aktivācijas piemēri PCT policikliskajā struktūrā (14. shēma). Ju (*Yu*) grupa[64, 65] ir aprakstījusi dažādu pentaciklisko triterpenoīdu reģioselektīvu C-H hidroksilēšanu, izmantojot Šēnekera (*Schönecker*) un Barana (*Baran*) vara katalizētos aerobos apstākļus ($Cu(OTf)_2$, $O_2$) (14. a shēma). Šajā gadījumā oksidēšanas vietas selektivitāti noteica pārejoša hirāla iminopiridīna virzošā grupa, kas tika ievadīta, izmantojot viegli pieejamu C(28) aldehīdu. Vairākas pētnieku grupas ir lietojušas Baldvina[66] (*Baldwin*) izstrādātās pieejas izmantošanu hidroksilgrupas selektīvai ievadīšanai neaktivētā C(23) metilgrupā (14. b shēma).[67, 68, 69] Savukārt oleanolskābes C(23) reģioselektīvu oksigenēšanu, izmantojot irīdija katalizētu C(3) hidroksilgrupas virzītu sililēšanu/Tamao-Fleminga oksidēšanas sekvenci, ir izpētījusi Hartviga (*Hartwig*) grupa (14. c shēma).[70] Jāatzīmē, ka Maulides (*Maulide*) grupa[71] nesen aprakstīja B gredzena reģioselektīvu C-H oksidēšanu oleanāna struktūrā, izmantojot C(23)-OH funkcionalitāti kā virzošo grupu (14. d shēma).




14. shēma. Literatūrā aprakstītie pentaciklisko triterpenoīdu C-H oksidēšanas piemēri.

Runājot par aminēšanas reakcijām, Lu (*Lu*) grupa ir izstrādājusi irīdija katalizētu C($sp^3$)-H aminēšanas reakciju oleanonskābes metiloksīma C(23) pozīcijā, izmantojot $TrocN_3$ kā amīna prekursoru (15. a shēma).[72] Betulīna karkass ir pētīts C($sp^3$)-H aminēšanā, kas tika panākts ar metalonitrēna izveidi no sulfamāta estera **63**. Vaitas (*White*) grupa ir atklājusi, ka [Mn(*t*BuPc)]$SbF_6$

katalizators veicina C-N saites veidošanos pie ekvatoriālās C(23) metilgrupas γ-C-H saites un nodrošina labu oksatiazinānu **64** iznākumu ar augstu reģio- un diastereoselektivitāti (15. b shēma).[73]

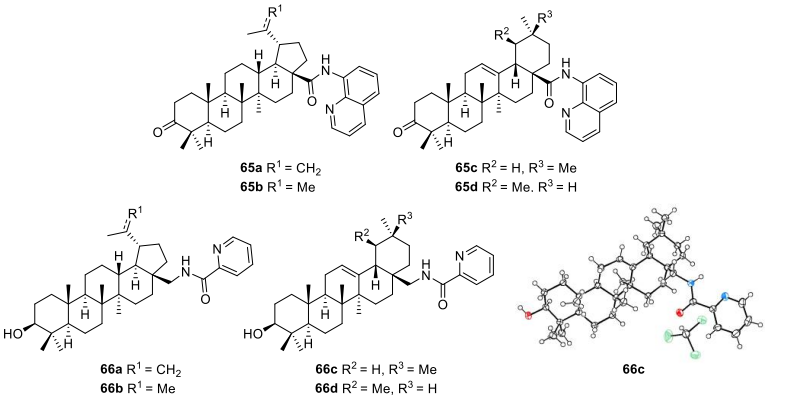



15. shēma. Literatūrā aprakstītie C-H pentaciklisko triterpenoīdu aminēšanas paņēmieni.

Pēc promocijas darba autora rīcībā esošās informācijas bez iepriekšminētajiem dažiem C-H hidroksilēšanas piemēriem un diviem vienīgajiem C-H aminēšanas piemēriem literatūrā nav datu par C-C saišu veidojošām C-H aktivācijas pieejām pentaciklisko triterpenoīdu molekulārajos karkasos. Tomēr ir aprakstīti daži veiksmīgi mazāku dabisko terpēnu molekulu C($sp^3$)-H arilēšanas piemēri.[74] Turklāt pēdējās desmitgades laikā ir izstrādātas vairākas C($sp^3$)-H arilēšanas stratēģijas, izmantojot dažādas virzošās grupas un katalītiskās sistēmas, kas ir piemērotas sarežģītu molekulu vēlīnajai funkcionalizēšanai.[75, 76, 77, 78] Līdz ar to šajā promocijas darbā tika izstrādāta iepriekš neaprakstītu palādija katalizētu pentaciklisko triterpenoīdu C($sp^3$)-H (het)arilēšana, kā arī rodija katalizētu betulīna karkasa D- un E-ciklu C-H aminēšana ar sekojošu aminogrupas funkcionalizēšanu.

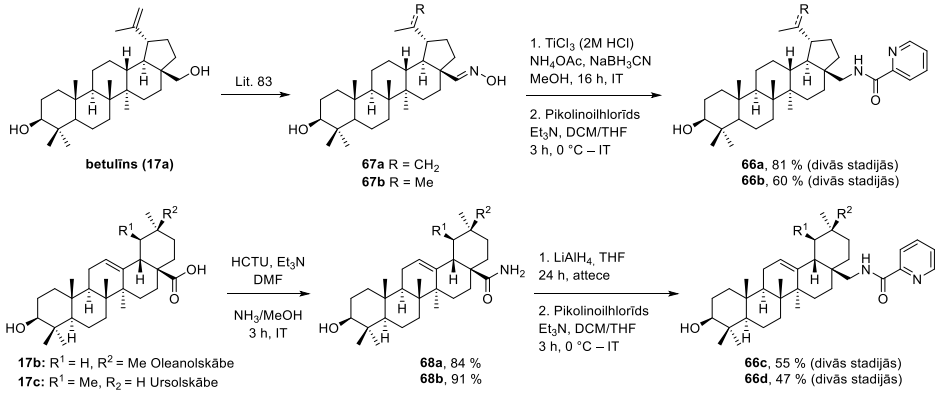
## 2.1. Pentaciklisko triterpenoīdu C-H (het)arilēšana un azetidinēšana

Pentaciklisko triterpenoīdu C($sp^3$)-H (het)arilēšanas pētījumi tika iesākti, iegūstot atvasinājumus, kas satur Dauguļa izstrādātās 8-aminohinolīnamīda un pikolīnamīda virzošās grupas.[79] Vienkāršākajā gadījumā tās ir savienotas ar triterpenoīda skeletu kā karboksamīdi **65a-d**, kas iegūstami no dabīgajām triterpēnkarbonskābem, vai ar konformacionāli fleksiblāku -$CH_2$-NH- saiti **66a-d** (8. att.).



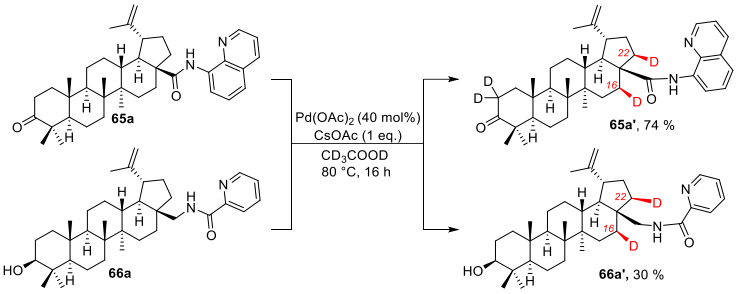

8. attēls. Triterpēnkarbonskābju 8-aminohinolīnamīdi **65a-d** un pikolīnamīdi **66a-d**.

8-Aminohinolīna amīdi **65a-d** tika iegūti amidēšanas reakcijās starp betulonskābi, ursonskābi, oleanonskābi **18a-c** un 8-aminohinolīnu, iepriekš pārveidojot šīs skābes par attiecīgajiem skābes hlorīdiem.[80,81] Pikolīnamīda[82] virzošā grupa tika ievadīta, izmantojot triterpenoīda C(28)-amīnu reakciju ar pikolinoilhlorīdu. Betulīnamīns un tā piesātinātais analogs tika iegūti, reducējot atbilstošos oksīmus[83] **67a** un **67b**. Komerciāli pieejamās oleanolskābes un ursolskābes tika pārveidotas par atbilstošajiem amīniem divos posmos.[84,85] *In situ* ģenerētie aktivētie esteri tika pārveidoti par amīdiem **68a** un **68b**, kuru reducēšana ar $LiAlH_4$ deva attiecīgos pirmējos amīnus, kas tika pārveidoti par pikolinamīdiem **66a** un **66b**, izmantojot iepriekš izstrādātus reakcijas apstākļus (16. shēma).




16. shēma. Pikolīnamīdu **66a-d** sintēze.

Lai izpētītu virzošo grupu saturošu PCT atvasinājumu spēju kompleksēt palādiju un veidot C-H deiterēšanas produktus, kas parādītu C-H aktivācijas procesa iespējamību, izejvielas **65a** un **66a** tika pakļautas C-H deiterēšanas eksperimentiem, izmantojot deiterētu etiķskābi kā šķīdinātāju $Pd(OAc)_2$ un CsOAc klātbūtnē (17. shēma). Abi substrāti nodrošināja C(16)/C(22) dideiterētus produktus. Balstoties daudzsološās C-H aktivācijas iespējās, tika pārbaudīti iespējamie reakcijas apstākļi C-H arilēšanas reakcijai. Pārsteidzoši, bet hinolīnamīda **65a** gadījumā visos izskatītos reakcijas apstākļos C-H arilēšana netika novērota.

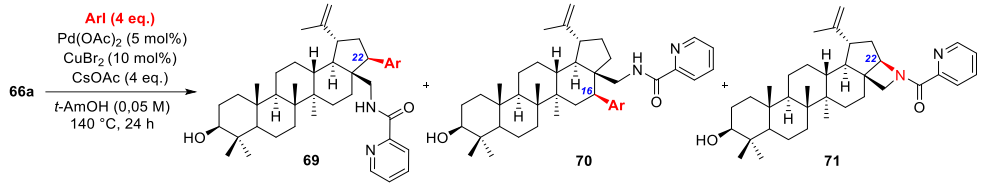



17. shēma. Savienojumu **65a** un **66a** C($sp^3$)-H deiterēšana; skābās -OH un -NH grupas ir attēlotas to nedeiterētā formā, jo produktu izdalīšanas procesā notiek ātra apmaiņa pret protoniem.

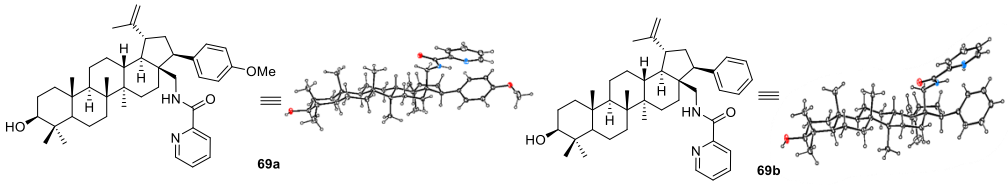
Tomēr konformacionāli elastīgākais pikolīnamīds **65a** izrādījās derīgs C-H arilēšanas reakcijām. Pikolīnamīda **66a** (1 eq.), 4-jodanizola (4 eq.), $Pd(OAc)_2$ (5 mol.%), $CuBr_2$ (10 mol.%)[86] un CsOAc (4 eq.) kombinācija, kā šķīdinātāju izmantojot *t*-AmOH, uzrādīja vislielāko efektivitāti, dodot C(22)- un C(16)-reģioizomēru **69a** un **70a** maisījumu attiecībā 92 : 8 ar 83 % kopējo iznākumu. Ar šiem C($sp^3$)-H arilēšanas apstākļiem tika pārbaudīts ariljodīdu komponentu klāsts (1. tabula). Elektronbagātie ariljodīdi uzrādīja labu reakcijas spēju, un C($sp^3$)-H arilēšanas produkti **69a-d/70a-d** tika iegūti ar kopējiem iznākumiem 50–83 % diapazonā (1. tabula). Divu arilēto savienojumu **69a,b** molekulārās struktūras tika nepārprotami pierādītas, izmantojot rentgenstruktūranalīzi (9. att.). Visos gadījumos tika novērota arī C(22)-azetidīna blakusprodukta **71** veidošanās. Elektrondeficītie jodarēni deva zemākus arilēto reģioizomēru iznākumus 29–54 % robežās. Savukārt jodarēni ar tādiem aizvietotājiem kā -COOMe, -C(O)Me, -CN, -Cl, $-NO_2$ (1. tabula) deva azetidīnu **71** kā galveno produktu ar iznākumiem 40–64 % robežās. Visaugstākais azetidīna iznākums tika novērots ar I-$C_6H_4$-CN (64 %), savukārt I-$C_6H_4$-$NO_2$ izmantošana nodrošināja selektīvu azetidīna veidošanos ar 61 % iznākumu, kas atviegloja tā izdalīšanu un attīrīšanu. Azetidīni kā C($sp^3$)-H arilēšanas blakusprodukti ir aprakstīti iepriekš. Piemēram, Vu (*Wu*) grupa iepriekš ir publicējusi mērķtiecīgu C-H azetidinēšanas protokolu, izmantojot AgOAc/$C_6F_5I$ uz vienkāršiem modeļsubstrātiem.[87] Ir zināma arī azetidīnu veidošanās no pikolīnamīdiem Pd-katalizatora, $PhI(OAc)_2$ un $Li_2CO_3$ klātbūtnē.[88, 89] Tomēr mēģinājumi, izmantot iepriekš minētos apstākļus bez vara piedevas, neuzrādīja izejvielas **66a** konversiju.

1. tabula

Pikolīnamīda **66a** C($sp^3$)-H arilēšanas substrātu klāsts un produktu iznākumi



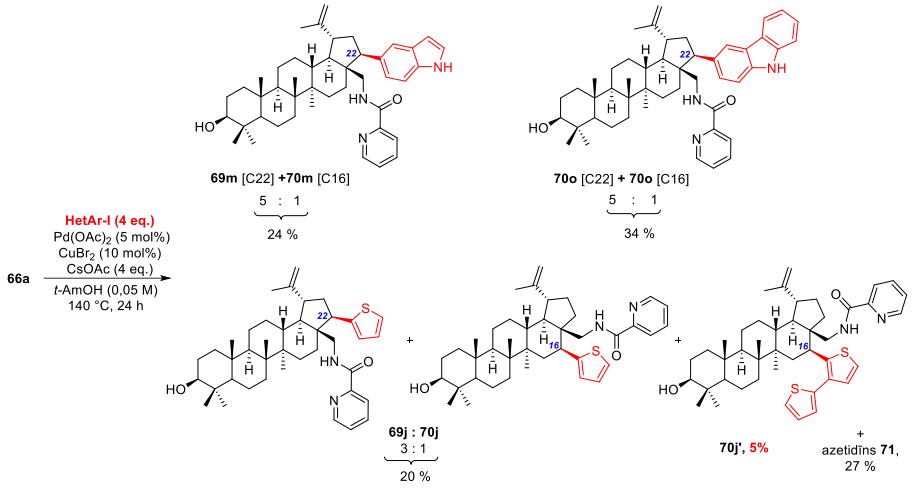

| **Ar** | **69a-i** iznākums (%) | **70a-i** iznākums (%) | **71** iznākums (%) |
|---|---|---|---|
|  | **69a**, 76 | **70a**, 7 | 10 |
|  | **69b**, 64 | **70b**, 9 | 26 |
|  | **69c**, 60 | **70c**, 5 | 19 |
|  | **69d**, 45 | **70d**, 6 | 10 |
|  | **69e**, 32 | **70e**, 6 | 36 |
|  | **69f**, 32 | **70f**, 6 | 56 |
|  | **69g**, 22 | **70g**, 7 | 40 |
|  | **69h**, 19 | **70h**, 12 | 64 |
|  | **69i**, 42 | **70i**, 12 | 44 |
|  | - | - | 61 |




9. attēls. Savienojumu **69a** un **69b** rentgenstruktūranalīze.

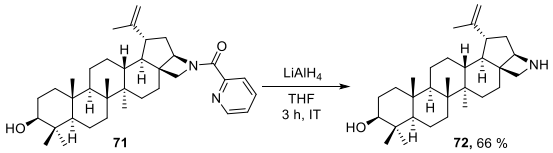
Tika pārbaudītas arī izejvielas **66a** C($sp^3$)-H (het)arilēšanas reakcijas ar 4-jod-*N,N*-dimetilanilīnu, 3-jodpiridīnu un 4-jod-1-metil-1*H*-pirazolu, taču izejvielas konversija netika novērota. Tomēr heteroarilēšana ar 5-jodindolu un 7-jodkarbazolu deva rezultātu, un sagaidāmie arilēšanas produkti **69m/70m** un **69o/70o** tika izdalīti attiecīgi ar 24 % un 34 % iznākumu, bet šoreiz bez azetidīna blakusprodukta veidošanās (18. shēma). Reakcija starp **66a** un 2-jodtiofēnu

deva produktu **69j/70j** un azetidīnu **65**, bet papildus tam tika novērots arī diarilēts produkts **70j'** 5 % apmērā. Interesanti, ka otrā C-H aktivācija tiofēna gadījumā notiek pie sākotnēji ievadītā tiofēna fragmenta produktā **70j** (18. shēma). Lai iegūtu citus dubultās arilēšanas produktus, izmantojot citus jodarēnus, tika palielināts reakcijas laiks, (het)ariljodīda komponentes koncentrāciju un katalizatora deva, tomēr nevienā citā gadījumā papildu dubultās arilēšanas produkti netika novēroti.




18. shēma. Pikolīnamīda **66a** C($sp^3$)-H heteroarilēšana.

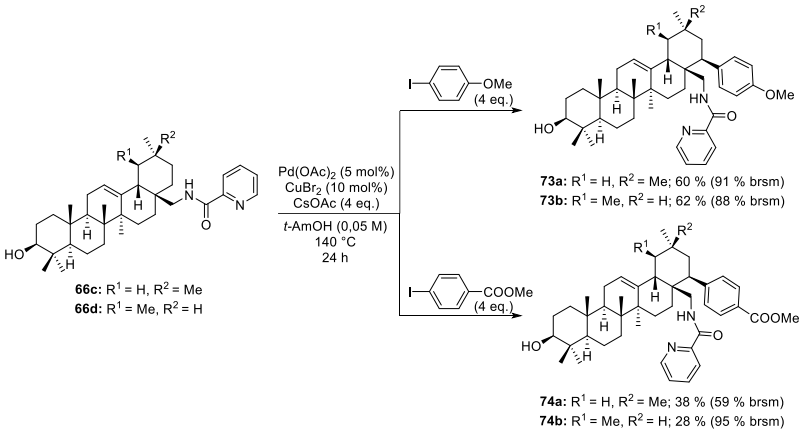
Lai nodrošinātu NH-azetidīnus tālākai sintētiskai izmantošanai, tika pētītas pikolinamīda fragmenta šķelšanas iespējas. Reducējošie šķelšanas apstākļi, izmantojot $LiAlH_4$/THF istabas temperatūrā, tika atzīti par efektīviem vēlamā produkta iegūšanai (19. shēma).




19. shēma. NH-Azetidīna **72** sintēze.

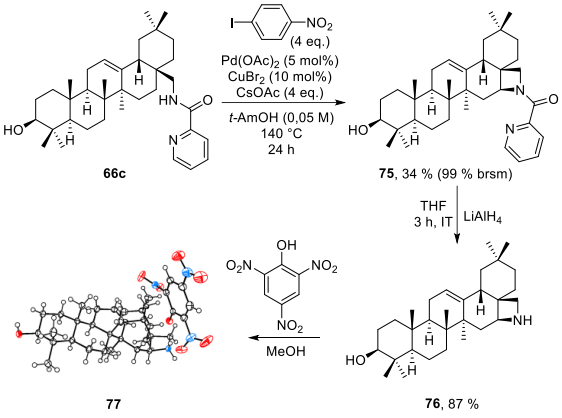
Iedvesmojoties no veiksmīgas betulīna karkasa arilēšanas, tika nolemts pētīt arī no oleanolskābes un ursolskābes pikolīnamīdu **66c,d** arilēšanu, izmantojot elektronbagāto 4-jodanizolu un elektrondeficīto 4-jodbenzoskābes metilesteri (20. shēma). Plānotā ursāna un oleanāna molekulārā skeleta transformācija vainagojās ar augstāku 19 : 1 reģioselektivitāti pie C(22), tomēr pilnīga izejvielu **66c** un **66d** konversija netika sasniegta. Līdzīgi kā betulīna karkasa gadījumā elektrondeficītais 4-jodbenzoskābes metilesteris deva ievērojami zemāku arilēšanas produktu **74a,b** iznākumu nekā reakcija ar 4-jodanizolu. Turklāt oleanāna un ursāna izejvielu **66c,d**

gadījumā blakusprodukta azetidīna klātbūtne praktiski netika novērota (blakusprodukts ap vai zem KMR detektēšanas robežas).




20. shēma. Oleanāna un ursāna atvasinājumu **66c**,**d** C($sp^3$)-H arilēšana.

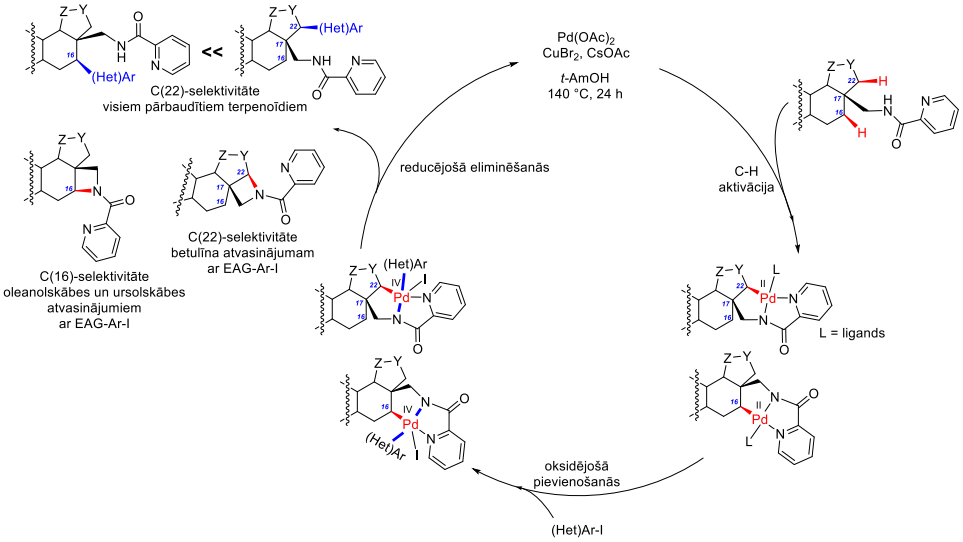
Oleanolskābes atvasinājuma **66c** C-H aktivācija 1-jod-4-nitrobenzola klātbūtnē nodrošināja izcilu C(16) selektivitāti, lai gan nedeva pilnu konversiju. Pēc virzošās grupas šķelšanas ar $LiAlH_4$ tika iegūts NH-azetidīns **76**. Tas tālāk tika pārveidots par kristālisku azetidīnija pikrātu **77**, kura molekulārā struktūra un līdz ar to arī C(16) reģioselektivitāte tika nepārprotami pierādīta ar rentgenstruktūranalīzes palīdzību (21. shēma).




21. shēma. Azetidīna **76** veidošanās no pikolīnamīda **66c**.

Saskaņā ar vispārpieņemto teoriju reducējošā eliminēšana, visticamāk, ir ātrumu noteicošā stadija C($sp^3$)-H arilēšanas procesā.[90] Analizējot novērotās ķīmiskās selektivitātes un reģioselektivitātes, var secināt, ka reducējošā eliminēšana notiek lēnāk palādija(IV) kompleksos,

kas satur elektrondeficītas arilgrupas. Šādos gadījumos reducējošā eliminēšanās ar C-N saites veidošanos var būt ātrāka par C-C saites veidošanos. Piemēram, betulīna rindā izmantojot 4-nitrojodbenzolu (4-$NO_2C_6H_4I$) (22. shēma), reducējošā eliminēšanās no C(22)-[Pd]-NC(O) sistēmas ir produktīvāka nekā no C(22)-[Pd]-Ar-EAG kompleksa, kā rezultātā veidojas azetidīns. Līdzīgi oleanāna rindā reducējošās eliminēšanās ātruma vispārējā tendence ir šāda: Ar-EDG > pikolinamīds > Ar-EAG. Tomēr oleanāna rindā C-H aktivācija ir lēnāka un sākotnēji notiek ar C(16) selektīvitāti, padarot to kinētiski salīdzināmu ar reducējošās eliminēšanas ātrumu no C(16)-[Pd]-NC(O) starpprodukta. Līdz ar to izejviela **66c**, reaģējot ar 4-$NO_2$-$C_6H_4I$, dod azetidīnu **77** C(16) pozīcijā. Turklāt azetidīna veidošanās pie C(22) oleanāna karkasā radītu nelabvēlīgu 1,3-diaksiālo mijiedarbību ar vienu no geminālajām C(20) metilgrupām, radot stēriskus traucējumus, kas betulīna molekulārajā struktūrā nav novērojami.




22. shēma. Iespējamais palādija katalizētas C($sp^3$)-H arilēšanas un azetidinēšanas mehānisms.

Noslēgumā var secināt, ka ir izstrādāta pirmā C-C saites veidojošo C($sp^3$)-H aktivācijas metode triterpenoīdos, izmantojot palādija katalizētu triterpenoīdu pikolīnamīducarilēšanu ar ariljodīdiem. Visiem trim pārbaudītiem lupāna, oleanāna un ursāna molekulārajiem karkasiem var īstenot arilēšanu ar labu C(22)-selektivitāti un vidējiem līdz labiem iznākumiem. Oleanāna un ursāna atvasinājumiem tika novērota augstākā C(22)/C(16) selektivitāte (līdz 19 : 1), savukārt betulīna atvasinājumi deva augstākus iznākumus (līdz 83 %). Elektronbagātie ariljodīdi deva arilēšanas produktus, bet elektrondeficītie ariljodīdi veicina C($sp^3$)-azetidinēšanu. Azetidinēšana īpaši labi notiek 4-nitrojodbenzola klātienē, un tās reģioselektivitāte bija atkarīga no terpenoīda tipa – betulīna atvasinājumi deva C(22)-azetidīnu, savukārt oleanāna atvasinājumam tika novērots C(16)-

azetidīns. Pikolinamīda grupu izdevās efektīvi nošķelt ar Zn/HCl. Azetidīna ciklu saturošie, kā arī arilētie triterpenoīdi piedāvā daudzsološas iespējas to tālākai izpētei medicīnas ķīmijas jomā.

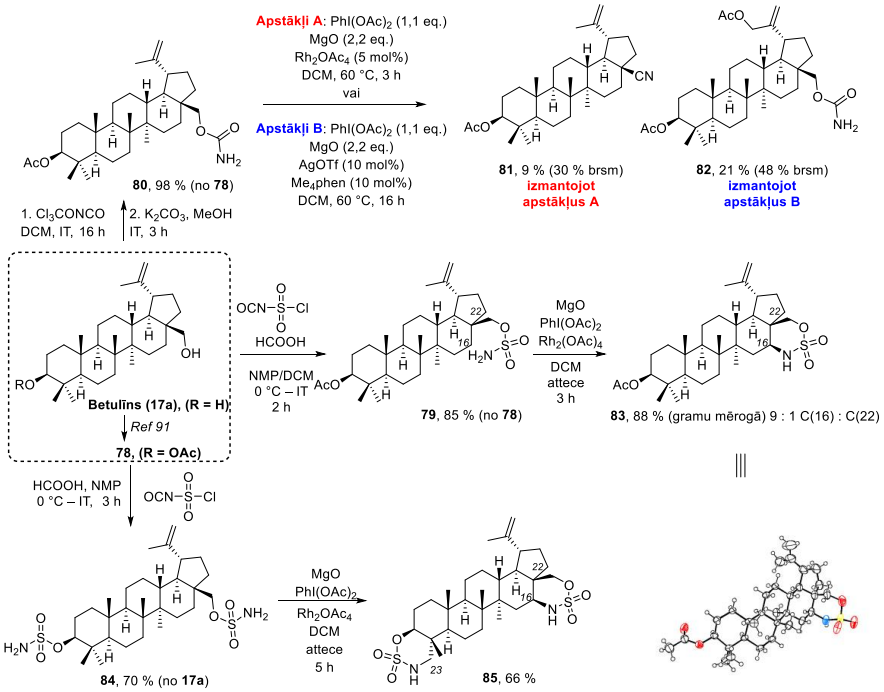
Par šiem pētījumiem var plašāk lasīt publikācijā: Kroškins, V., Lugiņina, J., Lācis, R., Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M. Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids. *ACS Omega.* **2025**, *10*, 27992–28019. (5. pielikums).

## 2.2. Pentaciklisko triterpenoīdu C-H aminēšana

Literatūrā nav publicētu precedentu par PCT skeleta D un E gredzenu C-H aminēšanu, izmantojot no C(28) atvasinātas virzošās grupas. Tomēr vairāki C-N saišu veidošanas piemēri, izmantojot starpmolekulāru C($sp^3$)-H aminēšanaas pieeju terpēnu, steroīdu un alkaloīdu molekulās, radīja interesi par attiecīgi piemērotu C(28) modificētu PCT atvasinājumu izstrādi. Šim nolūkam stika intezēti no C(28) spirta **78**[91] viegli pieejamie karbamāta un sulfamāta atvasinājumi. Balstoties promocijas darba autora zinātniskās grupas iepriekšējā pieredzē, tika izvēlēts izvairīties no reakcijām, kas notiek pēc brīvo radikāļu mehānisma, lai izslēgtu dubultsaites iespējamās blakusreakcijas. Tāpēc tika attīstīta metode, kas balstās pārejas metālu katalizētu nitrēna ģenerēšanā, ņemot vērā tā iespiešanos C-H saitē.

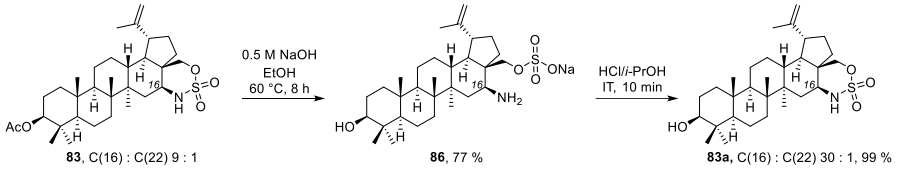
Tika atklāts, ka no betulīna atvasināts karbamāts **80** rodija un sudraba katalītiskajos apstākļos nedod paredzētos aminēšanas produktus. Tā vietā paaugstinātā temperatūrā (60 °C spiediena mēģene) un ilgākā reakcijas laikā tika detektēti izejvielas degradācijas produkti un C(28) nitrila **81**[92] veidošanās. Savienojuma **81** rašanos var izskaidrot ar C-H aminēšanas reakciju pie C(28), veidojot nestabilu četru locekļu ciklu, pēc kura dekarboksilēšanas un oksidēšanas PIDA klātienē varētu veidoties nitrils (23. shēma). Savukārt katalītiskajos apstākļos ar sudrabu, izmantojot dažādus sudraba avotus[93] (AgOTf, $AgPF_6$ vai $AgSbF_6$) kombinācijā ar MgO un $PhI(OAc)_2$ vai PhIO, tika novērota zema izejvielas konversija kopā ar degradēšanās produktu veidošanos. 3,4,7,8-Tetrametil-1,10-fenantrolīna ($Me_4$phen) kā liganda piedeva sudraba apstākļos veicināja alilpozīcijas C-H acetoksilēšanas reakciju, dodot produktu **82**.

Bija iepriecinoši konstatēt, ka sulfamāta esteris **79** pēc trīs stundām uzrādīja pilnīgu konversiju, un, reakcijas apstākļiem izmantojot 2,2 eq. MgO, 1,1 eq. $PhI(OAc)_2$ un 2 mol% $Rh_2(OAc)_4$ kombināciju[94], tika iegūti divi C-H aminēšanas reģioizomēri attiecībā 9 : 1. Pārākumā esošā izomēra **83** struktūra tika nepārprotami noteikta ar rentgenstruktūranalīzes palīdzību. Līdzīgā veidā tika sintezēts betulīna 3,28-di-*O*-sulfamāta esteris **84** ar 70 % iznākumu. Tas, izmantojot iepriekšējos apstākļus, tika veiksmīgi pārvērsts par dubultās C-H aminēšanas produktu **85**, veidojot C-N saites pie C(23) un C(16) pamatizomēra struktūrā (23. shēma).




23. shēma. Betulīna karkasa C-H aminēšana.

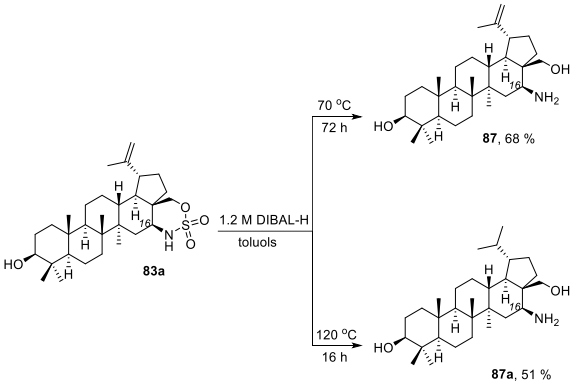
Tālāk tika pētīta iegūtā 1,2,3-oksatiazinān-2,2-diona **77** reakcijas spēja nukleofīlās cikla atvēršanas reakcijās, kas dotu pieeju 1,3-difunkcionalizētiem C(16)-aminoatvasinājumiem. Vairāki šīs pārvērtības mēģinājumi ar dažādiem nukleofīliem ($N_3^-$, $AcO^-$, $PhS^-$, morfolīns, ūdens), nenodrošināja pat minimālu izejvielas konversiju oksatiazināna gredzena zemās elektrofilitātes dēļ. Tikai bāziskā hidrolīze, izmantojot 0,5 M NaOH etanola šķīdumu, vainagojās ar nukleofīlo uzbrukumu sēra atomam, iegūstot jonogēnu 1,3-aminosulfātu **86**. Iegūtā sulfāta nātrija sāls paskābināšana izraisīja ātru ciklizēšanos atpakaļ par oksatiazināna gredzenu, iegūstot C(3)-hidroksi-PCT oksatiazināna atvasinājumu **83a** (24. shēma). Turklāt tika novērots, ka sulfāts **80** selektīvi izgulsnējas no etanola šķīduma, kā rezultātā sākotnējā savienojuma **77** C(16):C(22) 9 : 1 reģioizomēru attiecība uzlabojas līdz 30 : 1 savienojumā **86**. Savienojuma **86** izgulsnēšanas filtrāta analīze liecināja, ka **83a** mazākumā esošais C(22)-izomērs 0,5 M NaOH etanola šķīdumā nehidrolizējas un neveido jonogēnu C(22) sulfāta produktu, kas nodrošina pietiekamu polaritātes atšķirību selektīvai izgulsnēšanai. Tika izmēģināti arī vairāki stipri skābi un stipri bāziski hidrolīzes apstākļi sulfāta grupas nošķelšanai savienojumā **86**, lai iegūtu 1,3-aminospirta atvasinājumu, taču neviens no tiem nebija efektīvs.




**83**, C(16) : C(22) 9 : 1 **86**, 77 % **83a,** C(16) : C(22) 30 : 1, 99 %

24. shēma. Sulfāta **86** sintēze un ciklizēšana par **83a** skābā vidē.

Tālākā darba gaitā tika pētīti reducējošie apstākļi 1,2,3-oksatiazinān-2,2-diona cikla atvēršanai. DIBAL-H šķīdums toluolā izrādījās efektīvs, lai veiksmīgi atvērtu oksatiazīnu un izveidotu vēlamo 1,3-aminospirta atvasinājumu **87** ar 68 % iznākumu. Paaugstināta reakcijas temperatūra izraisīja ātrāku reakciju, tomēr tika novērota pilnīga dubultsaites piesātināšana (25. shēma).



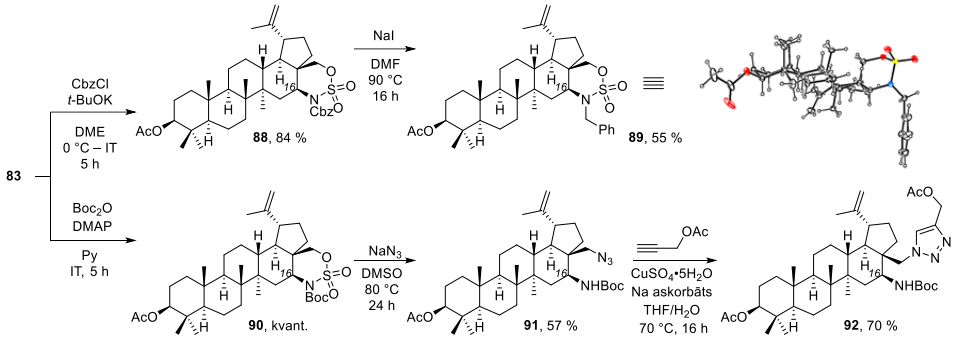

**83a** **87**, 68 % **87a**, 51 %

25. shēma. Savienojuma **83a** cikla atvēršana reducējošos apstākļos.

Lai palielinātu oksatiazināna gredzena elektrofilitāti un atvieglotu gredzena atvēršanas reakcijas ar nukleofīliem, ar kuriem pirms tam reakcija nenotika, tika veiktas divas dažādas NH-grupas karbamoilēšanas reakcijas. *N*-Cbz oksatiazināna **88** gredzena atvēršanas mēģinājumi galvenokārt beidzās ar Cbz grupas noškelšanu, un vēlamie cikla atvēršanas produkti veidojās tikai nelielā daudzumā. Interesanti, ka jodīda nukleofīla gadījumā tika novērota *N*-Cbz grupas transformācija par *N*-benzilgrupu. Tas ir skaidrojams ar Cbz grupas noškelšanu, *in situ* dekarboksilēšanos un izveidotā benziljodīda sekojošu reakciju ar brīvo NH-grupu. *N*-Benzilblakusprodukta **89** struktūra tika nepārprotami noteikta ar rentgenstaru difrakcijas analīzi (26. shēma).

*N*-Boc grupas izmantošana uzlaboja oksatiazināna reakcijas spēju, un azīda nukleofīla gadījumā tika iegūts 1,3-diaizvietotais produkts **91**. Tomēr citi nukleofīlie reaģenti (acetāts, tiofenolāts, morfolīns, cianīds, tiocianāts, fenolāts, metoksīds) joprojām izraisīja *N*-Boc grupas šķelšanos, saglabājot 1,2,3-oksatiazinān-2,2-diona gredzenu neskartu. Oksatiazināna zemo reakcijas spēju ar nukleofīliem var skaidrot ar betulīna C(28) neopentilpozīcijas statusu, ko stēriski

traucē kvaternārais centrs pie C(17).[95] Optimālie aminoazīda **91** sintēzes apstākļi tika iegūti, izmantojot 2 eq. $NaN_3$ 80 °C temperatūrā DMSO šķīdumā 24 stundas. Pēc tam iegūtais azīds **91** tika izmantots vara katalizētā azīda-alkīna 1,3-dipolārā ciklopievienošanas reakcijā (CuAAC) ar propargilacetātu, iegūstot triazolu **92** (26. shēma).

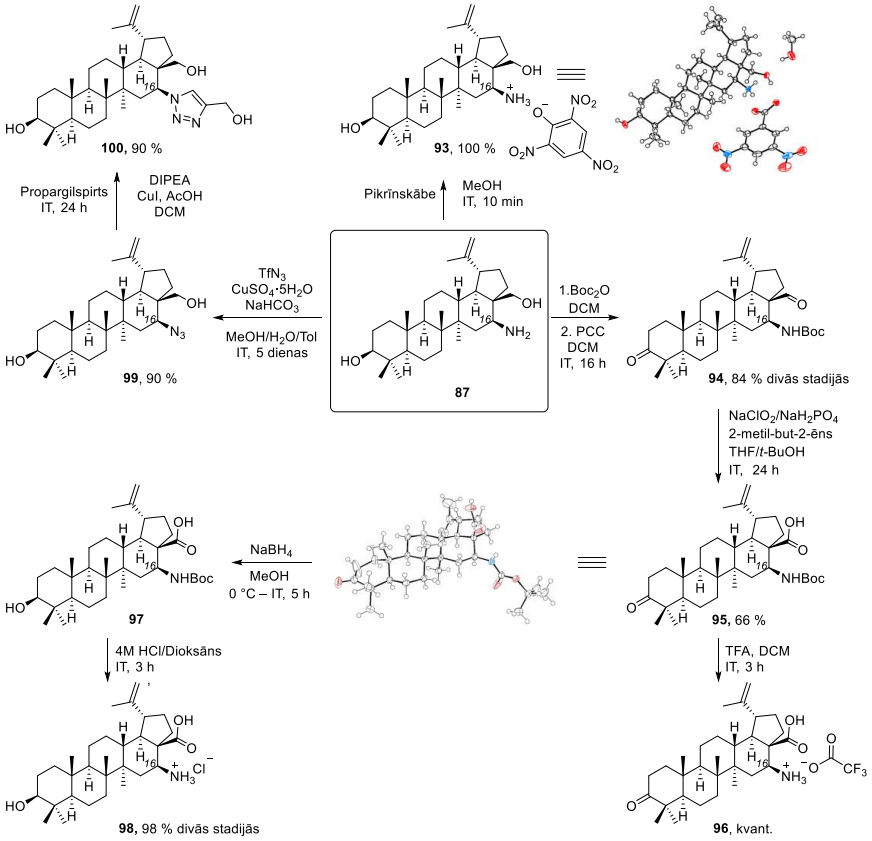



26. shēma. *N*-Aizsargātu oksatiazinānu **88** and **90** nukleofīlās cikla atvēršanas reakcijas.

Iegūtais 1,3-aminospirts **87** tika atzīts par daudzpusīgu izejvielu dažādām noderīgām sintētiskām pārvērtībām. Tā reakcija ar pikrīnskābi deva pikrāta sāli **93**, kura struktūra tika pierādīta ar rentgenstruktūranalīzi (27. shēma). Amīna aizsargāšana ar Boc grupu un sekojoša divu stadiju oksidēšana deva *N*-Boc-β-aminobetulīnskābi **95**, kuras diastereoselektīvā reducēšana pie C(3) deva *N*-Boc-β-aminobetulīnskābi **97**.

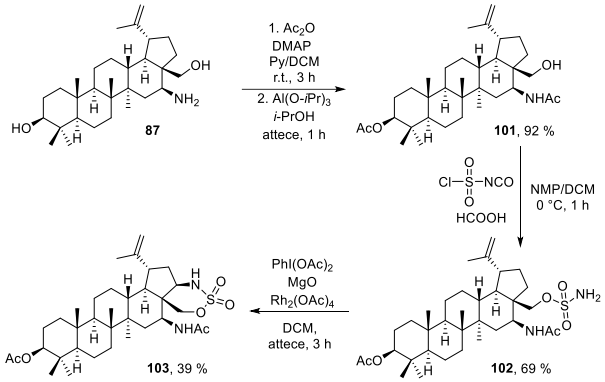
Abu aminoskābju Boc grupu noškelšanu var panākt ar TFA, iegūstot atbilstošās β-aminoskābes to trifluoracetāta sāls formā. Tomēr betulīnskābes atvasinājuma **97** gadījumā tika konstatēta C(3) hidroksilgrupas trifluoracilēšana. Tādēļ tika piemeklēti alternatīvi apstākļi, un 4M HCl/dioksānā izmantošana veiksmīgi nodrošināja β-aminoskābes **98** rašanos hidrogēnhlorīda sāls formā.

Tālāk 16-azidobetulīns **99** tika veiksmīgi iegūts no atbilstošā amīna, izmantojot trifluormetānsulfonilazīdu vara(II) piedevas klātbūtnē. Savienojuma **99** CuAAC reakcijā ar propargilspirtu tika iegūts C(16)-triazolilbetulīns **100**, kas kā modeļsavienojums parāda iespējas praktiski bezgalīgai jaunu betulīna-triazola konjugātu bibliotēkai (27. shēma).



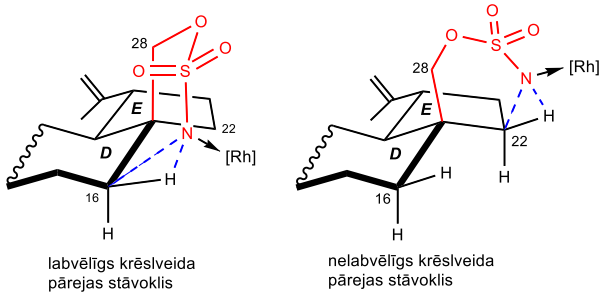

27. shēma. 1,3-Aminospirta **87** sintētiskās transformācijas.

Tālākā darba gaitā tika pārbaudīts, vai ir iespējams vēlreiz veikt C-H aminēšanas reakciju un ievadīt otru aminogrupu triterpenoīda struktūrā, izmantojot tādu pašu C(28) sulfamāta esteri. Šim nolūkam tika iegūts diacetāts **101**, izmantojot betulīna ķīmijā zināmu acilēšanas/deacilēšanas stratēģiju. Tad tas 0 °C temperatūrā tika apstrādāts ar *in situ* sagatavotu sulfamoilhlorīdu, iegūstot sulfamāta esteri **96**, kas tika pakļauts iepriekš izmantotajiem C-H aminēšanas apstākļiem. Mērķa oksatiazināns **103** pie betulīna C(22) tika iegūts ar vidēju iznākumu (28. shēma). Visdrīzāk, savienojuma **103** oksatiazināna ciklu var tālāk pārveidot līdzīgā veidā kā savienojumā **83**, kas paver vairākus potenciālus ceļus betulīna molekulārā karkasa tālākām transformācijām.




28. shēma. Sulfamāta **102** sintēze un pielietojums C-H aminēšanas reakcijā pie C(22).

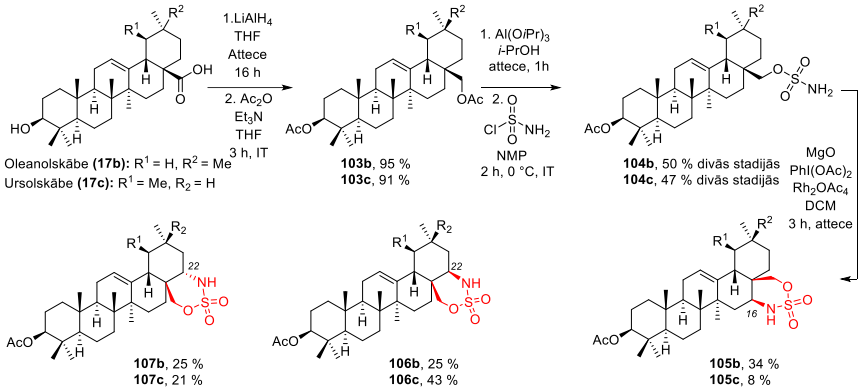
C-H aktivācijas reģio- un diastereoselektivitāti, visticamāk, nosaka substrāta kontrole. Metalonitrēna intermediāts iespiežas izejvielas **79** D-cikla ekvatoriālajā C-H saitē, nodrošinot produkta **77** veidošanos, kas satur jaunizveidoto ciklu stabilā krēsla konformācijā. Lupāna tipa PCT telpiskā uzbūve neļauj izveidot jaunu ciklu krēsla konformācijā pie E-gredzena (10. att.).




10. attēls. C-H iespiešanās iespējamie pārejas stāvokļi pie C(16) un C(22).

Visbeidzot, tika iesākti arī pētījumi par ursāna un oleanāna tipa sulfamāta esteru **104b,c** C-H aminēšanu. Izejvielas tika iegūtas no atbilstošajām komerciāli pieejamajām skābēm **17b,c** četrās stadijās. Iepriekš izmantotie C-H aminēšanas apstākļi deva pilnu izejvielas konversiju dažu stundu laikā, abos gadījumos iegūstot trīs produktu maisījumu: C(16) aminētu produktu **105b,c** un C(22) aminētu produktu diastereoizomēru maisījumu **106b,c** un **107b,c** (29. shēma). Ursāna struktūras C-H aminēšana izrādījās selektīvāka pret C(22) aminētu produktu, domājams, metilgrupu alternatīvā novietojuma dēļ E gredzenā. Tomēr ursāna gadījumā kopējais izolētais iznākums ir zemāks nekā oleanāna sērijā, kas skaidrojams ar ursāna tipa savienojumu sliktāku šķīdību organiskajos šķīdinātājos un tehniski sarežģītāku izdalīšanas procedūru. Reģioselektivitātes kritumu, salīdzinot ar betulīna molekulāro karkasu, var skaidrot ar atšķirīgo ursāna un oleanāna tipa PCT E gredzena izmēru un ortogonālo ekspozīciju, kam vairs nav *trans*-dekalīnam līdzīgā

struktūra. Lai iegūtu oksatiazināna cikla atvēršanas produktus un atvieglotu reģio- un diastereoizomēru atdalīšanu, aminēto savienojumu **105b-107b** un **105c-107c** maisījumi tika pakļauti sārmainās hidrolīzes apstākļiem, tomēr šīs reakcijas neuzrādīja izejvielu konversiju. Tālākie C-H aminēšanas un iegūto produktu sintētiskā lietojuma pētījumi ursāna un oleanāna tipa PCT rindās tiks veikti citu projektu ietvaros nākotnē.



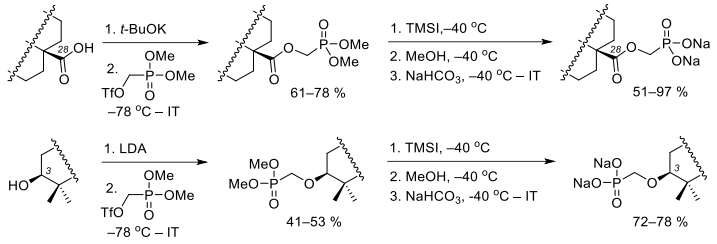

29. shēma. Oleanāna un ursāna atvasināto sulfamātu esteru **105b,c** sintēzē un izmantošanā C-H aminēšanas reakcijā.

Kopumā var teikt, ka ir izstrādāta jauna metode selektīvai C(16)-N saites veidošanai betulīna D-ciklā, izmantojot rodija katalizētu nitrēna C-H iespiešanos. Reakcijspējīgais sulfamāta esteris tika iegūts no dabīgā betulīna vairākos soļos. Neraugoties uz stēriskajiem traucējumiem un iespējamām pārgrupēšanās reakcijām C(28) pozīcijā, tika izstrādātas vairākas veiksmīgas oksatiazināna gredzena atvēršanas reakcijas: 1) reakcija ar NaOH deva aminosulfāta sāli; 2) reakcija ar $NaN_3$ veidoja 1,3-aminoazīdu, kas tika pārveidots par γ-amino C(28)-triazoliem; 3) reducējošā cikla atvēršana deva 1,3-aminospirtu, kas tālāk tika pārvērsts 16-aminobetulīnskābē un betulonskābē. Turklāt 16-aminobetulīnu var pārvērst par 16-azidobetulīnu. Tika parādīts, ka pēc C(16) funkcionalizēšanas iespējama arī otra nitrēna C-H iespiešanās C(22) pozīcijā. Izstrādātā metode nodrošina vairākus jaunus lupāna tipa triterpenoīdu atvasinājumus ar amino- vai azidogrupām, kas var būt noderīgas izejvielas turpmākai modificēšanai un bioloģiskās aktivitātes izpētei.

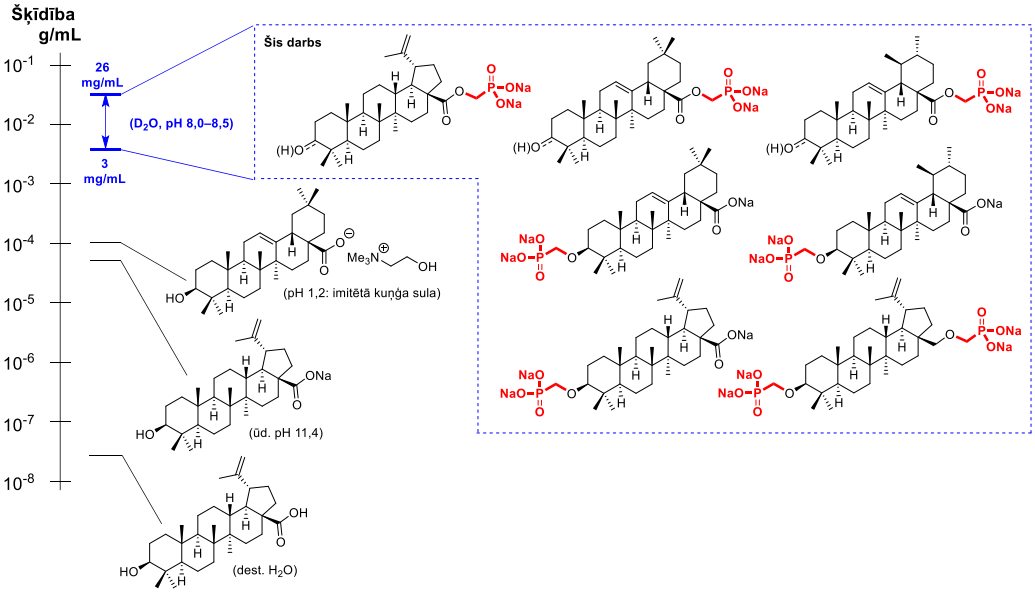
Plašāk par šajā nodaļā aprakstītajiem pētījumiem var lasīt: Kroškins, V., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M. Site-selective C-H amination of lupane type triterpenoids. *Eur. J. Org. Chem*. **2025**, 2500340. (6. pielikums).

# SECINĀJUMI

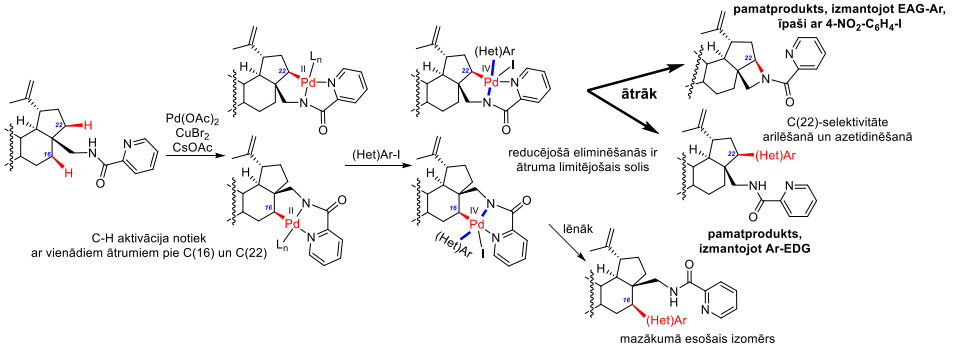
1. Neskatoties uz C(3) un C(28) neopentilnovietojumu, pie tiem esošās HO-grupas ir iespējams alkilēt, izmantojot (dimetoksifosforil)metiltrifluormetānsulfonātu. Alkilēšanu var panākt bāziskos apstākļos, izmantojot *t*-BuOK karbonskābes gadījumā un LDA spirtu gadījumā. Iegūtos metilfosfonāta starpproduktus var selektīvi demetilēt, izmantojot TMSI, vienlaikus saglabājot jaunizveidoto karbonskābes estera funkcionalitāti. Demetilēšanas selektivitāti var panākt, veicot visu procesu, ieskaitot neitralizācijas posmu, aptuveni –40 °C temperatūrā.



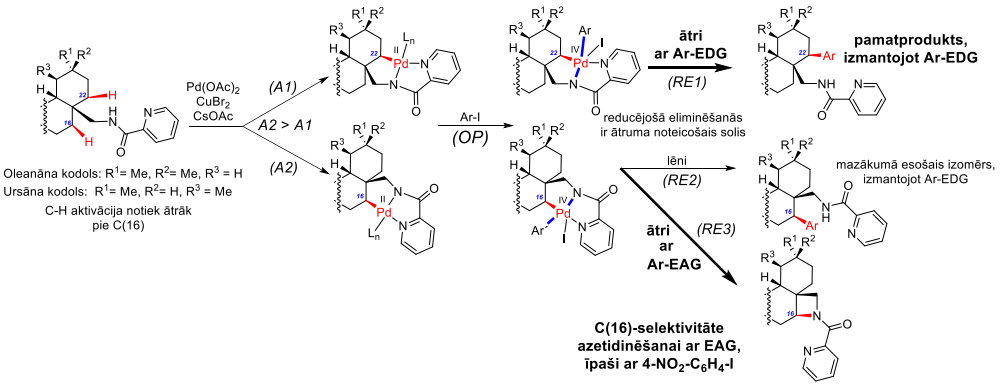

2. Iegūtie pentaciklisko triterpenoīdu-fosfonātu konjugāti C(28)(CO)-O-$CH_2$-P(O)$(ONa)_2$ un C(3/28)-O-$CH_2$-P(O)$(ONa)_2$, kam raksturīgs īsākais iespējamais metilēntiltiņš starp terpenoīda karkasu un fosfonāta daļu, uzrāda ievērojamu šķīdību ūdenī pH diapazonā no 8,0 līdz 8,5 (3–26 mg/mL). Šī šķīdība ir par vairākām kārtām augstāka nekā attiecīgajām triterpēnkarbonskābēm vai to sāļiem.



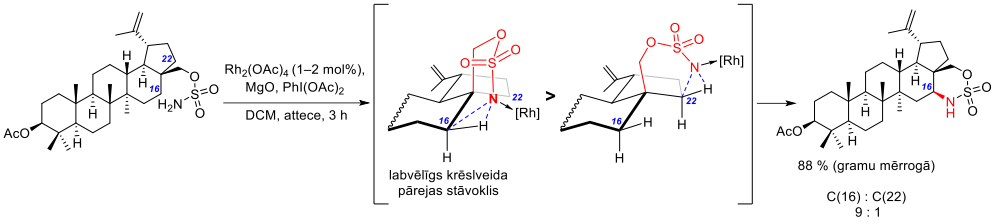
3. Betulīna rindā ātra un neselektīva C-H aktivācija notiek gan ar C(16)-H, gan ar C(22)-H, ko pierāda deiterēšanas eksperimenti, izmantojot gan pikolinamīda, gan hinolīnamīda virzošās grupas. Selektivitāti sekojošajās C-H arilēšanas un azetidinēšanas reakcijās galvenokārt nosaka reducējošās eliminēšanas stadija, kas šajā substrātu klasē abos gadījumos vieglāk notiek pie C(22). Arilgrupas ar elektronakceptoriem aizvietotājiem (piemēram, 4-nitrofenilgrupa) veicina C-N saiti dodošo reducējošo eliminēšanos, kā rezultātā veidojas C(22)-azetidīns. Savukārt arilgrupas ar elektrondonoriem aizvietotājiem veicina ātrāku reducējošo eliminēšanos no C-[Pd]-Ar starpproduktiem, kā rezultātā galvenokārt veidojas C(22)-arilēti produkti ar selektivitāti līdz 9 : 1.



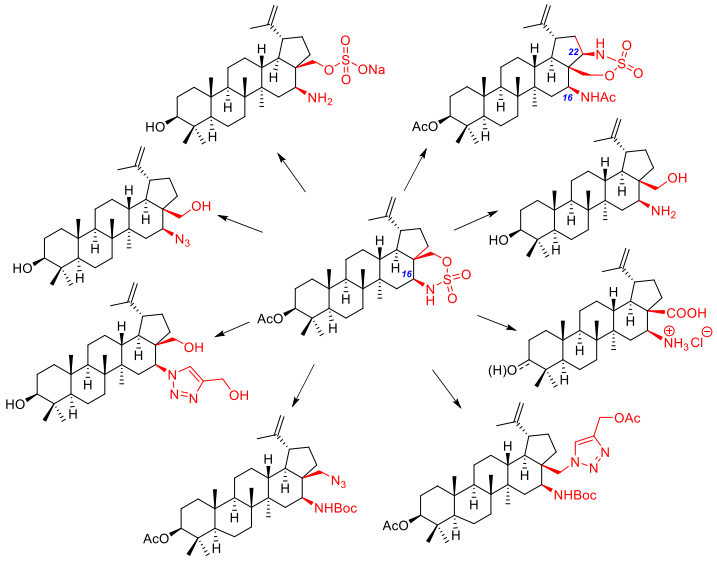

4. Ursāna un oleanāna tipa savienojumos C-H aktivācijas solis notiek ar C(16)-H selektivitāti (A2 > A1) un ir lēnāks nekā betulīna sērijā. Lietojot arilgrupas ar elektronakceptoriem aizvietotājiem (piemēram, 4-nitrofenilgrupu) C-H aktivācijas ātrums (A2 solis) kļūst salīdzināms ar reducējošās eliminēšanas ātrumu (RE3) no C(16)-[Pd]-NC(O) starpprodukta, kā rezultātā veidojas C(16)-azetidīna produkti. Toties, izmantojot arilgrupas ar elektrondonoriem aizvietotājiem, reducējošās eliminēšanās relatīvie ātrumi atbilst secībai $RE1_{EDG}$ > RE2 >> RE3, dodot priekšroku C(22)-arilētu produktu veidošanai ar C(22)/C(16) selektivitāti 19 : 1.



5. No betulīna atvasinātais 28-*O*-sulfamāta esteris ir efektīvs nitrēna prekursors rodija katalizētos apstākļos. Nitrēna iespiešanās C-H saitē notiek ar labu C(16)-H selektivitāti, dodot oksatiazināna produktu ar teicamu iznākumu multigramu mērogā.




6. Oksatiazīna ciklu var efektīvi atvērt ar azīda un hidrīda nukleofīliem, iegūstot starpproduktus, kas ir piemēroti tālākai funkcionalizēšanai. Izstrādātā metodoloģija ļauj sintezēt lupāna atvasinājumus ar dažādām modifikācijām C(16) un C(28). Svarīgi, ka pēc betulīna C(16)-funkcionalizēšanas joprojām ir iespējama arī nākamā nitrēna C-H iespiešanās, un tā notiek selektīvi C(22)-H pozīcijā.



## Pateicības

Paldies:

- Latvijas Republikas Ekonomikas ministrijai par finansiālo atbalstu (Nr. VPP-EM-BIOMEDICINA-2022/1-0001 "Valsts pētījumu projekts biomedicīnas, medicīnas tehnoloģiju un farmācijas jomā", projekts *BioMedPharm*);

- Kristapa Kļaviņa grupai par HRMS analīzēm;

- Anatolijam Mišņevam par rentgenstruktūranalīzēm;

- visai OĶTI grupai un īpaši Rihardam Lācim, Elzai Fedorovskai, Renāram Ozoliņam un Dinešam Kumaram par viņu ieguldījumu šī darba izstrādē;

- Jevgeņijai Lugiņinai un Mārim Turkam par pacietīgu un viedu vadīšanu, kā arī milzīgo atbalstu gadu gaitā!

# DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE

To be granted the scientific degree of Doctor of Science (Ph.D), the present Doctoral Thesis has been submitted for defence at the open meeting of RTU Promotion Council on 13 November 2025, at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena iela 3, Room 272.

OFFICIAL REVIEWERS

Senior Researcher Dr. chem. Mārtiņš Katkevičs,

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University of Latvia, Latvia

Professor, Dr. Zbigniew Pakulski,

Polish Academy of Sciences, Poland

DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for review to Riga Technical University for promotion to the scientific degree of Doctor of Science (Ph.D) is my own. I confirm that this Doctoral Thesis has not been submitted to any other university for promotion to a scientific degree.

Vladislavs Kroškins…….….

(*signature*)

Date …...……...….

The Doctoral Thesis has been prepared as a collection of thematically related scientific publications complemented by summaries in both Latvian and English. The Thesis unites three original research articles in SCI journals, one review, one patent and unpublished results.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl- |
| *t*-Am | *t*-amyl- |
| Ar | aryl- |
| Bn | benzyl- |
| Boc | *t*-butoxycarbonyl- |
| brsm | based on recovered starting material |
| BQ | benzoquinone |
| *t*-Bu | *t*-butyl- |
| Cbz | benzyloxycarbonyl- |
| CMD | concerted metalation deprotonation |
| cod | cyclooctadiene |
| Cp | cyclopentadienyl- |
| DCM | dichloromethane |
| DCE | dichloroethane |
| DG | directing group |
| DMAP | 4-dimethylaminopyridine |
| DMSO | dimethylsulfoxide |
| DIBAL-H | diisobutylaluminium hydride |
| DMF | *N*,*N*-dimethylformamide |
| EDTA | ethylenediaminetetraacetic acid |
| Esp | α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid |
| Eq | equivalent |
| h | hours |
| HAT | hydrogen atom transfer |
| HATU | *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate |
| HFIP | hexafluoro-2-propanol |
| LDA | lithium diisopropylamide |
| nbe | norbornene |
| NMP | *N*-methyl-2-pyrrolidone |
| NMR | nuclear magnetic resonance |
| OA | oxidative addition |
| Pc | phthalocyanine |
| PCC | pyridinium chlorochromate |
| PCT | pentacyclic triterpenoid |
| pfb | perflurobutyrate |
| PG | protecting group |
| Ph | phenyl- |
| phe | phenylalanine |
| PIDA | (diacetoxyiodo)benzene |
| Piv | pivaloyl- |
| phen | phenanthroline |
| Phs | phenylsulfamoyl- |
| PMB | 4-methoxybenzyl- |
| PPTS | pyridinium p-toluenesulfonate |
| *i*-Pr | *i*-propyl- |
| Py | pyridine |
| RE | reductive elimination |
| Tf | trifluoromethanesulfonyl- |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TM | transition metal |
| TMS | trimethylsilyl- |
| Troc | 2,2,2-trichloroethoxycarbonyl- |

# GENERAL OVERVIEW OF THE THESIS

## Introduction

Pentacyclic triterpenoids (PCTs) comprise a widespread family of natural isoprene-derived secondary metabolites, which display an extensive range of biological properties.[1,2,3,4] PCTs can be classified into three major groups: lupane **I** (betulinic acid, betulin and lupeol), oleanane **II** (oleanolic acid, erythrodiol, and β-amyrin) and ursane **III** (ursolic acid, uvaol, and α-amyrin) terpenoids (Fig. 1).[5]

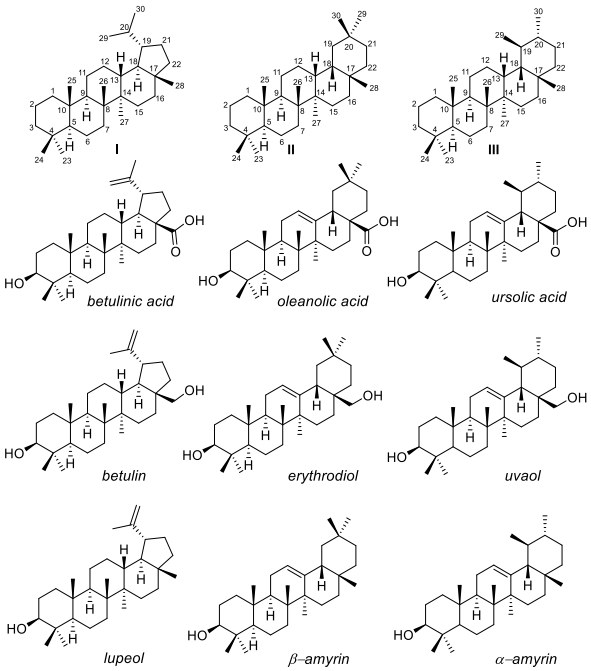



Fig. 1. Representative members of pentacyclic triterpenoids from the major lupane **I**, oleanane **II** and ursane **III** series.

Approximately a quarter of contemporary drugs are shaped by or derived from natural products. During the past four decades, either natural products or natural product derivatives, mimics of natural products, or compounds bearing a natural product pharmacophore have taken over more than half of the field of anticancer and anti-infective therapy.[6] Lowered toxicity profile in normal cells[7] and reduced side effects promote PCTs to be great multitarget drug candidates.

The ubiquity of PCTs in nature, sustainability and their facile isolation process have become the cause for many studies that have discovered potential therapeutic applications of these terpenoids. Among them, the most promising PCT applications are in the antitumor and antiviral

domains.[8,9,10,11,12] An emerging area of research on PCTs and their semi-synthetic derivatives involves the development of compounds with antibacterial[13] and antifungal activity,[14] as well as derivatives with potential therapeutic applications in the treatment of diabetes[15] and inflammatory diseases.[16]

Besides common medicinal applications, PCT can be successfully applied in cosmetology. For the cosmetic industry, betulin-containing birch bark extract was found to be a noteworthy natural raw material. A wide range of betulin-containing products can be found in well-known brands for face, body, and hair care. Furthermore, the properties of betulin and its derivatives that boost the burn and wound healing process were demonstrated by several companies.[17] In addition, a certain effect of betulin on collagen production is used in daily care creams, as well as in the anti-cellulite products.[18, 19]

The unique structural framework of PCTs, while biologically advantageous, presents notable synthetic challenges. Their rigid, polycyclic architecture and high degree of C-H bond saturation often limit the accessibility of diverse chemical transformations. Traditionally, derivatization efforts on PCTs have concentrated on reactive peripheral functional groups, particularly on the hydroxyl and carboxylic acid moieties at C(3) and C(28), and on the olefin moiety C(20) = C(29), including its allylic position at C(30).[20] While being valuable, such modifications exploit only a narrow subset of the molecular landscape, leaving the vast potential of the carbon framework underutilized.

In recent years, the development of transition-metal-catalyzed C-H functionalization has provided new opportunities for direct and selective transformation of otherwise inert C($sp^3$)-H bonds.[21] These strategies enable the synthesis of novel derivatives directly from advanced intermediates, eliminating the need for prefunctionalization and facilitating efficient late-stage diversification. Despite widespread application of these methods in other complex molecular systems, their implementation in triterpenoid chemistry has been surprisingly limited thus far.

This Thesis presents a series of studies aimed at expanding the synthetic toolbox for PCTs through innovative C-H functionalization strategies and strategic introduction of heteroatomic functionalities (Fig. 2). Specifically, two major catalytic platforms – rhodium-catalyzed C-H amination and palladium-catalyzed C-H arylation/azetidination – were developed and optimized to functionalize previously inaccessible positions within the triterpenoid core. The first approach developed in this Thesis involves palladium-catalyzed C($sp^3$)-H arylation and azetidination of triterpenoid-derived picolinamides. Here, the introduction of picolinamide as a flexible and effective directing group enabled regioselective arylation at C(22) and, in certain series, C(16). Unexpectedly, reactions with electron-deficient iodoarenes gave rise to C-N bond formation, leading to azetidine ring structures. This discovery expands the chemical diversity accessible from natural triterpenoids and introduces a new class of nitrogen-containing derivatives that may hold unique biological properties.

The second approach involves the rhodium-catalyzed intramolecular C-H amination of betulin-derived sulfamate esters, which enabled the formation of 1,2,3-oxathiazinane-fused triterpenoids

with high regioselectivity at the C(16) position. The installation of a directing group at C(28) strategically positioned the reactive intermediate in proximity to otherwise unreactive methylene sites, allowing for controlled formation of C-N bonds. These intermediates were subsequently transformed into 16-amino and 16-azido derivatives, which represent rare and synthetically valuable motifs in PCT chemistry. The possibility of sequential functionalization at C(22) further highlights the potential of this method for skeletal elaboration.

In addition to the aforementioned C-H functionalization strategies, a complementary line of research focused on enhancing the physicochemical properties of PCTs through the installation of phosphonate groups. By attaching methylene phosphonates at C(3) and/or C(28) via an alkylation strategy, a range of mono- and bis-phosphonate esters and their disodium salts were synthesized. The obtained sodium phosphonates exhibited excellent aqueous solubility – a characteristic not commonly observed in native PCTs. While solubility enhancement is specific to the phosphonate series, it demonstrates the utility of structural modifications in addressing formulation challenges.

In summary, the study presented in this Thesis introduces new and efficient methodologies for diversifying the PCT scaffold (Fig. 2). By unlocking chemically inert positions such as C(16) and C(22) for selective modification, these approaches provide access to previously unknown structural motifs. The developed synthetic toolbox will enable deeper exploration of the structure-activity relationship (SAR) of triterpenoids in the future and provide novel building blocks for the development of new triterpenoid-based pharmaceutically active compounds and/or cosmeceuticals.

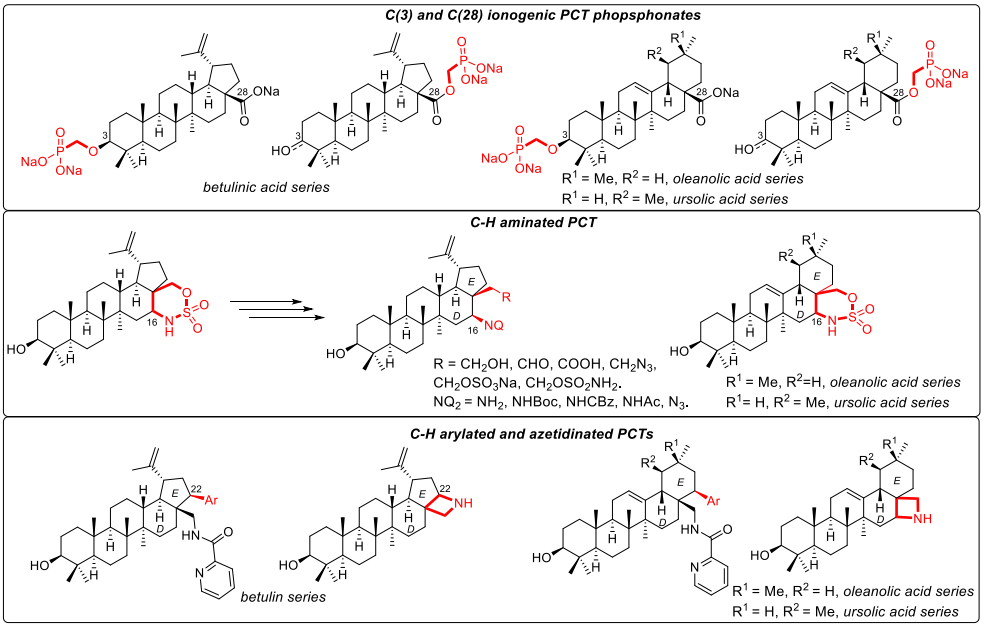



Fig. 2. Developed synthetic approaches enabling the site-selective C-H functionalization and solubility-enhancing modifications of pentacyclic triterpenoids (PCTs).

## Aims and objectives

The aim of the Thesis is the synthesis and solubility determination of ionogenic pentacyclic triterpenoid phosphonates and the development of synthetic methods towards C-H functionalized derivatives of pentacyclic triterpenoids.

To achieve the goal, the following tasks were set:

- Development of synthetic methodologies for PCT C(28) phosphonate conjugates via ester linkages and PCT C(3) phosphonate conjugates via ether linkages, along with evaluation of the aqueous solubility of the resulting compounds.
- Development of C($sp^3$)-H arylation and heteroarylation methodologies in the D/E rings of terpenoids, including C($sp^3$)-H deuteration studies and analysis of side products to elucidate the reaction mechanism and regioselectivity-determining factors.
- Synthesis of various C(16) and C(22) PCT (het)aryl derivatives, exploring the scope of applicable aryl halides.
- Development of a C($sp^3$)-H amination strategy for C-N bond formation within the D/E ring of betulin, followed by evaluation of the synthetic potential of the resulting aminobetulin derivatives through subsequent functionalization pathways.

## Scientific novelty and main results

This Thesis introduces a collection of novel synthetic transformations applied to pentacyclic triterpenoids. The most notable advances include:

- The design of previously unexplored ionogenic phosphonate derivatives of betulinic, oleanolic and ursolic acids was established. A scalable, convenient synthetic procedure suitable for PCT derivatives was developed, which afforded a series of differently linked PCT phosphonates. All obtained ionogenic PCT derivatives displayed high aqueous solubility up to 26 mg/mL and hydrolytic stability at pH 8.5. Cytotoxicity evaluation of the latter revealed that the obtained PCT-derived sodium phosphonates do not possess a significant cytotoxicity profile towards normal cells, providing promising possibilities for future medicinal chemistry research of established compounds.
- For the first time, synthetic procedures for regioselective palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids have been developed. The methodology demonstrates a successful use of picolinamide directing group for PCTs. The optimized C-H arylation reaction affords C($sp^3$)-arylation and heteroarylation products with C(22)/C(16) selectivity from 9 : 1 in the lupane (betulin) series to 19 : 1 in the oleanane and ursane series. On the other hand, changing electron-rich aromatic iodides to electron-poor aromatic iodides e28nabled C-N bond formation at PCT cores, furnishing betulin-derived C(22)-azetidine and oleanane-derived C(16)-azetidine.

- A novel catalytic method has been developed for achieving regioselective C-H amination on the betulin molecular scaffold using a rhodium catalyst. The transformation of a 28-*O*-sulfamate ester precursor enables intramolecular nitrene insertion, forming a fused 1,2,3-oxathiazinane-2,2-dione structure with high preference for functionalization at the C(16) position. Sequential functionalization was also developed, and it provides access to 16-amino-betulin, 16-azido-betulin, 16-amino betulinic and betulonic acids, among others. Moreover, introduction of a substituent at C(16) directs a second C-H amination to occur selectively at C(22) and provides a precursor of 16,22-diamino-betulin. The obtained products offer modular entry points for diversification and potential therapeutic development in the semi-synthetic triterpenoid domain.

In summary, the compound design proposed in this Doctoral Thesis, along with the developed synthetic methods for their preparation, provides preparative access to novel structural motifs previously unavailable in the chemistry of pentacyclic triterpenoids, thereby opening new opportunities for research in medicinal chemistry within this field.

## Structure and volume of the Thesis

The Doctoral Thesis has been prepared as a collection of thematically related scientific publications dedicated to the synthesis of ionogenic phosphonate and C-H functionalized PCT derivatives and studying their biological and synthetic applications. The Thesis consists of three original research articles published in SCI journals, one review, one patent and unpublished results.

## Publications and approbation of the Thesis

Results of the Thesis have been reported in three original research articles. One review has been published. One patent has been obtained. The main results have been presented at 13 conferences.

**Scientific publications**

**1.** **Kroškins, V**., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M. Site-selective C-H amination of lupane type triterpenoids. *Eur. J. Org. Chem*. **2025**, 2500340.

**2.** **Kroškins, V**., Lugiņina, J., Lācis, R, Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M. Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids. *ACS Omega*. **2025**, *10*, 27992–28019.

**3.** Lugiņina, J., **Kroškins, V**., Lācis, R., Fedorovska, E., Demir, Ö., Dubnika, A., Loca, D., Turks, M. Synthesis and preliminary cytotoxicity evaluation of water soluble pentacyclic triterpenoid phosphonates. *Sci. Rep*. **2024,** *14*, 28031.

**4.** **Kroškins, V**., Turks, M. Recent investigations in synthesis of oxathiazinanes by sulfamate estercyclization (microreview). *Chem. Heterocycl. Comp*. **2023**, *59*, 637–639.

**Obtained patents**

Lugiņina, J., **Kroškins, V**., Lācis, R., Fedorovska, E., Turks, M. Water-soluble triterpenoid phosphonates and synthesis method thereof. LV15836 B1, 20.03.2025.

**Results presented at the scientific conferences**

**1.** **Kroškins, V**., Lugiņina, J., Loča, D., Dubņika, A. Water Soluble Phosphonate Derivatives of Pentacyclic Triterpenoids. In *Balticum Organicum Syntheticum 2024*: *Abstract Book,* Latvia, Riga, 7–10 July 2024. Riga: 2024, p. 80.

**2.** **Kroškins, V**., Lugiņina, J., Turks, M. Regioselective C-H Amination of Lupane-Type Triterpenoids. In *Balticum Organicum Syntheticum 2024*: *Abstract Book,* Latvia, Riga, 7–10 July 2024. Riga: 2024, p. 81.

**3.** **Kroškins, V**., Lugiņina, J., Turks, M. Site Selective C-H Amination of Lupane Type Triterpenoids. In *24th Tetrahedron Symposium: Abstract Book*, France, Montpellier, 18–21 June 2024. Montpellier, p. 242.

**4.** Kumpiņš, V., **Kroškins, V**., Lugiņina, J., Turks, M. Site Selective C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *24th Tetrahedron Symposium: Abstract Book*, France, Montpellier, 18–21 June 2024. Montpellier, p. 243.

**5.** **Kroškins, V**., Lācis, R., Lugiņina, J., Turks, M. Palladium-Catalyzed C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *International Symposium on Synthesis and Catalysis 2023: Abstract Book*, Portugal, Evora, 5–9 September 2023. Evora: 2023, p. 204.

**6.** **Kroškins, V**., Lācis, R., Lugiņina, J., Loča, D., Turks, M. Synthesis of Phosphonate Derivatives of Pentacyclic Triterpenoids. In *International Symposium on Synthesis and Catalysis 2023: Abstract Book*, Portugal, Evora, 5–9 September 2023. Evora: 2023, p. 227.

**7.** **Kroškins, V**. C($sp^3$)-H Arylation of Pentacyclic Triterpenoids. In *13th Paul Walden Symposium on Organic Chemistry: Program and Abstract Book*, Latvia, Riga, 14–15 September 2023. Riga: 2023, p. 46.

**8.** **Kroškins, V**., Lugiņina, J., Turks, M. C-H Arylation of Pentacyclic Triterpenoids. In *81st International Scientific Conference of the University of Latvia 2023. Chemistry Section and Section of Institute of Chemical Physics: Book of Abstracts*, Latvia, Riga, March 17, 2023. Riga: University of Latvia Press, 2023, p. 11.

**9.** Lugiņina, J., **Kroškins, V**., Lācis, R., Loča, D., Turks, M. Pentaciklisko triterpenoīdu fosfonātu atvasinājumu sintēze. In *Konference "Inovāciju fonds – nozaru pētījumu programma: viedie materiāli, fotonika un biomedicīna"*, Latvia, Riga, November 18, 2023. Riga: 2023, pp. 1–2.

**10.** **Kroškins, V**., Lugiņina, J., Turks, M. Rh Catalyzed C-H Amination of Pentacyclic Triterpenoids. In: *Materials Science and Applied Chemistry 2022: Programme and Abstracts*, Latvia, Riga, October 21, 2022. Riga: 2022, p. 5.

**11.** **Kroškins, V**., Lugiņina, J., Jankovičs, K. C-H Activation of Lupane Type Triterpenoids. In: *80th International Scientific Conference of the University of Latvia 2022. Chemistry Section: Book of Abstracts*, Latvia, Riga, February 11, 2023. Riga: University of Latvia Press, 2022, p. 75.

**12.** Lugiņina, J., **Kroškins, V**., Mishnev, A., Turks, M. Palladium-Catalyzed C-H Activation of Triterpenoids. In: *Balticum Organicum Syntheticum 2022: Program and Abstract Book*, Lithuania, Vilnius, July 3–6, 2022. Vilnius: 2022, p. 115.

**13.** **Kroškins, V**., Lugiņina, J., Turks, M. C-H Amination of Pentacyclic Triterpenoids. In: *Balticum Organicum Syntheticum 2022: Program and Abstract Book*, Lithuania, Vilnius, July 3–6, 2022. Vilnius: 2022, p. 115.

# MAIN RESULTS OF THE THESIS

## 1. Synthesis and application of ionogenic pentacyclic triterpenoid phosphonates

Numerous natural compounds exhibit significant biological activity in both *in vitro* experiments and preclinical animal models. However, their effectiveness in human clinical trials often yields inconsistent outcomes. A key factor contributing to this gap between laboratory or animal research and human applications is the limited bioavailability of many natural products. A significant reason for the latter is the increased lipophilicity of many natural molecules. The concepts of hydrophobicity and lipophilicity are widely used regarding the sorption of organic compounds from aqueous media.[22] The hydrophobic effect narrates the predisposition of non-polar compounds to prefer a non-aqueous environment to an aqueous one. Nevertheless, absolute suppression of lipophilicity can lead to the stoppage of passive transport of active pharmaceutical ingredients through the membranes of organisms and following drug-receptor binding. As a result, conventional drugs are typically developed with a focus on ensuring good bioavailability and desirable pharmacokinetic properties, which is often a delicate objective to succeed.[23]

One of the most common strategies for improvement of physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds is the development of prodrugs – chemically modified forms of the pharmacologically active molecule that must undergo transformation *in vivo* to release the active parental molecule. Notably, that prodrug technique can be applied to increase aqueous solubility and bioavailability of hydrophobic non-polar compounds by introduction of polar ionogenic functionalities, and oppositely to enhance lipophilicity and permeability of polar hydrophilic molecules, by introduction of non-polar moieties.[24] Thus, the phosphate ester of prednisolone **1** is a representative example of a prodrug with improved aqueous solubility among steroidal drugs. Another example is the phosphate ester of miproxifene **2**, which displayed significantly enhanced aqueous solubility compared to parental miproxifene (Fig. 3).

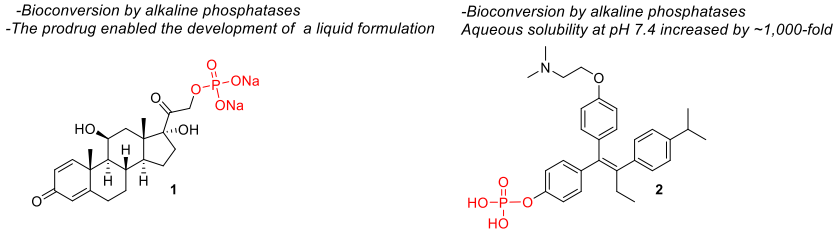



Fig. 3. Water-soluble prodrugs of prednisolone and miproxifene.

Enhanced lipophilicity of pentacyclic triterpenoid steroidal feedstock is a common limitation to the drugability of these complex natural molecules. To improve the undesirable properties of triterpenoids, prodrug strategies came into sight. Triterpenoid phosphates and sulfates, as well as

their conjugates with amino acids, polymers, or sugars, have been widely used to improve aqueous solubility and oral bioavailability (Fig. 4).[25]

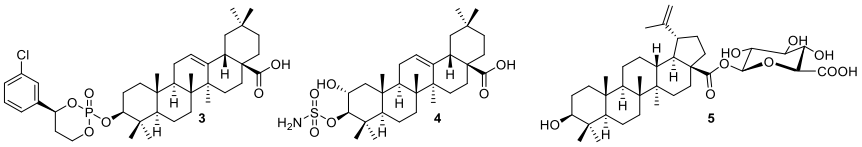


Fig. 4. Oleanolic acid phosphate precursor **3** and water-soluble PCT derivatives **4** and **5**.

Improvement of aqueous solubility can also be achieved by the installation of stable polar ionogenic functionalities, ensuring salt forms of biologically active compounds.[26] Salts of acidic and basic drugs generally have greater aqueous solubilities than their corresponding acid or base forms. Indeed, introduction of new functional groups as well as presence of new counterion in the molecules can affect the protein binding, bio-distribution and metabolism of modified molecules.

Triterpenic acids themselves can be easily transformed into corresponding salts by a simple neutralization reaction with a variety of inorganic and organic bases. For example, sodium and potassium betulinates **6** can be obtained by treatment of betulinic acid with NaOH and KOH ethanolic solution. However, solubility tests of the latter were significantly obscured due to the formation of colloids at concentrations above 0.02 mg/g. Organic counterion containing choline oleanolate **7** exhibits the best solubility (81.7 μg/mL) in a simulated gastric juice (aqueous solution of NaCl and sodium dodecyl sulfate, which was adjusted to pH 1.2 by HCl solution).[27, 28]

Many semisynthetic cationic PCT derivatives were synthesized by various functional group transformations at PCT core C(3), C(28) and double bond during the past decade. Different PCT cores were decorated with various ammonium **10**,[29] imidazolium **11**[30] and guanidinium **12**[31] moieties bearing diverse counterions through different types and sizes of linkers. Analogously, C(28), C(30), and C(2) PCT triphenylphosphonium salts[32] have been produced and biologically evaluated. Unfortunately, solubility data of these cationic PCT conjugates were not reported.

Anionic derivatives of semi-synthetic PCT analogues include mostly sulfate[33, 34] and phosphate[35, 36, 37] derivatives, that can be obtained via sulfation or phosphorylation of C(3)-OH and/or C(28)-OH groups (Fig. 5). Monophosphorylated and diphosphorylated PCTs were found to be multipurpose molecules in terms of biochemistry, by changing the spatial and electronic environment of the molecule. Nevertheless, comprehensive aqueous solubility data are not yet reported.

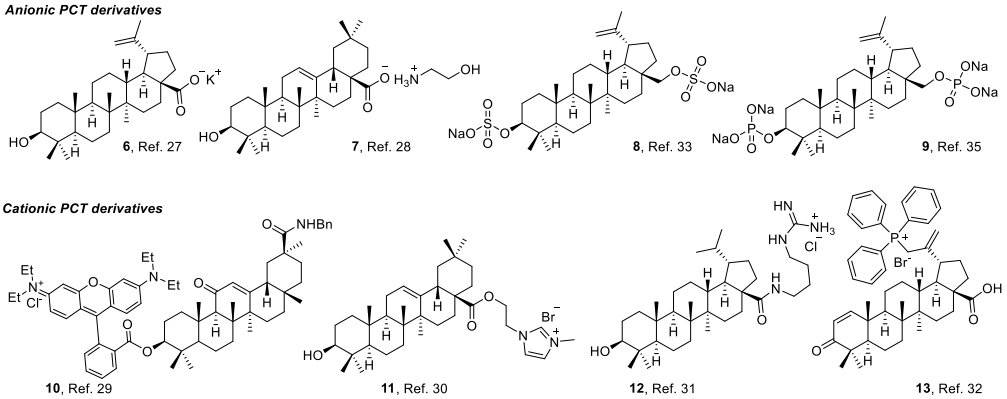



Fig. 5. Previously reported ionogenic PCT derivatives.

Replacing of phosphate group with the isosteric phosphonate group can significantly reduce the hydrolytic instability issues. This approach has demonstrated the prominence of phosphonate derivatives as a class of stable biologically active compounds delivering a series of antiviral nucleotide drugs.[38, 39] A few examples of the utility of phosphonates as phosphate mimics in a PCT series have been published. Introduction of the phosphonate moiety to the triterpenoid core can be done by amide bond **14**[40] or C-C bond **15**[41] (Fig. 6). To the best of our knowledge, there is only one example of PCT-phosphonate **16** linked by C(28) carboxylic ester reported.[42] However, the transformation of known PCT phosphonates into phosphonic acids or their salts remains unexplored prior to our research. Solubility data of such phosphonate salts are not available either.

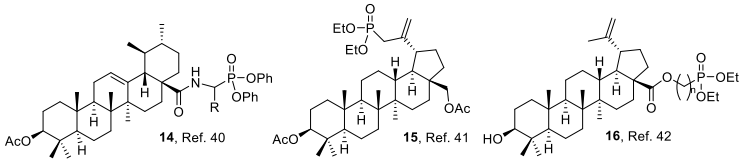


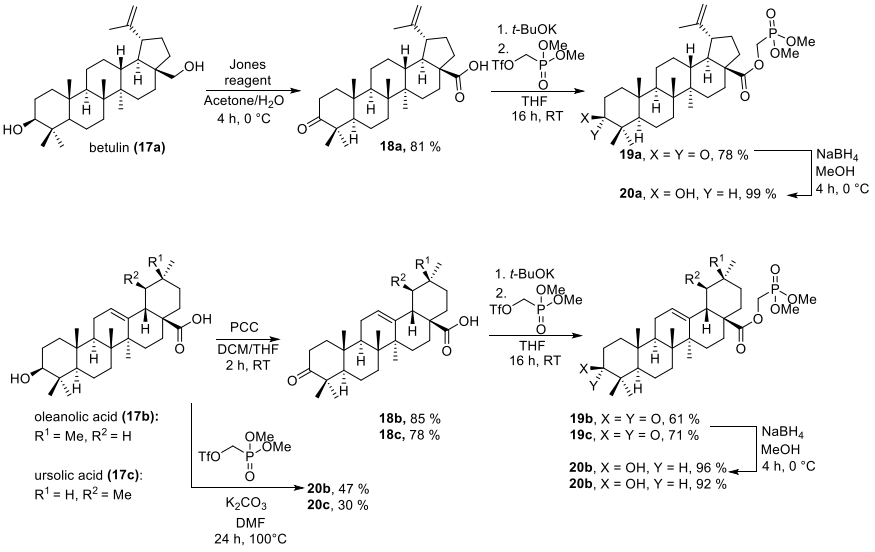

Fig. 6. Previously reported PCT phosphonate conjugates.

In this Thesis, a design and synthetic approach has been developed towards novel pentacyclic triterpenoid phosphonate derivatives of type C(17)-COO-$CH_2$-*P,* C(3)-O-$CH_2$-P and C(3/28)-O-$CH_2$-*P*, where the simplest possible methylene linker was utilized to attach the phosphonate fragment via ester or ether bond. It should be highlighted that previously reported triterpenoid C(28) esters display sufficient stability in acidic and basic media.[43] Herein, we reveal in the Thesis that such triterpenoid-based phosphonate esters are easily achievable, can be smoothly converted to the resultant salt form, and the latter exhibit significantly enhanced aqueous solubility.

Initially, we attempted to install the target phosphonate moiety by a simple esterification reaction of 3-oxo PCT carboxylic acids with dimethyl (hydroxymethyl)phosphonate, but no efficient conditions were found. The problem was solved by the transfer of the reaction site one

atom further from the C(17) quaternary center, overcoming the steric hindrance of the triterpenic core. For that purpose, we decided to switch reactivity and explore a possible carboxylate alkylation reaction.

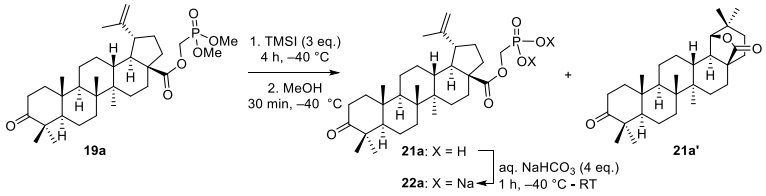
*t*-BuOK was suitable for the rapid deprotonation of 3-oxo triterpenic acids **18a-c**, and following alkylation with (dimethoxyphosphoryl)methyl trifluoromethanesulfonate in anhydrous THF afforded desired esters **19a-c** in good yields (Scheme 1). The used triflate is readily available from the previously mentioned alcohol.[44] A similar approach using (dimethoxyphosphoryl)methyl trifluoromethanesulfonate in a combination with 3-hydroxy triterpenic acids **17b**, **c** provided direct access to compounds **20b**,**c** (process **17b**, **c** → **20b**, **c** (Scheme 1), thus far with a lower yield due to formation of side products. To improve chemoselectivity between target C(17)-COOH and unwanted C(3)-OH alkylation in the transformation **17b**, **c** → **20b**,**c** , $K_2CO_3$ was used as a weaker base. The latter protocol also resulted in undesirable transesterification between C(17)-COOH and phosphonic acid methyl ester moiety of the alkylation reagent, producing C(17)-COOMe side product accompanied by $TfOCH_2P(O)(OH)(OMe)$. The diastereoselective C(3) reduction of PCT phosphonate conjugates **19a-c** was found to be more optimal, providing clean transformations and access to C(3)-OH phosphonate derivatives **20a-20c**.




Scheme 1. Synthesis of target PCT phosphonates **19a-c** and **20a-c**.

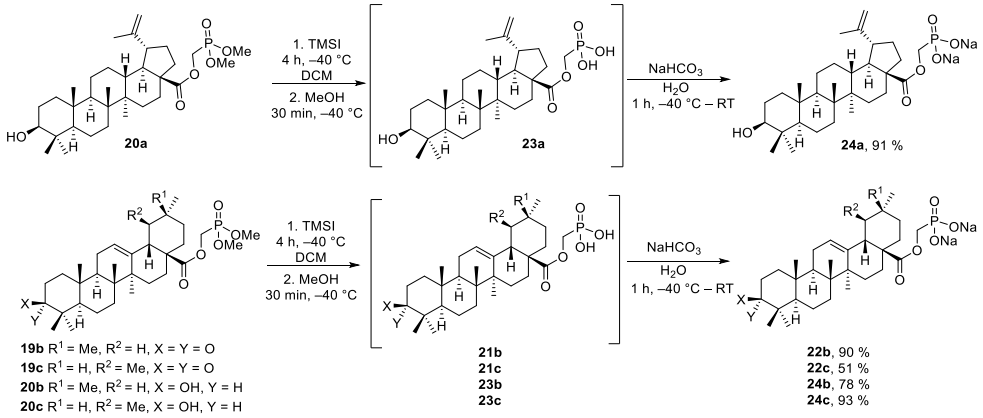
Next, we investigated the transformation of the obtained phosphonates into sodium phosphonates **22a-c** and **24a-c** utilizing TMSI assisted demethylation followed by the transformation of formed phosphonic acids **21a-c** and **23a-c** into the corresponding sodium salts. Starting with the betulonic acid derived phosphonate **19a**, we found that required temperature for

the demethylation must be –40 °C (Scheme 2). At increased temperatures cleavage of the previously installed ester bond was observed and betulinic acid olefin moiety underwent cationic rearrangements.[45] We discovered that the methanolysis of the intermediate *O*-TMS-phosphonates and subsequent neutralization of HI including formation of phosphonic acid disodium salt by addition of aqueous sodium bicarbonate solution must be performed also at a decreased temperature.




Scheme 2. Demethylation of compound **19a**.

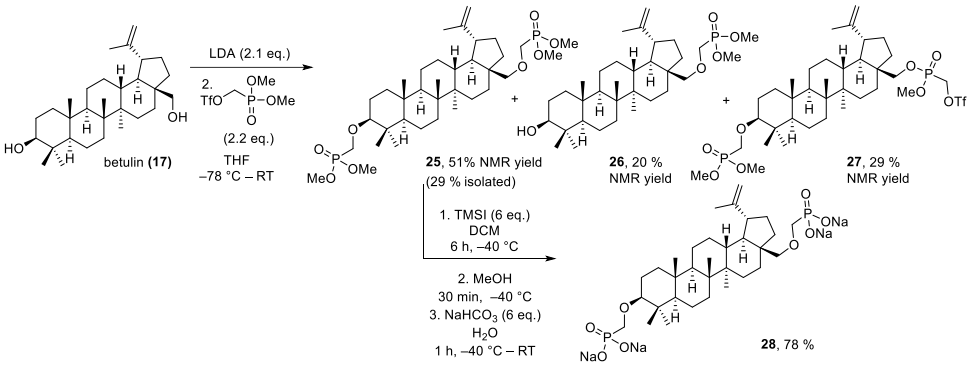
The developed demethylation conditions were successfully applied on all other compound series consisting of betulinic acid derivative **20a** with free C(3)-OH group, 3-oxo-series of oleanolic and ursolic acid-derived phosphonates **20b**,**c** and their corresponding C(3)-OH derivatives **21b**,**c**, providing target products **22a-c** and **24a-c** in good to excellent yields (Schemes 2 and 3).




Scheme 3. Synthesis of triterpenic acid-derived sodium phosphonates **22b,c** and **24a-c**.

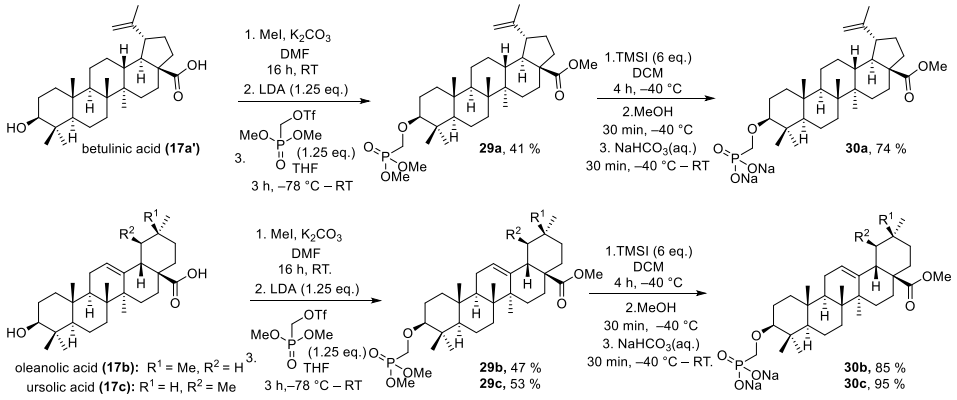
The obtained products **22a-c** and **24a-c** exhibited high hydrolytic stability, and an eventual cleavage of the carboxylate ester bond was not observed even after heating under two different basic conditions: (1) 60 °C in 1.5 M NaOH/MeOH solution for 6 h; (2) 100 °C in the presence of 4 equiv. NaOH in $H_2O$ for 24 h. The obtained ionic PCT derivatives displayed excellent aqueous solubility, which can be demonstrated by the acquisition of their $^1$H NMR spectra in $D_2O$.

Afterwards, we investigated the introduction of the phosphonate moiety to PCT via an ether bond. Starting with betulin, the most abundant natural PCT-3,28-diol, we examined a one-pot double alkylation possibility involving both hydroxyl groups. The utility of such strong bases as NaH, *t*-BuOK, *n*-BuLi and MeMgBr in combination with previously used (dimethoxyphosphoryl)methyl triflate or tosylate was found to be ineffective. We have finally found that combining triflate alkylation reagent (2.2 equiv.) and betulin Li-dialkoxide generated from LDA (lithium diisopropylamide) (2.1 equiv.) afforded the target product **25** in 29 % isolated yield (Scheme 4). The desired product **25** was accompanied by the C(28)-*O*-monoalkylation product **26** and C(28)-*O*-phosphonylation product **27** in the **25** : **26** : **27** ratio 51 : 20 : 29 (by NMR). Formation of the latter is a result of the alkoxide attack on the phosphorous center due to the presence of two competing electrophilic reaction centers in (dimethoxyphosphoryl)methyl trifluoromethanesulfonate. The obtained tetramethyl bis-phosphonate **25** was successfully converted to tetrasodium salt **28** (78 %) using the previously developed TMSI conditions.



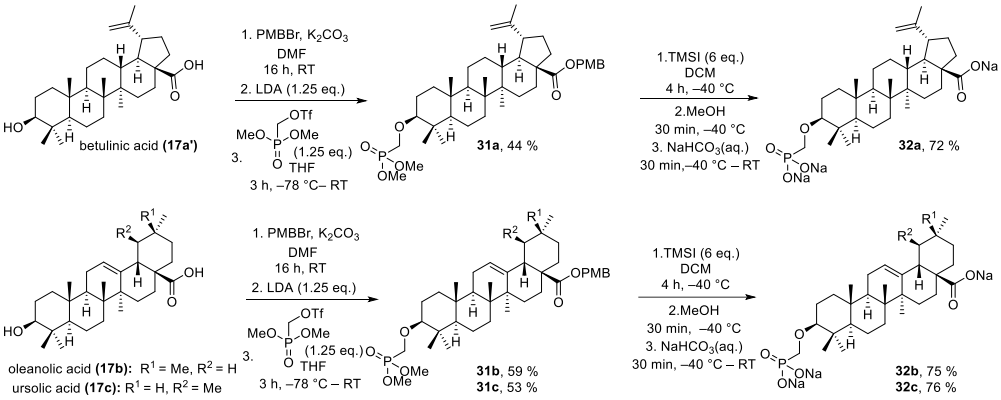

Scheme 4. Synthesis of bis-phosphonate **28**.

Next, we synthesized also mono-phosphonate PCT derivatives at C(3). For that purpose, betulinic acid, oleanolic acid and ursolic acid were protected as methyl esters. Application of previously developed LDA/triflate combination afforded a series of C(3) ethers in a moderate yield (Scheme 5). Besides target products, also starting materials and degradation of alkylating reagent were observed after reaction workup.




Scheme 5. Synthesis and demethylation of methyl-protected PCT derivatives **29a-c**.

We expected that previously developed TMSI conditions would demethylate both phosphonate and C(28) carboxylic acid methyl ester, providing desired trisodium salts. However, C(28) methyl ester displayed enhanced stability, affording products **30a-c**. Implementation of alternative conditions for ester cleavage, such as 6M KOH/EtOH at reflux, LiI/DMF/DMSO reflux was found to be ineffective. Therefore, we decided to change methyl ester to a more labile 4-methoxybenzyl ester. As expected, treatment of C(3) ethers **31a-c** containing C(28) PMB-protection with TMSI and subsequent methanolysis and neutralization furnished target PCT ionogenic derivatives **32a-c** in good yields (Scheme 6).




Scheme 6. Synthesis and demethylation of PMB-protected PCT derivatives **14a-c**.

All obtained ionogenic PCT sodium phosphonates were subjected to solubility tests in water (Fig. 7). A quantitative $^1$H-NMR approach in $D_2O$, using potassium hydrogen phthalate as an external standard, was used for the precise calculation of solubility. The basic forms of

phosphonates[46] were ensured by the careful addition of NaOD, maintaining pH 8.0-8.5 during the quantification, which is 2–3 units higher than the pKa of phosphonic acid disalt.[47] Predictably, our newly designed PCT phosphonates **22a-c**, **24a-c, 32a-c,** and **28** possessed excellent aqueous solubility in a range from 3 mg/mL to 26 mg/mL (pH 8.0–8.5) (Fig. 6). This is at least two orders of magnitude higher than the reported solubility data of the parent natural triterpenic acids. For example, aqueous solubility of oleanolic and betulinic acids is < 0.1 μg/mL at neutral pH and can be increased to 42.1 μg/mL for betulinic acid and 99.5 μg/mL for oleanolic acid at pH 11.8.[22] Also, natural ursolic acid displays similarly low aqueous solubility,[20] which may be expanded to a certain point by various modern drug delivery systems.[18,19] Phosphonic acids are more acidic and easier to ionise than carboxylic acids. This ionic character helps to increase the aqueous solubility as demonstrated by here reported compounds.

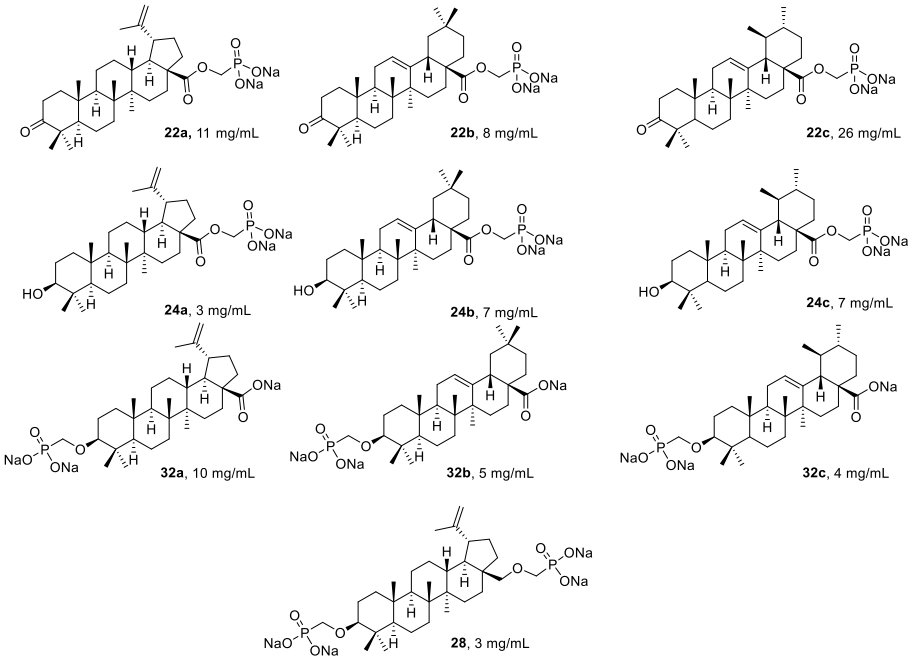



Fig. 7. Aqueous solubility ($D_2O$) of PCT phosphonates at pH 8.0–8.5.

In collaboration with Dr A. Dubņika and Prof. D. Loča (RTU Institute of Biomaterials and Bioengineering) cytotoxic activity of the obtained compounds was determined at various concentrations (10–50 μM) against human-derived osteosarcoma cell line MG-63 (ATCC, CRL-1427) and mouse-derived preosteoblast cell line MC3T3-E1 (ATCC, CRL-2593). For the comparison, naturally occurring betulinic (**17a'**), oleanolic (**17b**) and ursolic (**17c**) acids, as well as their 3-oxo analogs **18a-c** and doxorubicin, were also subjected to cytotoxicity tests. The

designed water-soluble PCT-derived phosphonates and the natural triterpenic acids, including their 3-oxo-analogs, were found to be harmless to the MC3T3-E1 cells.

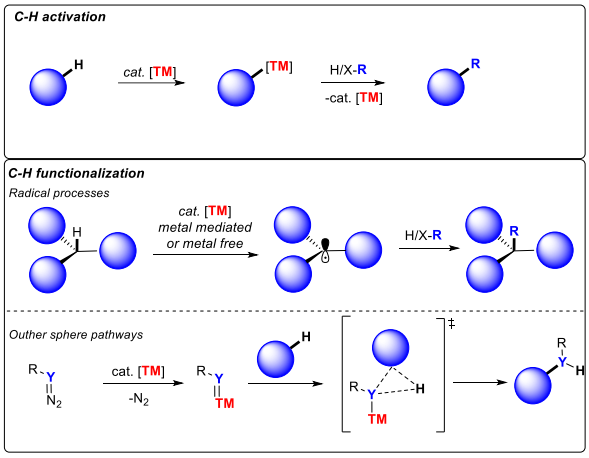
As an interesting exception should be mentioned the concentration-dependent cell viability drop of MC3T3-E1 cells in the presence of oleanonic acid ($0.49 \pm 0.12$ relative metabolic activity at 50 μM of **18b**). To a lesser extent, ursonic acid affected the metabolic activity of MC3T3-E1 cells ($0.72 \pm 0.09$ relative metabolic activity at 50 μM of **2c**). Nonetheless, the MG-63 cell line revealed somewhat lower metabolic activity in the presence of oleanonic acid-derived phosphonate **24b** ($0.73 \pm 0.05$ relative metabolic activity at 50 μM of **24b**) than in the presence of its parental oleanonic acid ($1.03 \pm 0.18$ for **18b**). It is interesting to note that ursolic acid **17c** and ursonic acid **18c** showed a cytotoxic effect towards the MG-63 cell line in the cell viability tests ($0.28 \pm 0.04$ and $0.67 \pm 0.04$ relative metabolic activity at 50 μM of **17c** and **18c**, respectively).

In summary, it is possible to synthesize pentacyclic triterpenoid phosphonates linked to the terpene core via ether or ester-type functional groups and the shortest possible methylene bridge. The TMSI-induced demethylation of the phosphonates was optimized to avoid acid-induced rearrangement side reactions. Both disodium phosphonates with ester linkage derived from betulinic, oleanolic, and ursolic acids, including their 3-oxo forms, and trisodium salts of ether-linked phosphonic and terpenic carboxylic acids were obtained. The salts exhibited high aqueous solubility (3–26 mg/mL at pH 8.0–8.5), quantified by qNMR. Their high solubility even allows structural characterization in $D_2O$ by NMR. Preliminary cytotoxicity tests indicate low toxicity to normal cells, which opens opportunities for further research into their use in antiviral, antimicrobial, antidiabetic, and anti-inflammatory therapies.

More information about these studies can be found in the publication by Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Demir, Ö., Dubnika, A., Loca, D., Turks. M., Synthesis and Preliminary Cytotoxicity Evaluation of Water-Soluble Pentacyclic Triterpenoid Phosphonates. *Sci. Rep*. **2024**, *14*, 28031 (Appendix 1); in the patent – Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Turks, M., Water-Soluble Triterpenoid Phosphonates and Synthesis Method Thereof, LV15836 B1, 20.03.2025 (Appendix 2); as well as in Appendix 3 on the synthesis of PCT 3-*O*-methylphosphonates.

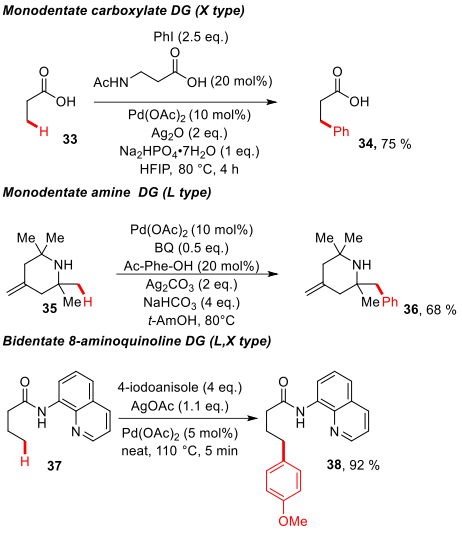
## 2. C-H activation of pentacyclic triterpenoids

Transformative metal catalysis has driven significant advancements in molecular synthesis, making it possible to construct increasingly complex compounds.[21] Transition metal-catalyzed C-H activation, which involves inner-sphere C-H bond cleavage to generate a carbon-metal bond, proposes a sustainable and cost-effective approach to organic synthesis. The terms C-H activation and C-H functionalization are often used equivalently, but some difference is hidden in the mechanism.[48] C-H activation specifically involves an organometallic process where a C-H bond is cleaved to form a direct bond between carbon and a metal (Scheme 7). In contrast, C-H functionalization is a broader term that does not require the formation of a C-M bond and includes both inner-sphere and outer-sphere mechanisms. Outer-sphere C-H functionalization typically occurs through radical pathways, hydrogen atom transfer (HAT), or insertions involving metal carbenoids, oxo, or nitrenoid species, among other processes.



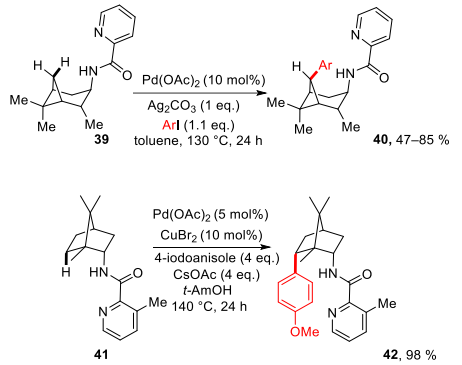

Scheme 7. Schematic representation of C-H activation and C-H functionalization.

Achieving complete control over chemoselectivity and site-selectivity remains a significant challenge for synthetically suitable C-H activations. Site-selectivity can be handled by the electronic or steric characteristics of the substrate, as well as through chelation assistance. To facilitate the latter, a variety of monodentate and bidentate directing groups – either naturally present in the substrate (Scheme 8: Compounds **33** and **35**) or intentionally introduced (Scheme 8: Compound **37**) – have been developed to enable proximity-driven, transition metal-catalyzed C-H activation.[49,50,51,52]




Scheme 8. C($sp^3$)-H activation employing different types of directing groups.

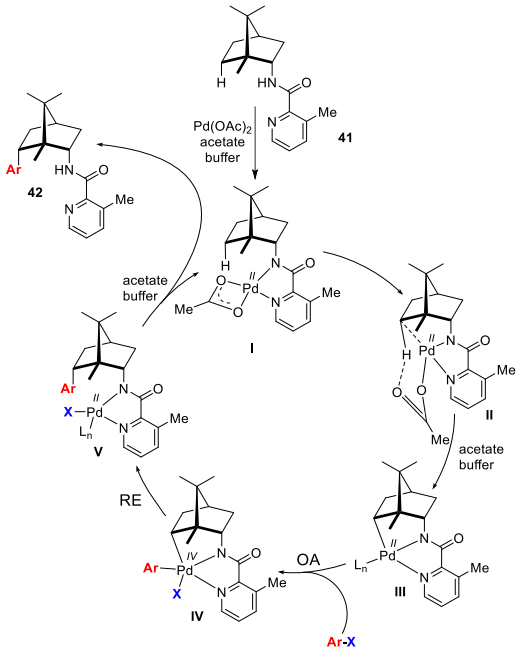
Notable applications of C-H arylation and diversification of natural products have been reported during the past few decades. For example, picolinamide directing group bearing pinamine **39** can be selectively decorated with differently substituted aromatic rings (Scheme 9).[53] Sheppard and coworkers reported a synthetic protocol for installation of a 4-anisole moiety into the bornylamine scaffold **41** utilizing different pyridyl directing groups, among which the 2-methylpyridyl moiety provided the best regioselectivity.[54]




Scheme 9. C-H arylation of terpene natural products.

The mechanism of palladium-catalyzed C-H arylation starts with palladium coordination to the directing auxiliary and ligand exchange to give complex **I** (Scheme 10). Afterwards C-H activation

step proceeds via concerted metalation deprotonation (CMD) pathway.[55] The latter involves a coordination of the C-H bond with the palladium to form a palladium-carbon σ-complex **II**. The calculated transition state shows that the carbon-metal bond begins to form at the same time as the proton is transferred to the carboxylate group, leading to the formation of a metal complex **III.** Compared to other possible processes, such as oxidative addition of the C-H bond to the metal, CMD is significantly lower in energy.[56] Aryl iodide oxidative addition to complex **III** affords palladium(IV) species **IV,** and subsequent C-C reductive elimination and ligand exchange produce the palladium complex **V**, which releases the target arylation product.

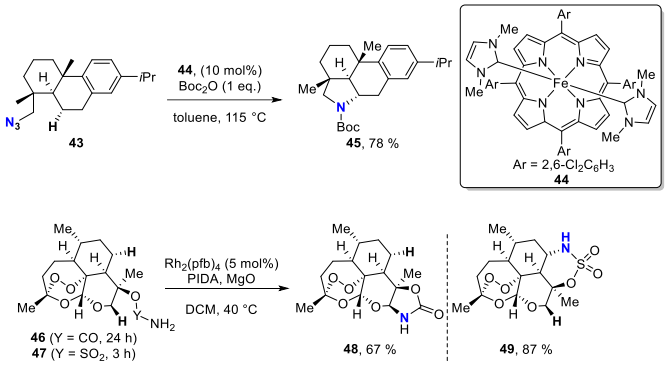



Scheme 10. Palladium-catalyzed C-H arylation mechanism.

Metal additives such as copper(II) and silver(I) salts often play crucial roles in Pd-catalyzed C-H activation reactions, helping to improve reactivity, selectivity, or even enabling certain transformations that would otherwise not proceed efficiently. Copper additive can regenerate Pd(II) species, which can suffer reduction to Pd(0) and stop the Pd(II)/Pd(IV) catalytic cycle. In some cases, copper(II) salts assist directly in C-H bond cleavage by acting as a Lewis acid that activates the substrate or a Brønsted base (especially with acetate ligands) that assists deprotonation (especially in CMD: concerted metalation-deprotonation pathway).[57] The role of Ag(I)-salts has been described for various Pd-catalyzed C-H activation processes. Generally, silver additives can be used as a terminal oxidant or as a halide scavenger; however, many studies on heterometallic Pd-Ag catalysis suggest that palladium and silver can work together during the entire catalytic cycle. In some cases, silver carboxylates can directly activate (cleave) C-H bonds in arenes,

forming aryl-silver(I) species. These aryl-Ag intermediates can then transfer the aryl group to a palladium complex, helping to form the desired product.[58]

The transformation of unactivated C-H bonds into C-N bonds via C-H insertion was applied for the synthesis of different amino derivatives of terpene natural products (Scheme 11). It has been proposed that a metal-nitrenoid species serves as a crucial intermediate in the C-H bond cleavage process, generated through the transfer of a nitrene group from an aminating agent to the metal center. Directed nitrene insertions have been achieved in intramolecular aminations using different amino or azido tethered groups like sulfonamides, sulfamides, sulfamates, carbamates or azides, sulfonylazides and carbonylazides. For example, azido derivative of leelamine **43** was used as a nitrene precursor in the presence of an iron catalyst **44** at elevated temperature to give the pyrrolidine derivative **45** (Scheme 11). Artemisinin-derived carbamate **46** and sulfamate **47** in the presence of a rhodium catalyst and PIDA were cyclized to oxazolidinone **48** and oxathiazinane **49,** respectively, displaying opposite to each other regioselectivity of nitrene C-H insertion.

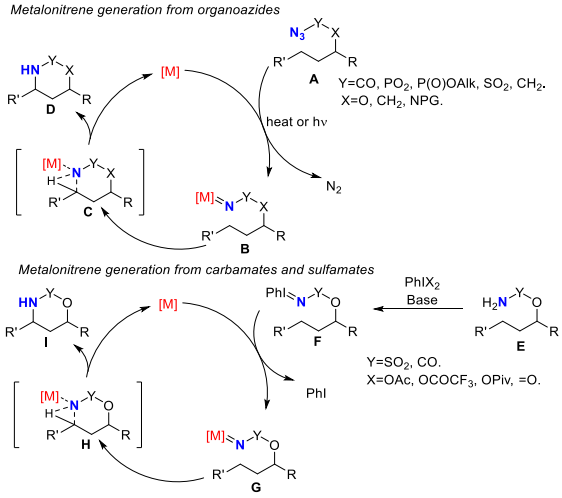



Scheme 11. Intramolecular C-H amination of azido derivative of leelamine **43**[59] and artemisinin-derived carbamate **46** and sulfamate **47**.[60]

Metalonitrene species **B** can be generated by UV-light irradiation or thermal decomposition of organozides **A** in the presence of a suitable transition metal (Scheme 12). Carbamates and sulfamates serve as effective nitrene precursors in the presence of hypervalent iodine reagents, forming iminoiodinane intermediates **F**, that further interact with the transition metal catalyst to give desired metalonitrene **G**. Intramolecular nitrene insertion reactions proved to be a powerful tool in the synthesis of various *N*-heterocycles, providing high chemo- and site selectivities. Nevertheless, sulfamate and carbamate cyclization can also proceed via a metal-free radical pathway by a variation of the Hofmann-Löffler-Freytag reaction as well as via π-selective Lewis acid-catalyzed amine addition to unsaturated systems.[61,62]

Recent advances in the synthesis of oxathiazinane rings from sulfamate esters, including the utility of nitrene-type intermediates, which will also be discussed in Section 2.2 of the Thesis, can be read in a review article by Kroškins, V., Turks, M., Recent Investigations in Synthesis of

Oxathiazinanes by Sulfamate Ester Cyclization (microreview), *Chem. Heterocycl. Comp.*, **2023,** *59*, 637–639, (Appendix 4).



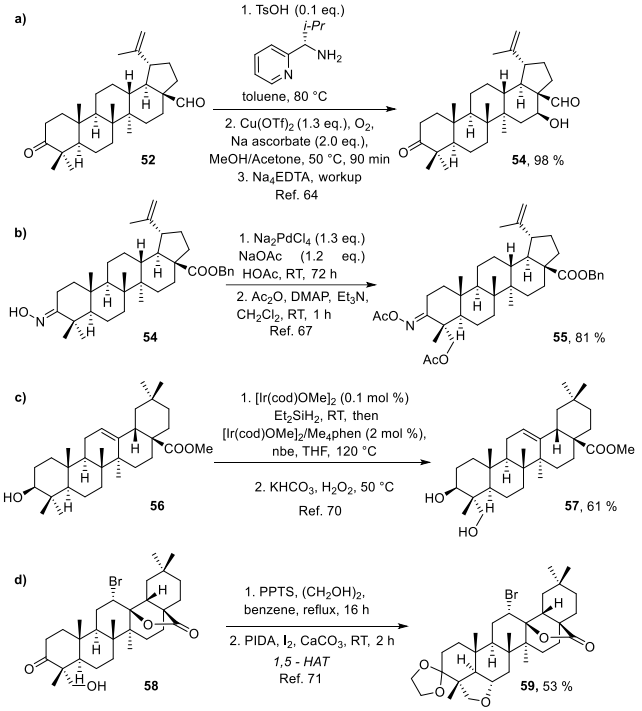

Scheme 12. Mechanisms of metalonitrene generation and following insertion in the C-H bond.

The intermolecular C-H insertion approach does not require directing group introduction steps; however, it usually results in lower selectivity. For example, phenylsulfamate ($PhsNH_2$) in the presence of rhodium catalyst and $PhI(OPiv)_2$ was used as an intermolecular C-H amination reagent, providing C-N bond formation of complex natural product **50** in 38 % yield (Scheme 13).[63]


Scheme 13. Intermolecular C-H amination of natural product **50**.

A vast majority of known synthetic transformations for the decoration of PCT core involve the utility of biogenetic C(3) and C(28) C-O functionalities and the available olefin moiety.[24] Despite that, the terpenoid structure of PCTs is packed with multiple C($sp^3$)-H bonds, which theoretically can be functionalized by exploiting a transition metal-catalyzed C-H activation approach. However, reactivity and regioselectivity issues make functionalization of the triterpene core challenging for synthetic chemists. A prerequisite for regioselective derivatization of such complex compounds via activation of C-H bonds is the presence of functional handles for the attachment of suitable residues to their carbon skeleton. Literature analysis on C($sp^3$)-H activation in the PCT core has shown only a few examples (Scheme 14).

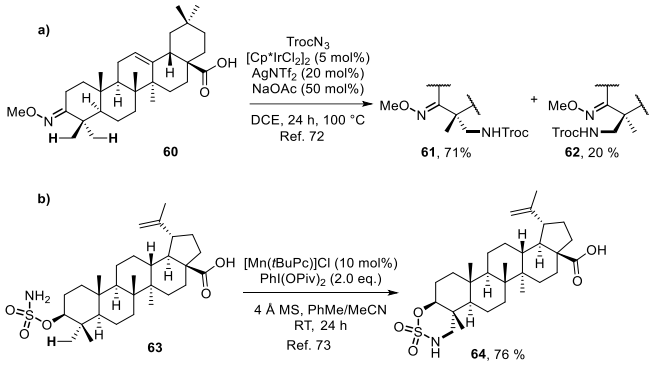
Thus, the Yu group[64, 65] has reported site-selective C-H hydroxylation of various pentacyclic triterpenoids utilizing Schönecker and Baran's copper-mediated aerobic conditions ($Cu(OTf)_2$, $O_2$) (Scheme 14, a). In this case, the site-selectivity has been controlled by the transient chiral pyridine-imino directing group, which was introduced using easily available C(28) aldehyde. Several research groups demonstrated the employment of Baldwin's[66] developed approach for the selective introduction of a hydroxyl group on a non-activated C(23) methyl group (Scheme 14, b).[67, 68, 69] Site-selective oxygenation of oleanolic C(23) using iridium catalyzed C(3) hydroxyl group-directed silylation/Tamao-Fleming oxidation sequence was investigated by Hartwig (Scheme 14, c).[70] Notably, the Maulide group[71] recently reported a protocol for regioselective functionalization of the B ring in oleanane core using hydroxylated C(23) group as the key functionality for further linear reaction sequence (Scheme 14, d).




Scheme 14. Previously reported C-H oxidation examples on the PCT core.

On the other hand, the Lu group developed Ir-catalyzed C($sp^3$)-H amination reaction using $TrocN_3$ as amine precursor at C(23) of oleanolic acid-derived methyloxime **60** (Scheme 15, a).[72] The betulin scaffold was also investigated in intramolecular metallonitrene-based C($sp^3$)-H amination of sulfamate ester **63**. White's group discovered that [Mn(*t*BuPc)]$SbF_6$ catalyst

preferentially forms C-N bond at the γ-C-H bond of the equatorial C(23) methyl group and provided oxathiazinane **64** with high site- and diastereoselectivity (Scheme 15, b).[73]




Scheme 15. Previously reported C-H amination examples on the PCT core.

To the best of our knowledge, besides the abovementioned few examples of C-H hydroxylation and the only two C-H amination examples, there are no reports on C-C bond-forming C-H activation approaches within the pentacyclic triterpenoid scaffolds; however, some successful examples of C($sp^3$)-H arylation of smaller natural terpene molecules were reported.[74] Moreover, during the past few decades, a plethora of C($sp^3$)-H arylation methods using different directing groups and catalytic systems, and suitable for the late-stage functionalization of complex molecules, were developed.[75,76,77,78] Hence, this Thesis describes previously unexplored site-selective palladium-catalyzed C($sp^3$)-H (het)arylation of pentacyclic triterpenoids.

## 2.1. C-H arylation and azetidination of pentacyclic triterpenoids

The studies were started by preparing PCT derivatives bearing 8-aminoquinolinamide and picolinamide directing groups developed by Daugulis,[79] which are connected to the triterpenic skeleton either by an innate carboxylic amide **65a-d** or by a more flexible -$CH_2$-NH- linker **66a-d** (Fig. 8).

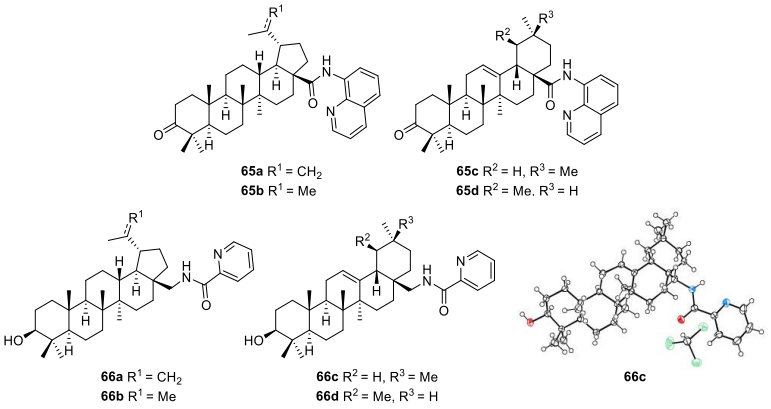
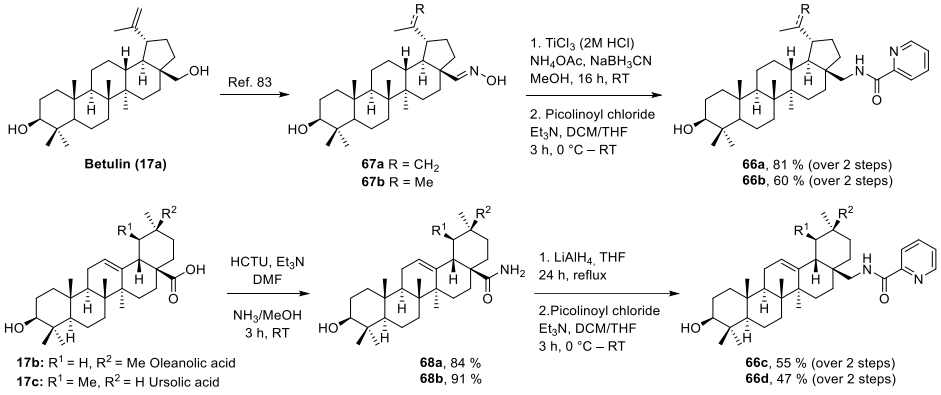



Fig. 8. Triterpenic 8-aminoquinolinamides **65a-d** and picolinamides **66a-d**.

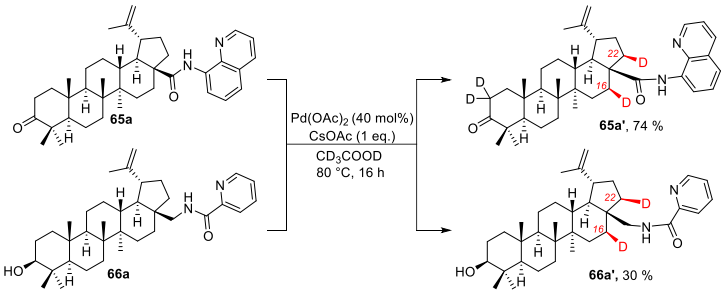
8-Aminoquinoline amides **65a-d** were prepared by simple coupling of betulonic, ursonic and oleanonic acids with an 8-aminoquinoline, with pre-transformation of acids into an acid chloride.[80, 81] Picolinamide[82] directing auxiliary was installed by triterpenic C(28) amine reaction with picolinoyl chloride. Betulinamine and its saturated congener were obtained from the reduction of corresponding oximes[83] **67a** and **67b**. Commercially available oleanolic and ursolic acids were converted into corresponding amines in two steps.[84, 85] *In situ*-generated activated esters were converted into amides **68a** and **68b**. Reduction of the latter with $LiAlH_4$ afforded primary amines, which were converted into picolinamides **68a** and **68b** using previously developed reaction conditions (Scheme 16).




Scheme 16. Synthesis of picolinic amides **66a-d**.

To explore the ability of the obtained directing group bearing PCT derivatives to complex palladium and provide C-H deuteration products that would demonstrate the feasibility of the C-H

activation event, betulin-derived starting materials **65a** and **66a** were subjected to C-H deuteration experiments using deuterated acetic acid as a solvent in the presence of $Pd(OAc)_2$ and CsOAc (Scheme 17). Both substrates provided C(16)/C(22) double-deuterated products. Inspired by the possibility of the C-H activation event, we started screening possible reaction conditions for the C-H arylation reaction. Surprisingly, no efficient reaction conditions for C-H arylation were found in the case of quinolinamide **65a**.

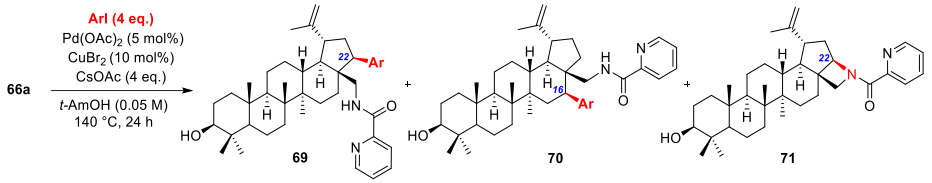



Scheme 17. C($sp^3$)-H deuteration of **65a** and **66a**; for clarity, the acidic -OH and -NH groups are depicted in their non-deuterated form as they undergo fast proton exchange during the isolation process.

Nevertheless, conformationally more flexible picolinamide **66a** was found to be an appropriate starting material for the target C-H arylation reactions. The combination of picolinamide **66a** (1 equiv.), 4-iodoanisole (4 equiv.), $Pd(OAc)_2$ (5 mol%), $CuBr_2$ (10 mol%)[86] and CsOAc (4 equiv.) in *t*-AmOH was found to be the most efficient reagent combination yielding a mixture of C(22)- and C(16)-regioisomers **69a** and **70a** in a 92:8 ratio with 83 % total yield. With suitable C($sp^3$)-H arylation conditions in hand, we examined the scope of the aryl iodide components (Table 1). Electron-rich aryl iodides displayed good reactivity, and C($sp^3$)-H arylation products **69a-d/70a-d** were obtained in the summary yield range 50–83 % (Table 1). Two molecular structures of compounds **69a** and **70b** were unambiguously proven by their single crystal X-ray analysis (Fig. 9). In all cases, the formation of C(22)-azetidine byproduct **71** was observed. Arylation employing iodoarenes with electron-withdrawing substituents resulted in decreased yields of arylated regioisomers within a 29–54 % yield range. On the other hand, iodobenzenes with substituents such as -COOMe, -C(O)Me, -CN, -Cl, $-NO_2$ (Table 1) afforded azetidine **71** as the major product in 40–64 % yields. The highest azetidine yield was observed with I-$C_6H_4$-CN (64%), but I-$C_6H_4$-$NO_2$ provided it as a single reaction product in 61 % yield, which facilitated its isolation and purification. Azetidines as C($sp^3$)-H arylation byproducts have been reported before, and a targeted C-H azetidination protocol employing $AgOAc/C_6F_5I$ on simple model substrates has been previously reported by Wu and co-workers.[87] Furthermore, there are also reports on azetidine formation from picolinamide in the presence of Pd-catalyst, $PhI(OAc)_2$ and $Li_2CO_3$.[88, 89] However, in our hands, these copper-free conditions did not result in any conversion of starting material **66a**.

Table 1

Scope and Isolated Yields of C($sp^3$)-H Arylation Products of Picolinamide **66a**.




| **Ar** | Yield of **69a-i** (%) | Yield of **70a-i** (%) | Yield of **71** (%) |
|---|---|---|---|
|  | **69a**, 76 | **70a**, 7 | 10 |
|  | **69b**, 64 | **70b**, 9 | 26 |
|  | **69c**, 60 | **70c**, 5 | 19 |
|  | **69d**, 45 | **70d**, 6 | 10 |
|  | **69e**, 32 | **70e**, 6 | 36 |
|  | **69f**, 32 | **70f**, 6 | 56 |
|  | **69g**, 22 | **70g**, 7 | 40 |
|  | **69h**, 19 | **70h**, 12 | 64 |
|  | **69i**, 42 | **70i**, 12 | 44 |
|  | - | - | 61 |

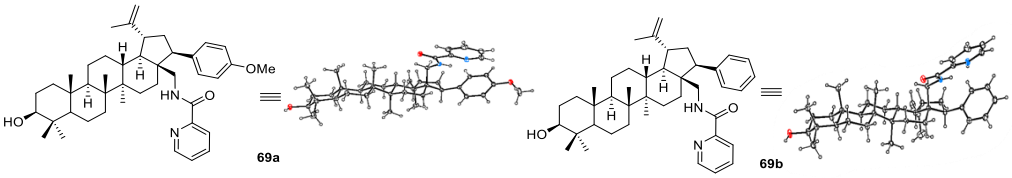
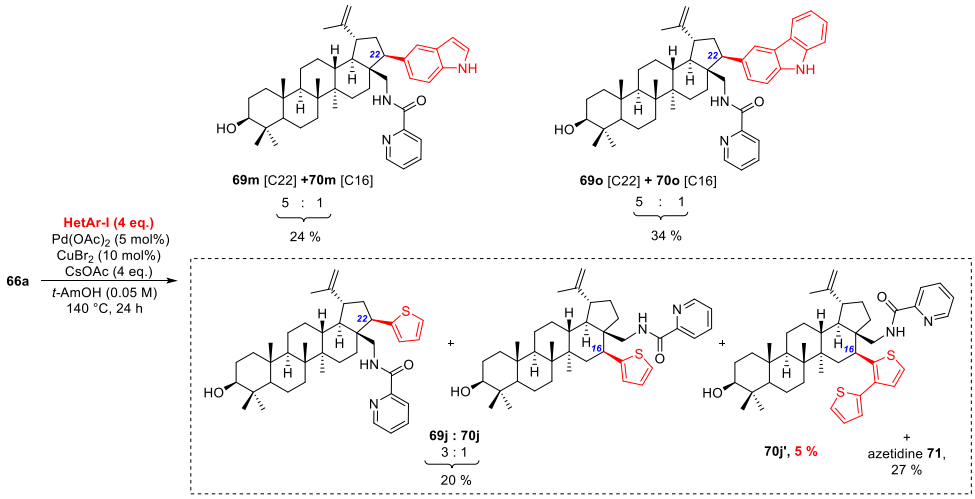



Fig. 9. Single crystal X-ray diffraction analysis of **69a** and **69b**.

We have tested also C($sp^3$)-H (het)arylation reactions of **66a** with 4-iodo *N,N*-dimethyl aniline, 3-iodopyridine and 4-iodo-1-methyl-*1H*-pyrazole, but no conversion of starting material was observed. Moreover, we have tried hetarylation employing 5-iodo indole and 7-iodo carbazole (Scheme 18), and the expected arylation products **69m/70m** and **69o/70o** were isolated in 24 % and 34 % yields, respectively, albeit without formation of azetidine.

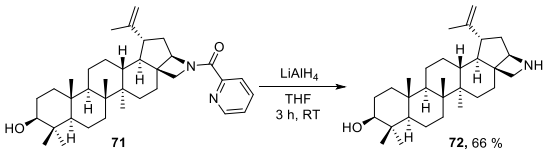
Reaction between **66a** and 2-iodo thiophene resulted in the formation of products **69j/70j** and azetidine **71,** and furthermore detectable amount of diarylated product **70j'** (5 %) was observed. The second C-H activation has taken place at the firstly installed thiophene moiety in product **70j** (Scheme 18).

To obtain other double arylation products utilizing other aromatic iodides, increased reaction time, higher concentration of an (het)aryl iodide component, as well as higher catalyst loading were applied; however, no additional double arylation products were detected.




Scheme 18. C($sp^3$)-H hetarylation of picolinamide **66a**.

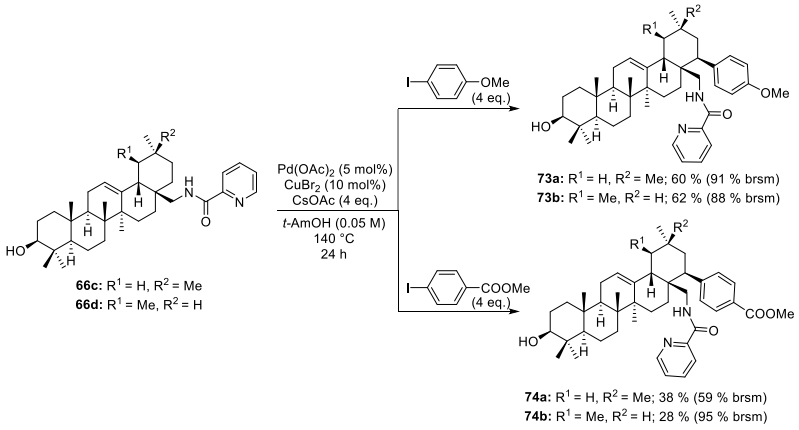
To provide NH azetidines for further synthetic applications, we explored the cleavage of the picolinamide moiety. Reductive cleavage conditions employing $LiAlH_4$ in THF at room temperature were found to be efficient to afford the desired product **72** (Scheme 19).




Scheme 19. Synthesis of unprotected azetidine **72**.

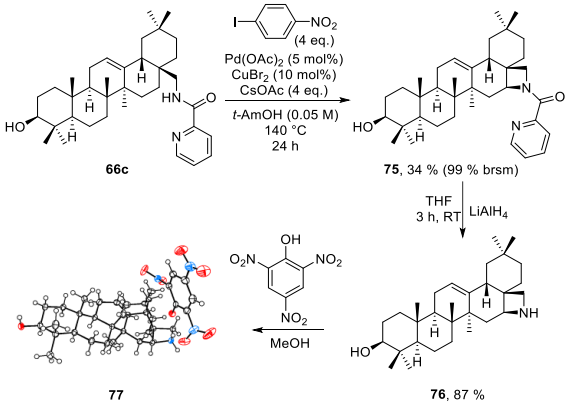
Inspired by the successful arylation of betulin core, we have also examined the arylation of oleanolic and ursolic acid-derived picolinamides **66c**,**d** employing electron-rich 4-methoxyphenyl iodide and electron-poor 4-iodobenzoic acid methyl ester (Scheme 20). Target transformation of ursane and oleanane cores resulted in a higher 19 : 1 site-selectivity at C(22); however, full conversion of **66c** and **66d** was not reached. Similar to the observation in the betulin series, the

electron-deficient 4-iodobenzoic acid methyl ester gave significantly lower yields of arylation products **74a,b** than the reaction with 4-methoxyphenyl iodide. Remarkably, the presence of side product azetidine was detected only in trace amounts in the case of oleanane and ursane starting materials **66c,d**.



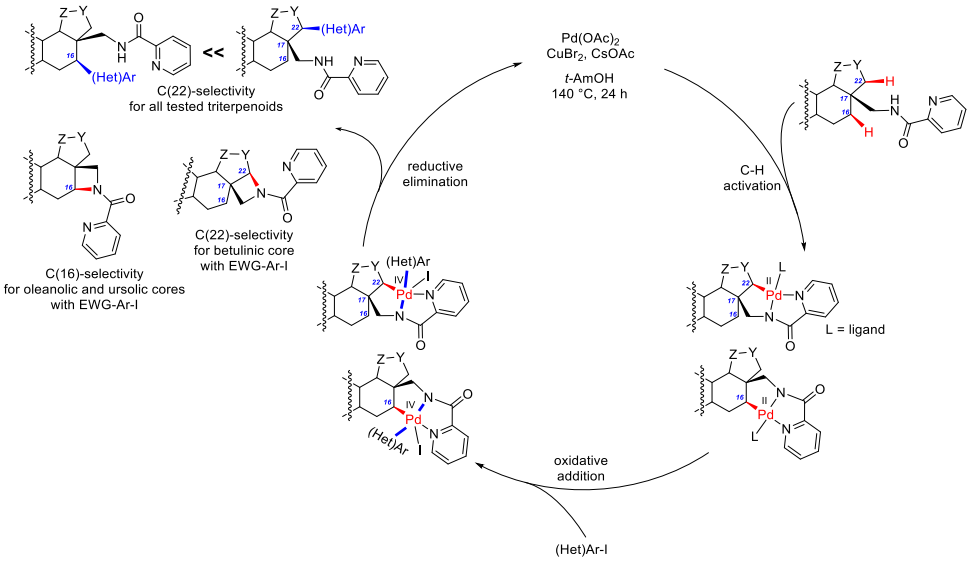

Scheme 20. C($sp^3$)-H arylation oleanane and ursane derivatives **66c**,**d**.

C-H activation of oleanane derivative **66c** in the presence of 1-iodo-4-nitrobenzene gave excellent C(16) selectivity, albeit incomplete conversion. Following reductive cleavage of the directing group with $LiAlH_4$ afforded corresponding azetidine **76**, which was further transformed into crystalline azetidinium picrate **77**. The molecular structure of the latter and thus the C(16)-regioselectivity was unambiguously established by its single crystal X-ray diffraction analysis (Scheme 21).




Scheme 21. Azetidine **76** formation from oleanane-derived picolinamide **66c**.

Based on generally accepted concepts, reductive elimination is most likely the rate-limiting step in the C($sp^3$)-H arylation process.[90] Analyzing the observed regioselectivity patterns, we can conclude that reductive elimination proceeds more slowly in palladium(IV) complexes bearing aryl groups with electron-withdrawing substituents. In such cases, the formation of a C-N bond via reductive elimination can outcompete C-C bond formation. In the betulinic series, for example, when 4-nitroiodobenzene (4-$NO_2$-$C_6H_4I$) is used in the oxidative addition step (Scheme 22), the reductive elimination from the C(22)-[Pd]-NC(O) intermediate is favored over that from the C(22)-[Pd]-Ar-EWG complex, resulting in the formation of an azetidine. Similarly, in the oleanane series, the general trend in reductive elimination rates is observed as follows: Ar-EDG > picolinamide > Ar-EWG. However, in this case, the C-H activation step is slower and occurs selectively at C(16), making it kinetically comparable to the rate of reductive elimination from the C(16)-[Pd]-NC(O) intermediate. Consequently, starting material **66c** affords azetidine **75** at the C(16) position upon reaction with 4-$NO_2$-$C_6H_4I$. Moreover, azetidine formation at C(22) in the oleanane scaffold would create an unfavorable 1,3-diaxial interaction with one of the geminal C(20) methyl groups – a steric hindrance that is absent in the betulin molecular framework.




Scheme 22. Plausible Pd-catalyzed C($sp^3$)-H arylation and azetidination mechanism.

In summary, we developed the first C-C bond-forming C($sp^3$)-H activation method in triterpenoids via palladium-catalyzed arylation of triterpenoid picolinamides with aryl iodides. The tested betulin, oleanane, and ursane scaffolds underwent selective C(22)-arylation in moderate to good yields. Oleanane and ursane derivatives gave high C(22)/C(16) selectivity (up to 19 : 1), while betulin-based substrates provided the highest yields (up to 83 %). Electron-rich aryl iodides

favored arylation, whereas their electron-deficient counterparts promoted C($sp^3$)-azetidination. The latter was exclusively observed in the presence of 4-nitroiodobenzene, and its regioselectivity varied by the employed scaffold. Thus, betulin gave C(22)-azetidine, while oleanane gave C(16)-azetidine. The picolinamide group can be cleanly removed using Zn/HCl. The obtained arylated and azetidine-fused triterpenoids offer promising platforms for further medicinal chemistry research.

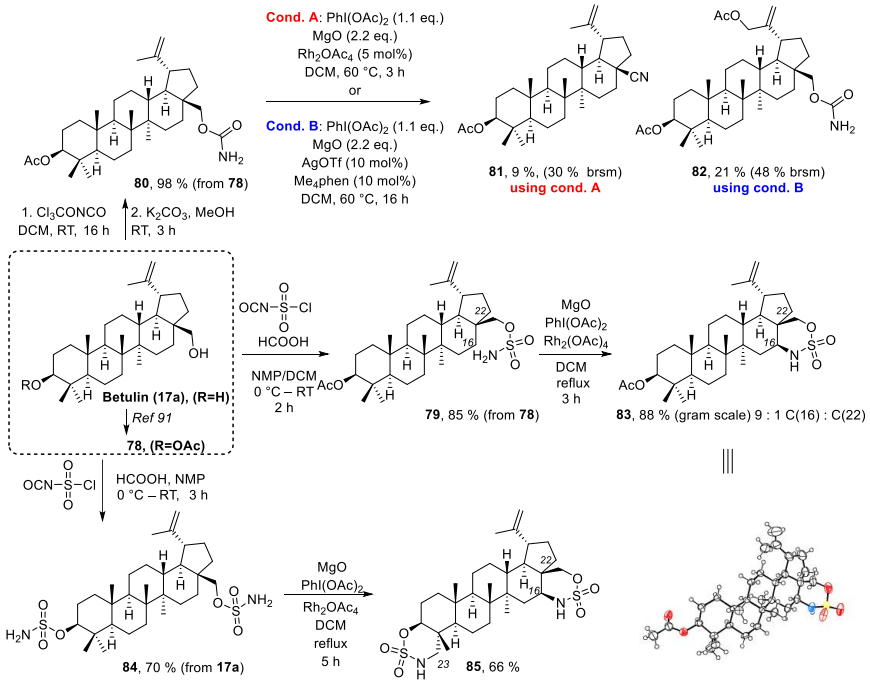
More information about these studies is available in the publication by Kroškins, V., Lugiņina, J., Lācis, R., Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M., Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids, *ACS Omega.* **2025**, *10*, 27992–28019, (Appendix 5).

## 2.2. C-H amination of pentacyclic triterpenoids

Absence of C-H amination examples in literature on PCT skeleton D and E ring, employing C(28) derived directing auxiliaries and several examples of C-N bond formation via intermolecular C($sp^3$)-H amination in terpene, steroid and alkaloid molecules, caused an interest in developing PCT derivatives bearing functional handles at C(28) suitable for C-H amination reaction. For that purpose, we decided to synthesize from C(28) alcohol **78**[91] easily available carbamate and sulfamate esters. Based on our previous experience, we chose to avoid radical involving conditions to escape possible double bond interaction and proceed with transition metal catalyzed nitrene generation and following the C-H insertion approach.

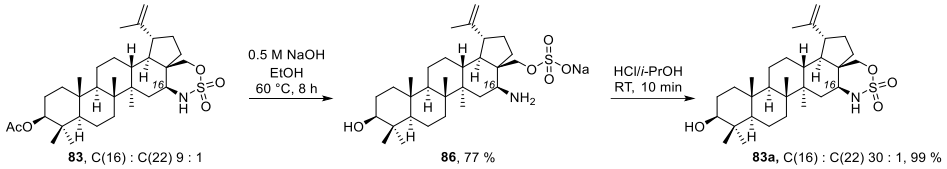
We have found that the carbamate tethered betulin derivative **80** does not provide the expected amination products under Rh- and Ag-catalytic conditions. Instead, upon increased temperature (60 °C in pressure tube) and longer reaction time, formation of degradation products and C(28) nitrile **81** was detected. Formation of the latter can be explained by C-H amination reaction at C(28), forming an unstable 4-membered ring, which rapidly underwent decarboxylative oxidation by PIDA to yield the nitrile[92] (Scheme 23). Switching to silver catalysis employing different silver sources[93] like (AgOTf, $AgPF_6$ or $AgSbF_6$) in combination with MgO and $PhI(OAc)_2$ or PhIO, revealed weak conversion of the starting material and slow formation of degradation products. Catalytic $Me_4$phen additive promoted the allylic C-H acetoxylation reaction to yield product **82**.

It was gratifying to find that sulfamate ester **79** displayed full conversion after 3 h, and two regioisomers in 9 : 1 ratio were obtained using the following reaction conditions: 2.2 equiv. MgO, 1.1 equiv. $PhI(OAc)_2$ and 2 mol% $Rh_2(OAc)$.[94] The structure of major isomer **77** was unambiguously determined by X-ray diffraction analysis. Similarly, betulin 3,28-di-O-sulfamate ester **84** was prepared with 70 % yield. The latter smoothly underwent double C-N bond formation using previous conditions to yield C(23) and C(16)aminated product **85** as the major isomer (Scheme 23).



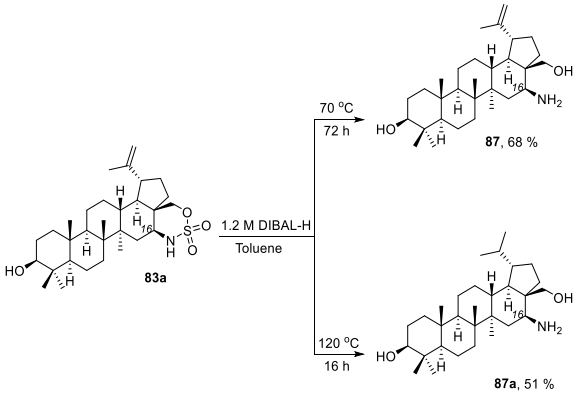

Scheme 23. C-H amination of betulin core.

Next, we explored the reactivity of the obtained 1,2,3-oxathiazinane-2,2-dione **83** in nucleophilic ring-opening reactions to cleave the ring and obtain 1,3-difunctionalized C(16)-amino derivatives. Several attempts for this transformation employing vigorous reaction conditions and different nucleophiles (e.g., $N_3^-$, $AcO^-$, $PhS^-$, morpholine and water) did not provide any conversion of the starting material due to the low electrophilicity of the oxathiazinane ring. Only basic hydrolysis using 0.5M NaOH ethanolic solution led to nucleophilic attack at the sulfur atom, yielding ionogenic 1,3-aminosulfate **86**. Acidification of the obtained sulfate sodium salt induced rapid ring closure back to the oxathiazinane ring, giving C(3)-hydroxy-oxathiazinane derivative **83a**. (Scheme 24). Moreover, we noticed that sulfate **86** undergoes selective precipitation from ethanolic solution, which results in an improvement of the initial C(16):C(22) 9 : 1 regioisomer ratio in compound **7** to 30 : 1 for compound **86**. Filtrate analysis of compound **86** precipitation has revealed that the minor C(22)-isomer of **83a** did not undergo ring opening in the presence of 0.5 M NaOH ethanolic solution and did not form ionogenic C(22) product, ensuring sufficient polarity difference for selective precipitation. Several strongly acidic and strongly basic hydrolytic conditions have been applied to cleave the sulfate moiety from the intermediate **86**, to obtain 1,3-aminoalcohol derivative, but none of them were found to be efficient.




Scheme 24. Synthesis of sulfate **86** and its cyclization to **83a** in acidic media.

Application of reductive conditions using DIBAL-H solution in toluene was found to be useful to succeed ring opening of the oxathiazinane ring to establish the desired 1,3-aminoalcohol motif **87** with 68 % yield. Increased reaction temperature caused faster conversion of the reaction material; however, complete reduction of the double bond was observed (Scheme 25).

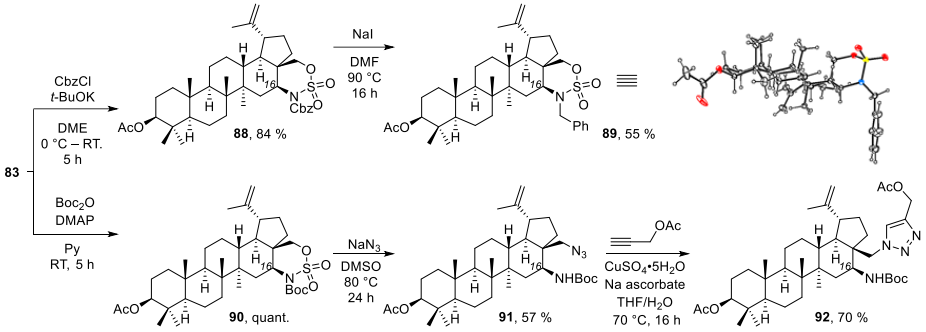



Scheme 25. Reductive ring opening of 1,2,3-oxathiazinane-2,2-dione **83a**.

To increase the electrophilicity of the oxathiazinane ring and facilitate ring-opening reactions with previously unreactive nucleophiles, two different carbamoylations of the -NH moiety were accomplished. Then the ring-opening attempts of *N*-Cbz oxathiazinane **88** resulted mostly in Cbz deprotection, and the desired ring-opening products were formed only in trace amounts. Curiously, in the case of iodide nucleophile, we have observed Cbz-group transformation into *N*-benzyl group. The latter can be explained by *in situ* decarboxylation of the Cbz group, benzyl iodide formation and following *N*-benzylation of the oxathiazinane ring. The structure of *N*-benzyl side product **89** was determined unambiguously by X-ray diffraction analysis (Scheme 26).

Switching the *N*-Cbz group to the *N*-Boc group improved selectivity towards the formation of the desired 1,3-substituted product **91** in the case of the azide nucleophile. Nevertheless, other nucleophilic reagents (e.g., acetate, thiophenolate, morholine, cyanide, thiocyanate, phenolate and methoxide) still resulted in *N*-Boc group cleavage, keeping the 1,2,3-oxathiazinane-2,2-dione ring intact. Poor reactivity of nucleophiles can be explained by C(28) of the betulin core being a neopentyl position, which is sterically hindered by the quaternary center at C(17) atom.[95] Optimal

conditions for the synthesis of aminoazide **91** used 2 equivalents of $NaN_3$ at 80 °C in DMSO solution for 24 h. Next, the obtained azide **91** was employed in CuAAC (copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition) reaction with propargylic acetate in the presence of $CuSO_4 \cdot 5H_2O$ to yield triazole **92** (Scheme 26).

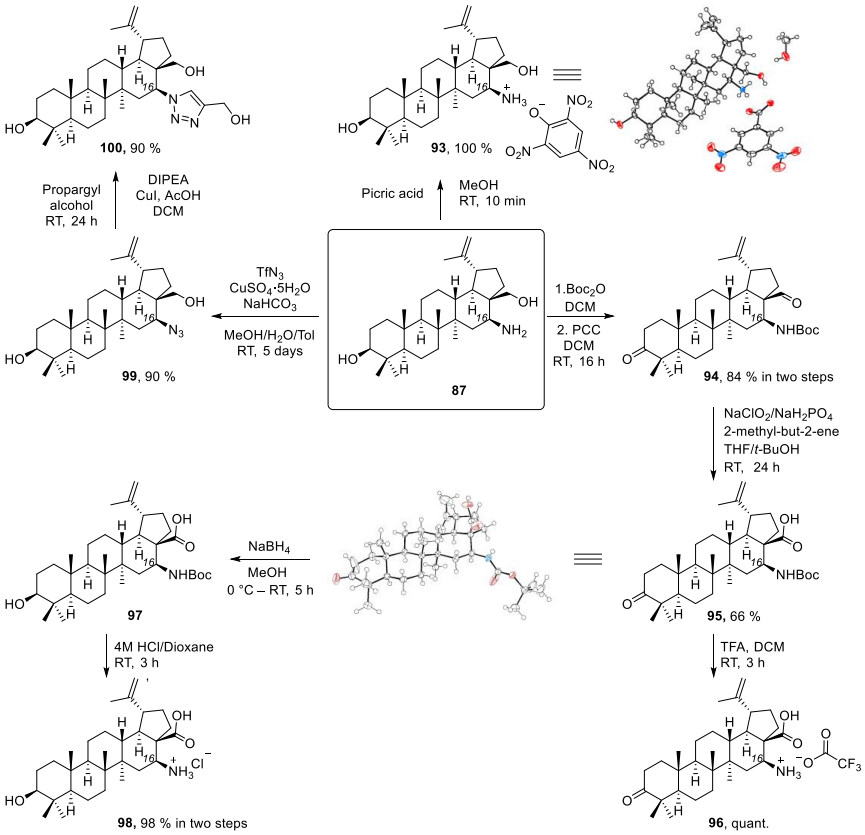



Scheme 26. Nucleophilic ring opening studies of *N*-protected oxathiazinanes **88** and **90**.

Obtained 1,3-aminoalcohol **87** was found to be a versatile feedstock for various useful synthetic transformations. Reaction of the latter with picric acid afforded picrate salt **93**, the structure of which was proved by single-crystal X-ray analysis (Scheme 27). Boc protection of amine functionality and the following two-step oxidation furnished *N*-Boc-*β*-amino betulonic acid **95**. Diastereoselective reduction of the latter at C(3) afforded *N*-Boc-*β*-amino betulinic acid **97**.

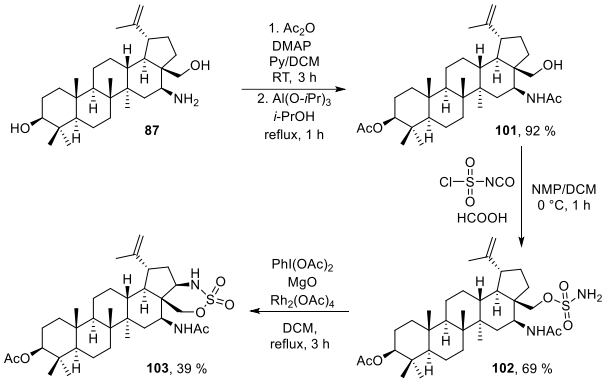
Boc deprotection of both amino acids to give corresponding *β*-amino acids in their trifluoroacetate salt form can be achieved by TFA treatment. However, in the case of betulinic acid derivative **97,** a trifluoroacylation of the C(3) hydroxyl group was detected. Therefore, 4 M HCl/dioxane was found to be more efficient for selective *N*-Boc deprotection to yield *β*-amino acid **98** in its hydrogen chloride salt form.

Next, 16-azido-betulin **99** can be smoothly obtained from the corresponding amine *via* diazotransfer reaction, utilizing trifluoromethanesulfonyl azide in the presence of copper(II) additive. With compound **99** in hand, copper(I)-catalyzed azide-alkyne cycloaddition furnished C(16)-triazolyl betulin **100** as a model compound for a virtually endless library of novel betulin-triazole conjugates (Scheme 27).




Scheme 27. Synthetic transformations of 1,3-aminoalcohol **87**.

At this point, we also explored the possibility of installing the second amino functionality at the triterpenoid core using the same sulfamate ester linker one more time. Accordingly, diacetate **101** was prepared *via* a protection/deprotection sequence and then carefully treated with *in situ* prepared sulfamoyl chloride at 0 ºC, delivering sulfamate ester **102**. The latter was subjected to previously used C-H amination conditions. Target oxathiazinane **103** at betulin C(22) was obtained with moderate yield (Scheme 28). There is an expectation that the oxathiazinane cycle in compound **103** can be further transformed in a comparable way to that of compound **83**, which opens potential pathways for further transformations of the betulin core.




Scheme 28. Synthesis of sulfamate **102** and its application in C-H amination at C(22).

Regio- and diastereoselectivity of C-H activation most probably is determined by substrate control. The intermediate metallonitrene likely tends to insert into the equatorially aligned C-H bond of the D-ring of starting material **79**. This provides product **83** containing the newly formed cycle in a low-energy chair-like conformation. The intrinsic properties of the lupane core do not permit chair-like conformation of the newly formed cycle if it is attached to the E-ring (Fig. 10).

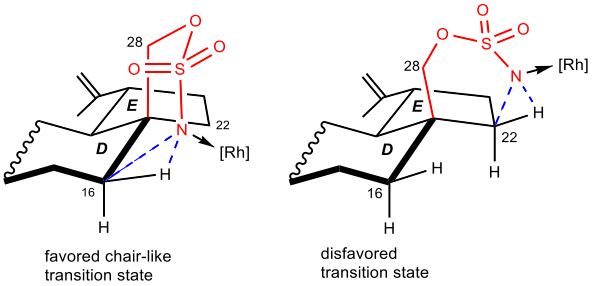
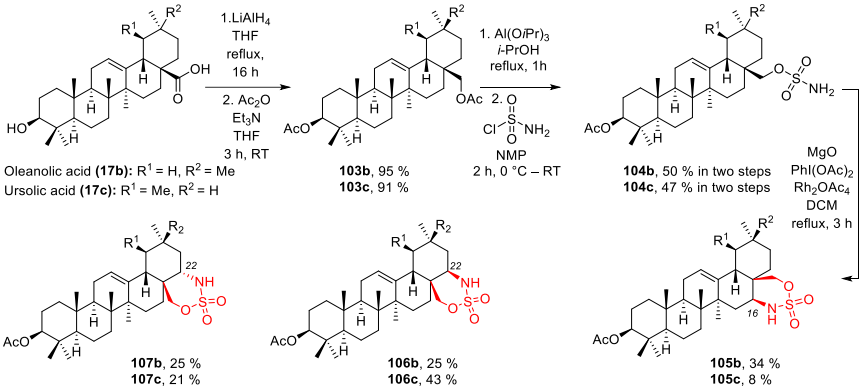



Fig. 10. C-H insertion transition states at C(16) and C(22).

Finally, we started the investigation of C-H amination of oleanane and ursane-derived sulfamate esters **104b,c**, which were obtained from corresponding commercially available acids **17b,c** in four steps. Same conditions as previously used resulted in full consumption of starting material, in a few hours delivering a mixture of three major products in both cases (Scheme 29): C(16) aminated product **105b,c** and a diastereomeric mixture of C(22) aminated products **106b,c** and **107b,c**. C-H amination of ursane core turned out to be more selective towards C(22) aminated product, presumably due to alternative location of methyl substituents at the E ring. Nevertheless, in comparison to the reaction of its oleanane counterpart, the total isolated yield was lower due to worse solubility in organic solvents and thus a more difficult isolation procedure. The loss of site selectivity compared to the betulin core can be explained by the different size and orthogonal

exposition of the triterpenoid E-ring. To obtain ring-opening product and facilitate easier separation of regio- and diastereoisomers, mixtures of aminated compounds **105b-107b** and **105c-107c** were subjected to previously successfully used ring-opening conditions. However, this time, attempted hydrolysis with NaOH failed to induce any conversion of starting material, displaying superior stability of oleanane- and ursane-derived oxathiazinanes. Further studies on C-H amination and the synthetic applications of the resulting products in ursane- and oleanane-type PCT series will be pursued in future projects.



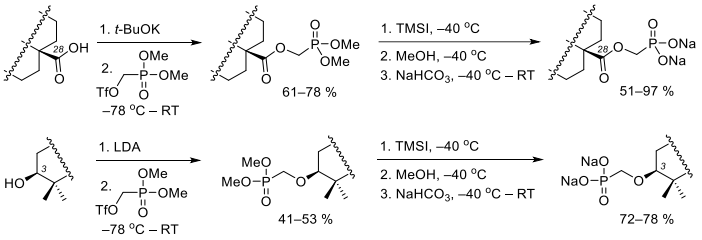

Scheme 39. Preliminary research of the synthesis and C-H amination reactions of oleanane- and ursane-derived sulfamate esters **104b,c**.

In summary, we have developed a novel synthetic method for site-selective C(16)-N bond formation on the D-ring of betulin using rhodium-catalyzed nitrene C-H insertion. Sulfamate ester, as the key starting material, was synthesized from natural betulin in a few steps. Despite the steric hindrance and rearrangement risk at the neopentylic C(28) position, several successful ring-opening reactions of the resulting oxathiazinane were achieved: 1) NaOH treatment yielded an aminosulfate salt; 2) $NaN_3$ gave a 1,3-aminoazide, which is a precursor to γ-amino C(28)-triazoles; 3) reductive ring-opening afforded a 1,3-aminoalcohol, leading to 16-amino-betulinic and betulonic acids. Additionally, 16-amino-betulin was transformed into 16-azido-betulin via diazotransfer. Notably, a second nitrene C-H insertion is possible at C(22) if the C(16) position is already aminated. The developed approach gives a straightforward approach to new lupane-type triterpenoid derivatives with amino or azido groups, offering valuable platforms for further modification and bioactivity studies in medicinal chemistry.

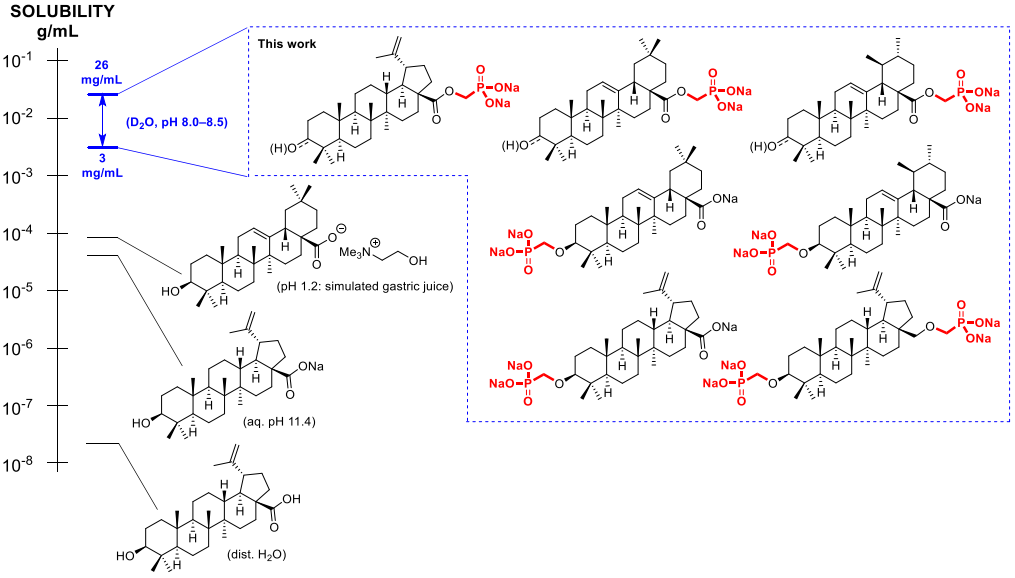
For more information on the studies described in this chapter, see the publication by Kroškins, V., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M., Site-selective C-H amination of lupane type triterpenoids, *Eur. J. Org. Chem*., **2025**, 2500340, (Appendix 6).

# CONCLUSIONS

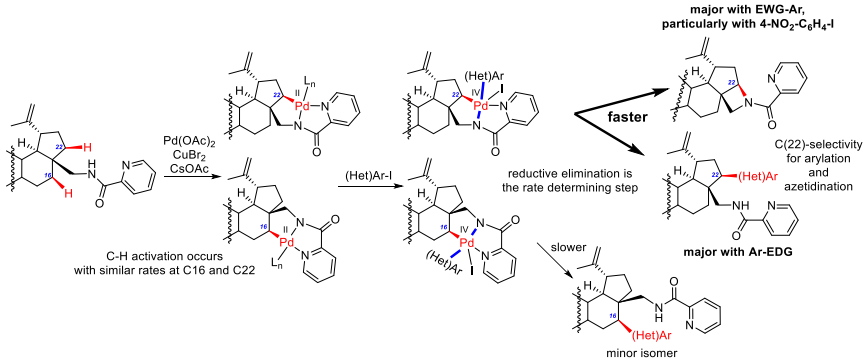
1. Despite the sterically hindered neopentyl environment at the C(3) and C(28) positions, the corresponding hydroxyl groups can be successfully alkylated with (dimethoxyphosphoryl)methyl trifluoromethanesulfonate. The alkylations are achieved under basic conditions, with *t*-BuOK employed for carboxylic acids and LDA for alcohols. The resulting methyl phosphonate intermediates can be selectively demethylated using TMSI while preserving the newly formed carboxylic ester moiety. The latter chemoselectivity can be ensured by conducting the entire sequence, including the neutralization step, at approximately –40 °C.



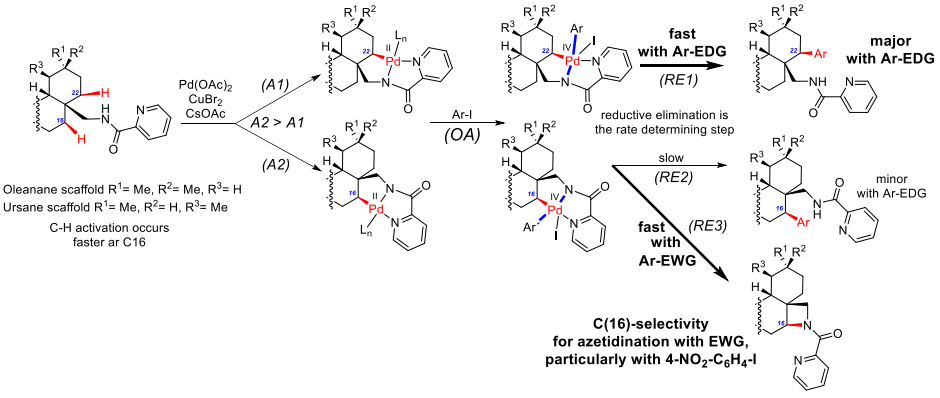

2. The obtained pentacyclic triterpenoid-phosphonate conjugates of types C(28)(CO)-O-$CH_2$-P(O)$(ONa)_2$ and C(3/28)-O-$CH_2$-P(O)$(ONa)_2$, featuring a minimal methylene linker between the terpenoid core and the phosphonate moiety, reveal remarkable aqueous solubility in the pH range 8.0–8.5 (3-26 mg/mL). This solubility is several orders of magnitude higher than that of the corresponding triterpenic acids or their salts.



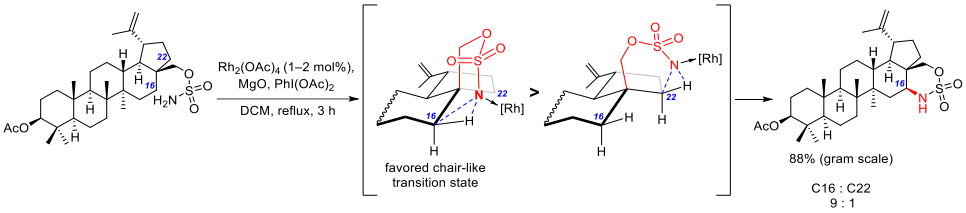
3. In the betulin series, a fast and non-selective C-H activation occurs at both C(16)-H and C(22)-H, as proved by deuteration experiments, using both picolinamide and quinolinamide directing groups. The selectivity in subsequent C-H arylation and azetidination reactions is determined primarily by the reductive elimination step, which proceeds more readily at C(22) in either case. When electron-withdrawing aryl substituents (e.g., 4-nitrophenyl) are used, reductive elimination across the C-N bond is favored, resulting in azetidine formation at C(22). On the other hand, aryl groups bearing electron-donating substituents facilitate faster reductive elimination from C-[Pd]-Ar intermediates, leading to predominant formation of C(22)-arylated products, with selectivity ratios up to 9 : 1.



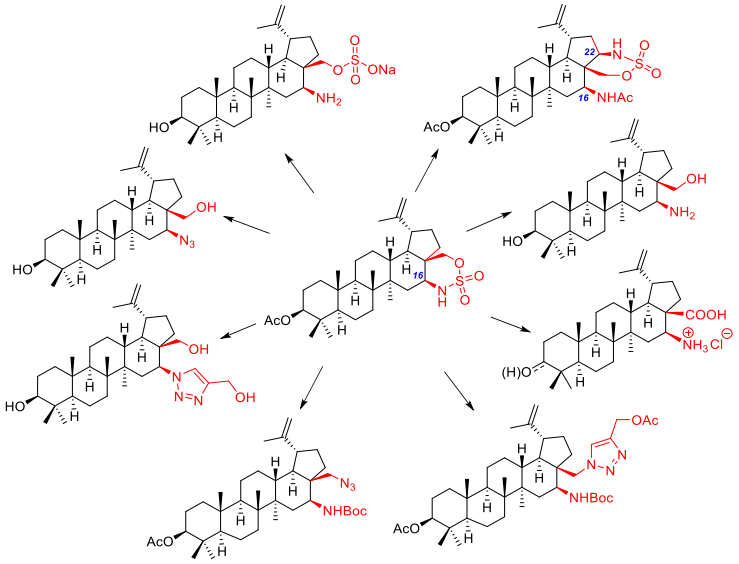

4. In the ursane and oleanane series, the C-H activation step occurs with C(16)-H selectivity (A2 > A1) and is slower compared to the betulin series. In the presence of electron-deficient aryl substituents (e.g., 4-nitrophenyl), the rate of C-H activation (step A2) becomes comparable to the rate of reductive elimination (RE3) from the C(16)-[Pd]-NC(O) intermediate, leading to the formation of C(16)-azetidine products. On the other hand, when electron-rich aryl substituents are used, the relative rates of reductive elimination follow the order $RE1_{EDG}$ > RE2 >> RE3, favoring formation of C(22)-arylated products with C(22)/C(16) selectivity 19 : 1.



5. Betulin-derived 28-*O*-sulfamate ester serves as an effective nitrene precursor under rhodium-catalyzed conditions. Nitrene insertion into the C-H bond proceeds with good selectivity for the C(16)-H and affords oxathiazinane product in excellent yield on a gram scale.




6. The oxathiazinane ring can be efficiently opened by azide and hydride nucleophiles, yielding intermediates amenable to further functionalization. The developed methodology enables the preparation of lupane derivatives bearing diverse modifications at the C(16) and C(28) positions. Notably, following functionalization at the C(16) position of betulin, a second nitrene C-H insertion remains feasible, and it proceeds selectively at the C(22)-H position.



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# Pielikumi / Appendices

Pielikums I

Appendix I

Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Demir, Ö., Dubnika, A., Loca, D., Turks, M

# Synthesis and preliminary cytotoxicity evaluation of water soluble pentacyclic triterpenoid phosphonates

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# Synthesis and preliminary cytotoxicity evaluation of water soluble pentacyclic triterpenoid phosphonates

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**Synthesis, solubility and cytotoxicity evaluation of anionic phosphonates derived from betulin, betulinic acid, oleanolic acid and ursolic acid is reported. Phosphonate moieties were successfully installed at terpenoid C28 by carboxylic acid deprotonation/alkylation sequence using (dimethoxyphosphoryl)methyl trifluoromethanesulfonate as alkylation reagent. Also, betulin-derived and ether-linked bis-phosphonate is obtained and characterized. After demethylation in the presence of TMSI the resulting phosphonic acids were transformed into their disodium salts. All target compounds display excellent water solubility, which was determined by qNMR in $D_2O$. Cytotoxicity tests were performed in different concentrations of each compound (10–50 μM) against human osteosarcoma cell line MG-63 and osteoblast precursor cell line MC3T3-E1. Improved aqueous solubility and low cytotoxicity profile of the newly designed triterpenoid phosphonates reveal high potential for various medicinal chemistry and pharmacological applications in the future.**

**Keywords** Pentacyclic triterpenoids, Phosphonates, Cytotoxicity, Aqueous solubility

People have used various plant-derived products as remedies for illnesses since prehistoric times. Also, in the modern era, approximately a quarter of drugs are inspired by or derived from natural products. This is particularly pronounced in anticancer and anti-infective areas, where during the past four decades, more than half of drugs are either natural products or natural product derivatives, mimics of natural products, or compounds bearing natural product pharmacophore[1]. The use of naturally abundant agents can help to reduce toxic and side effects due to low toxicity profile in normal cells[2]. Enhanced safety and cost-effectivity promote natural products to great multitarget drug candidates[3].

Pentacyclic triterpenoids (PCTs) belong to a widespread family of natural isoprene-derived secondary metabolites, which exhibit a broad spectrum of biological properties[4–8]. PCTs can be classified into three major groups: lupane (betulin, betulinic acid, and lupeol), oleanane (oleanolic acid, maslinic acid, erythrodiol, and β-amyrin) and ursane (ursolic acid, uvaol, and α-amyrin)[9]. The ubiquity of PCTs in nature, renewability and their facile isolation process have resulted in numerous studies that have explored potential therapeutic applications of these terpenoids. Among them, the most promising PCTs applications are in the anticancer and antiviral domains[10–16]. Emerging application fields of PCTs and their semi-synthetic derivatives include the search for antibacterial[8,17] and antifungal agents[18,19], and compounds that can treat diabetes[20,21] and inflammatory conditions[22,23].

However, the development of PCTs drugs is often jeopardized by their physicochemical properties that are characteristic of natural plant compounds – poor solubility in physiological media and low bioavailability[24–29]. The latter can be explained by the high lipophilicity of the steroidal core[30], which leads to extremely low aqueous solubility. For example, the solubility of betulinic acid in distilled water is 21 ng/mL and 40.1 μg/mL at pH 11.4 in sodium phosphate solution[31]. Improvement of aqueous solubility is a possible option to overcome this limitation[32], and it can be achieved by chemical modifications of the terpenoid structure[33–35].One of the approaches is to decorate the lipophilic carbon skeleton either with heteroatoms[36–38] or with polar ionogenic groups[39].

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PCTs such as betulinic, ursolic and oleanolic acids possess intrinsic polar ionogenic carboxylate group at C(28), which can be easily transformed into different anionic salts by treatment with alkali and quaternary ammonia hydroxides (Fig. 1). As an example, choline oleanolate displayed the best solubility (81.7 μg/mL) in a simulated gastric juice (aqueous solution of NaCl and sodium dodecyl sulfate, which was adjusted to pH 1.2 by HCl solution)[40,41]. However, solubility studies of potassium and sodium PCT carboxylates did not show satisfactory results, due to the formation of colloids at concentrations above 0.02 mg/g, which significantly complicated the solubility determination.

On the other hand, various semi-synthetic cationic PCT conjugates were reported during the past decade. Various ammonium[42,43], guanidinium[44] and imidazolium[45] moieties possessing diverse counterions were attached to PCTs cores through different type and size linkers. Similarly, C(2), C(28) and C(30) PCT triphenylphosphonium salts have been synthesized and biologically evaluated[46,47]. Unfortunately, solubility data of these cationic PCTs were not reported.

Speaking about alternative semi-synthetic anionic PCT derivatives, sulfate[48–50] and phosphate[51–60] groups have been added to the PCTs cores by corresponding sulfation or phosphorylation of C(3)-OH or/and C(28)-OH groups. PCT-derived mono and diphosphates provide a wide range of biological applications. However, detailed aqueous solubility studies thereof are not available. Even if *O*-phosphorylation and *O*-sulfatation of terpenoids may improve their biological activity properties by making structural and spatial changes[61], the use of such modified compounds can be hampered by low hydrolytic stability[62,63].

The latter issue can be overcome by replacing the phosphates with isosteric and isoelectronic, yet more stable phosphonates. This approach has made phosphonate derivatives a prominent class of biologically active compounds that have been developed particularly well in the area of antiviral nucleotide drugs[64–67]. Phosphonates as phosphate mimics have also been studied in the triterpenoid series, but the reported examples are quite scarce. Thus, phosphonate moieties have been attached to the PCT core by an amide bond[68] or C-C bond (Fig. 1)[69,70]. To the best of our knowledge, there is only one example of PCT-phosphonate connected by C(28) carboxylic ester[71]. Nevertheless, the conversion of the reported phosphonates to phosphonic acids or their salts is still unexplored, and the water solubility of such ionogenic species has not been described.

Herein, we report the design and synthesis of novel pentacyclic triterpenoid – phosphonate conjugates of type C(17)-COO-$CH_2$-*P* and C(3/28)-O-$CH_2$-*P*, where the phosphonate moiety is attached to the terpenoid core by

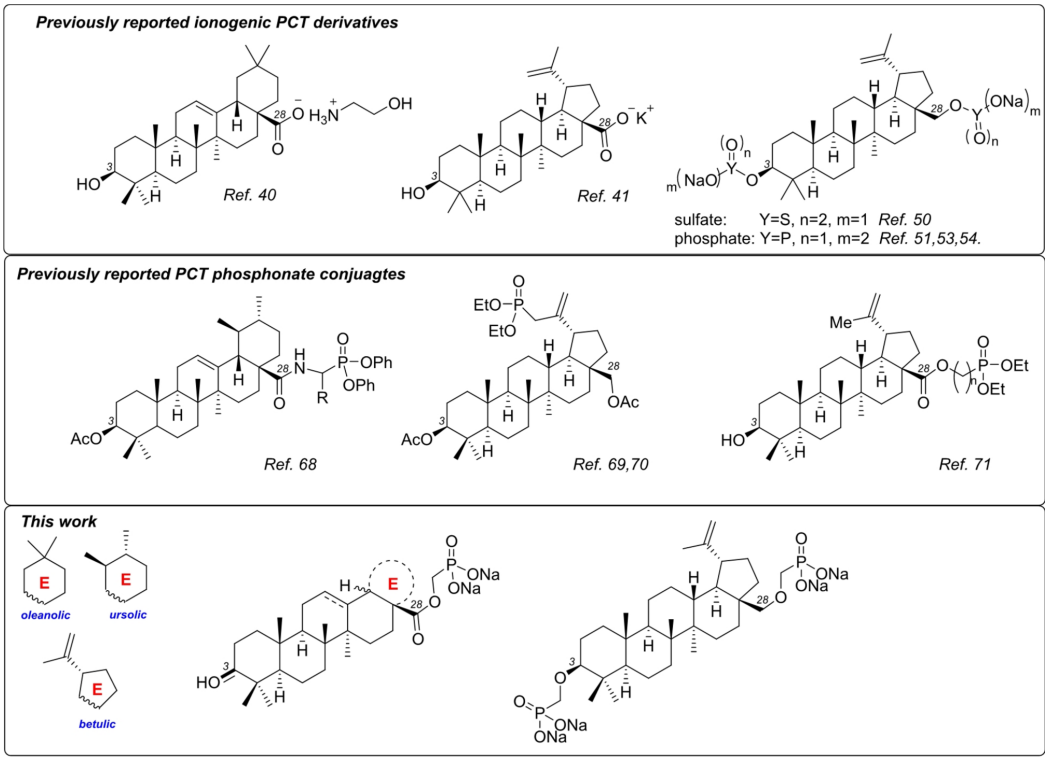



**Fig. 1**. Previously reported ionogenic PCTs, PCT-derived phosphonate conjugates and the original target molecules.

the simplest possible methylene linker and chemically bound by ester or ether moiety (Fig. 1). It is important to note, that the PCT's C(28) esters are hydrolytically stable and can resist basic and acidic treatment[72–74]. Thus, we demonstrate with the present report that such phosphonate esters and phosphonate sodium salts are straightforward to achieve and the latter are very soluble in aqueous solutions, which is often a delicate task to achieve in the field of triterpenoid chemistry.

## Results and discussion

### Synthesis

Initially, we speculated that the incorporation of methylene phosphonate moiety can be achieved through the ester bond formation between the triterpenic acid C28 carboxylate group and dialkyl (hydroxymethyl) phosphonate via activation of carboxylic acid. For this purpose, we have prepared a series of 3-oxo PCT carboxylic acids **2a**-**c** starting from commercially available betulin **1a**, oleanolic acid **1b** and ursolic acid **1c**. 3-Oxo triterpenic acids **2a**-**c** were successfully converted into corresponding acyl chlorides by $SOCl_2$ treatment, but further reaction with dimethyl (hydroxymethyl)phosphonate was found to be inefficient, due to low conversion of the chloride into the desired product. Following screening of the reaction conditions did not bring the desired result, and the best yield that we reached was 30%. The weak reactivity of triterpenic acid chlorides can be explained by the steric hindrance at C(28) position. Some sources demonstrate that PCT acid halides are capable of reacting with amines[75] and phenols[76], but insufficient nucleophilicity of alcohols, together with the electron withdrawing effect of phosphonate moiety, makes it even more complicated.

Therefore, we decided to switch reactivity and explore a possible carboxylate alkylation reaction[77], in which the reaction site is one atom further from the C(17) quaternary center.

We discovered that 3-oxo triterpenic acids **2a**-**c** underwent rapid deprotonation followed by alkylation with (dimethoxyphosphoryl)methyl trifluoromethanesulfonate in the presence of *t*-BuOK in anhydrous THF (Fig. 2). The used triflate is readily available from the previously mentioned alcohol[78]. The desired esters **3a**-**c** were obtained in good yields. Next, 3-hydroxy triterpenic phosphonates **4a**-**c** were obtained by diastereoselective reduction of C(3) ketones. A similar approach using (dimethoxyphosphoryl)methyl trifluoromethanesulfonate in a combination with 3-hydroxy triterpenic acids **1b**, **c** provided a direct access to compounds **4b**, **c** (process **1b**, **c** → **4b**, **c** Fig. 2), yet with a lower yield due to side reactions that implied laborious purification of the products. For the transformation **1b**, **c** → **4b**, **c** $K_2CO_3$ was used as a weaker base to achieve a better selectivity between C(17)-COOH and C(3)-OH alkylation, but this required a solvent change to DMF for a better solubility if the base. The latter protocol resulted also in transesterification between C(17)-COOH and phosphonic acid methyl ester moiety of the alkylation reagent yielding C(17)-COOMe side product accompanied by $TfOCH_2P(O)(OH)(OMe)$, the separation of which required additional reverse phase chromatography on C18-silica. Therefore, the developed sequence **2** → **3** → **4** is optimal, as it provides clean transformations and ensures access to both C(3)-OH and C(3) = O series of triterpenoids.

With the whole series of the desired phosphonates in hand, next we examined the transformation of phosphonates into sodium phosphonates 7**a**-**c** and **8a**-**c** employing TMSI assisted demethylation followed by the conversion of phosphonic acids **5a**-**c** and **6a**-**c** into their salts (Table 1; Fig. 3). Starting with the betulonic acid derived phosphonate **3a** (Table 1), we found that the demethylation must be carried out at -40 °C. At higher temperatures betulinic acid olefin moiety underwent cationic rearrangements[79] and cleavage of the previously installed ester was observed (Table 1, entries 1, 2). We supposed that the methanolysis of the intermediate *O*-TMS-phosphonates could also be accomplished at a lowered temperature, but the undesired side product was still formed during the evaporation of the solvent (Table 1, entry 3). Neutralization of HI before warming up

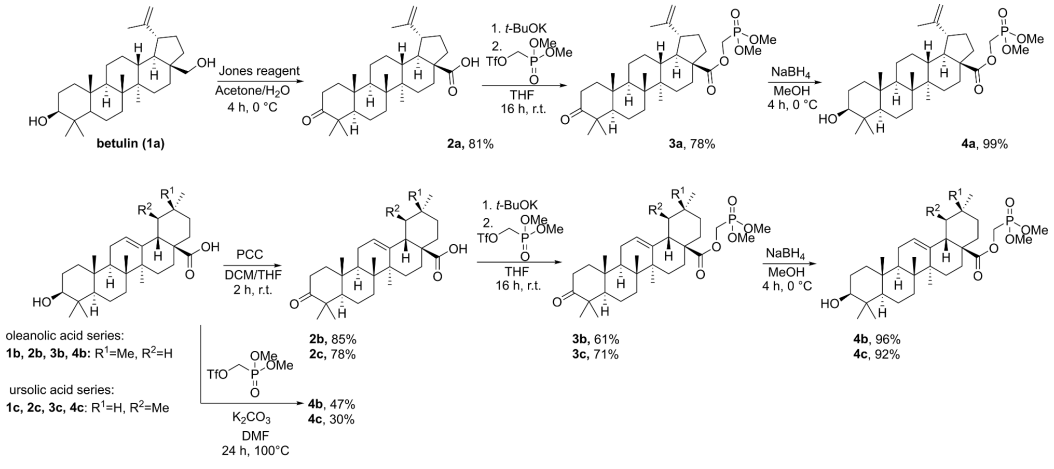
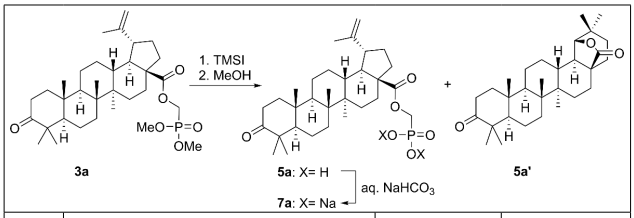



**Fig. 2**. Synthetic route for the preparation of phosphonic esters **4a**-**c**.




| Entry | Conditions | Yield of **7a** (%) | Yield of **5a'** (%) |
|---|---|---|---|
| 1 | 1. TMSI (5 equiv.), 2 h, RT<br>2. MeOH, 30 min, 0 °C | 0 | 83 |
| 2 | 1. TMSI (3 equiv.), 1 h, – 40 °C → 0 °C<br>2. MeOH, 10 min, 0 °C | 43 | 25 |
| 3 | 1. TMSI (3 equiv.), 4 h, – 40 °C<br>2. MeOH, 10 min, -78 °C | 50 | 16 |
| **4** | 1. **TMSI (3 equiv.), 4 h, – 40 °C**<br>2. **MeOH, 30 min, – 40 °C**<br>3. **$NaHCO_3$(4 equiv.), 1 h, – 40 °C → RT** | **97** | 0 |

**Table 1**. Demethylation studies of 3-oxo-PCT phosphonate **3a**.

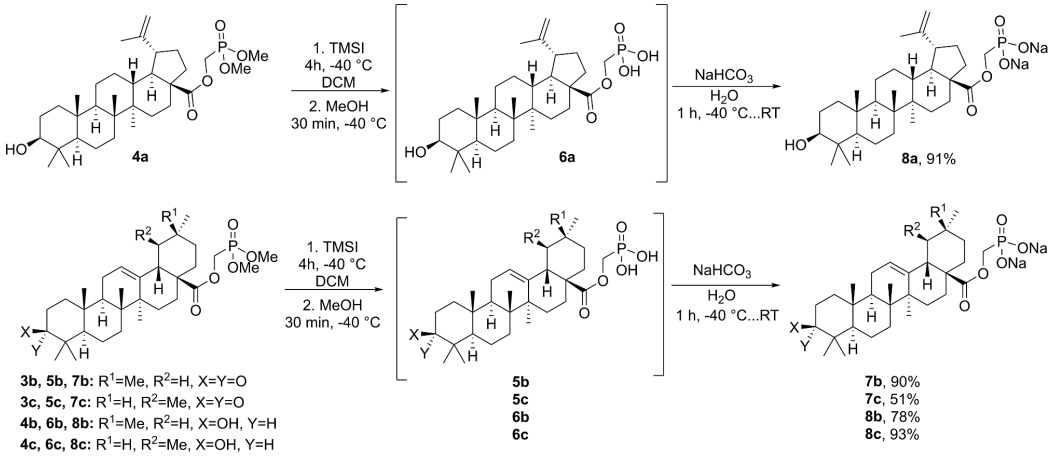



**Fig. 3**. Synthesis of triterpenic acid derived sodium phosphonates **7b**, **c** and **8a-c**.

the reaction mixture was found to be crucial (Table 1, entry 4). Therefore, sodium bicarbonate aqueous solution must be added subsequently at a lowered temperature, ensuring neutralization of HI and formation of sodium salt **7a**.

The developed demethylation conditions for the transformation **3a → 7a** were successfully applied on all other compound series consisting of betulinic acid derivative **4a** with free C(3)-OH group, 3-oxo-series of oleanolic and ursolic acid-derived phosphonates **3b**, **c** and their corresponding C(3)-OH derivatives **4b**, **c** (Fig. 3). The target products **7a-c** and **8a-c** were obtained in good to excellent yields and isolated by a simple precipitation/centrifugation approach.

As expected, the obtained products **7a-c** and **8a-c** were hydrolytically very stable and an eventual cleavage of the carboxylate ester bond was not observed even after heating under two different basic conditions: (1) 60 °C in 1.5 M NaOH/MeOH solution for 6 h; (2) 100 °C in the presence of 4 equiv. NaOH in $H_2O$ for 24 h. The obtained ionogenic derivatives revealed excellent water solubility, which can be nicely demonstrated by the acquisition of their $^1$H NMR spectra in $D_2O$ (Fig. 4).

Next, we investigated the installation of phosphonate moiety via an ether bond (Table 2). Starting with betulin, the most abundant natural PCT-3,28-diol, we examined a one-pot double alkylation possibility involving both hydroxyl groups. Application of such strong bases as NaH, *t*-BuOK, *n*-BuLi and MeMgBr in combination with (dimethoxyphosphoryl)methyl trifluoromethanesulfonate or tosylate were found to be ineffective (Table 2, entries 1–6). On many occasions we detected the degradation of alkylating reagent. To our delight, we have finally found that combining triflate alkylation reagent (2.2 equiv.) and betulin Li-dialkoxide

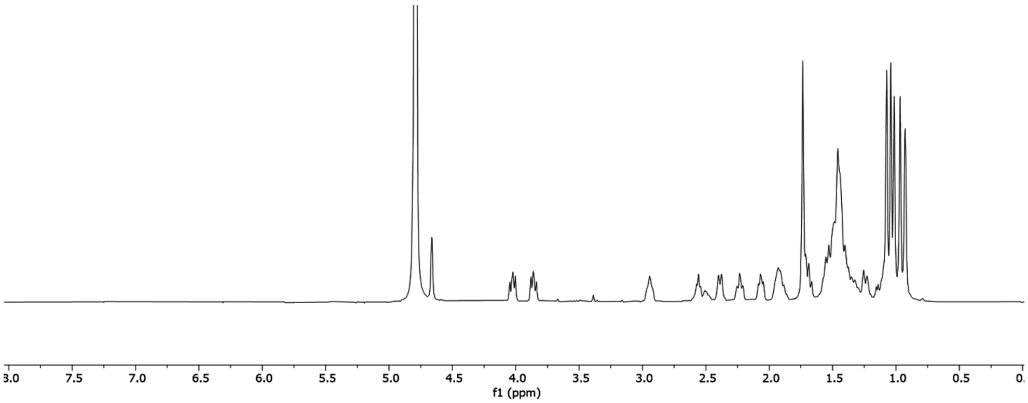
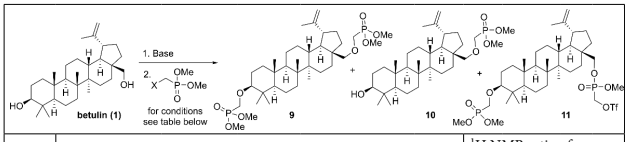



**Fig. 4**. $^{1}$H-NMR (500 MHz, $D_2O$) spectrum of 3-oxo-oleanolic acid-derived sodium phosphonate **7b** (5 mg/mL).




| Entry | Reaction conditions | | | | | $^{1}$H NMR ratio of products, % (isolated yield, %) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Base (equiv.) | X (equiv.) | Solvent | Temperature (°C) | Time (h) | **1** | **9** | **10** | **11** |
| 1. | NaH (2.0) | OTf (2.2) | THF | 0 °C → RT | 3 | 100 | 0 | 0 | 0 |
| 2. | *t*-BuOK (2.1) | OTf (2.2) | THF | RT → 50 °C | 3 | 100 | 0 | 0 | 0 |
| 3. | MeMgCl (2.2) | OTs (4.0) | THF | RT | 36 | 0 | 0 | 0 | 0 |
| 4. | MeMgCl (2.2) | OTs (4.0) | THF | 40 °C | 16 | 0 | 0 | 0 | 0 |
| 5. | MeMgCl (2.2) | OTs (4.0) | CyHex | 75 °C | 16 | 100 | 0 | 0 | 0 |
| 6. | *n*-BuLi (2.1) | OTf (2.5) | THF | -78 °C → RT | 3 | 0 | 10 | 41 | 49 |
| 7. | LDA (2.4) | OTf (2.6) | THF | -78 °C – RT | 3 | 0 | 6 | 72 | 22 |
| 8. | LDA (2.4) | OTf (2.2) | THF | -78 °C → RT | 3 | 0 | 40(14) | 42 | 18 |
| **9.** | **LDA (2.1)** | **OTf (2.2)** | **THF** | **-78 °C → RT** | **3** | **0** | **51(29)** | **20** | **29** |
| 10. | LDA (2.1) | OTf (2.1) | THF | -78 °C → -30 °C | 3 | 61 | 9 | 24 | 6 |
| 11. | LDA (2.1) | Br (2.1) | THF | -78 °C → RT | 3 | 0 | 0 | 0 | 0 |

**Table 2**. Method development for the synthesis of tetramethyl bis-phosphonate **9**.

arising from LDA (lithium diisopropylamide) (2.1 equiv.) provided the expected product **9** in 29% isolated yield (Table 2, entry 9). The desired product **9** was accompanied by the C(28)-*O*-monoalkylation product **10** and C(28)-*O*-phosphonylation product **11** in the **9**:**10**:**11** ratio 51:20:29 (by NMR). The latter arises from the alkoxide attack on the phosphorous center due to the presence of two competing electrophilic reaction centers in (dimethoxyphosphoryl)methyl trifluoromethanesulfonate. The obtained tetramethyl bis-phosphonate **9** was converted to tetrasodium salt (78%) using the previously developed TMSI conditions (Fig. 5).

## Compound solubility and cytotoxicity evaluation

The obtained PCT-derived sodium phosphonates were subjected to water solubility tests (Table 3). For this purpose, we used a quantitative $^{1}$H-NMR approach in $D_2O$, using potassium hydrogen phthalate as an external standard (for experimental details see Supporting Information). The presence of the basic forms of phosphonates[80] was ensured by the careful addition of NaOD, maintaining pH 8.0–8.5 during the quantification, which is 2–3 units higher than the pKa of phosphonic acid disalt[81]. As expected, our newly designed phosphonates **7a-c**, **8a-c** and **12** exhibited excellent aqueous solubility in a range from 3 to 26 mg/mL (pH 8.0–8.5). This is by at least two to three orders of magnitude higher than the reported solubilities of the parent natural triterpenic

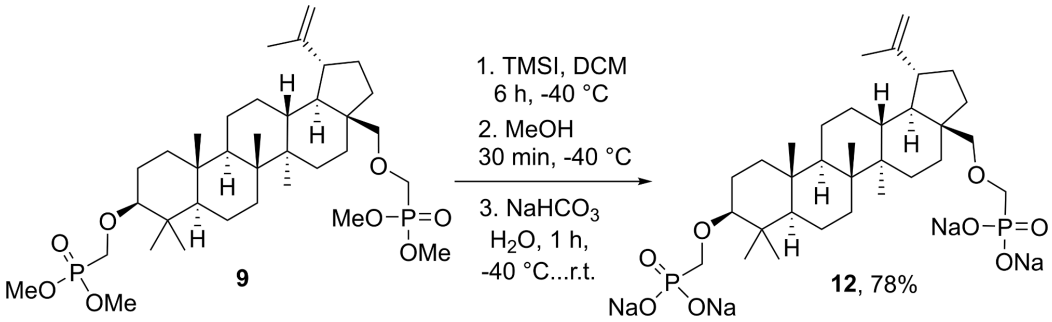



**Fig. 5**. Synthesis of betulin-derived tetrasodium bis-phosphonate **12**.

acids. For example, aqueous solubility of oleanolic and betulinic acids are < 0.1 μg/mL at neutral pH and can be increased to 42.1 μg/mL for betulinic acid and 99.5 μg/mL for oleanolic acid at pH 11.8[31]. Also, parent ursolic acid exhibits a similarly low aqueous solubility[29], which can be enhanced to some extent by various modern drug delivery systems[26–28]. Indeed, phosphonic acids are more acidic and easier ionizable than carboxylic acids. This ionic character helps to increase the aqueous solubility as exemplified by here described compounds. On the other hand, a direct numerical comparison of the aqueous solubility of compounds **7a-c**, **8a-c** and **12** with the reported triterpenoid phosphate/phosphonate analogs[51–60] is burdened as most of the previous reports describe the obtained enhanced solubility in a qualitative manner.

All target compounds were studied to determine their cytotoxic activity at various concentrations of each compound (10–50 μM) against human-derived osteosarcoma cell line MG-63 (ATCC, CRL-1427) and mouse-derived preosteoblast cell line MC3T3-E1 (ATCC, CRL-2593) (Table 4 and Figures S1-S4 in the Supporting Information). For the comparison, naturally occurring betulinic, oleanolic (**1b**) and ursolic (**1c**) acids as well as their 3-oxo analogs **2a-c** and doxorubicin, were also subjected to the cytotoxicity tests. As expected, the designed water-soluble PCT-derived phosphonates and the natural triterpenic acids, including their 3-oxo-analogs, were harmless to the MC3T3-E1 cells. As an interesting observation and exception should be mentioned the concentration-dependent cell viability drop of MC3T3-E1 cells in the presence of oleanonic acid (0.49 ± 0.12 relative metabolic activity at 50 μM of **2b**). To a lesser extent, ursonic acid affected the metabolic activity of MC3T3-E1 cells (0.72 ± 0.09 relative metabolic activity at 50 μM of **2c**).

Nevertheless, in the presence of oleanonic acid-derived phosphonate **8b** the MG-63 cell line revealed somewhat lower metabolic activity (0.73 ± 0.05 relative metabolic activity at 50 μM of **8b**) than in the presence of its parental oleanonic acid (1.03 ± 0.18 for **2b**). It is interesting to note that ursolic acid (**1c**) and ursonic acid (**2c**) showed a cytotoxic effect towards MG-63 cell line in the cell viability tests (0.28 ± 0.04 and 0.67 ± 0.04 relative metabolic activity at 50 μM of **1c** and **2c**, respectively).

In summary, we have developed a practical synthetic approach for introduction of the simplest phosphonate moiety, containing only single methylene group, into the PCT core via an ester and an ether bond. The corresponding TMSI induced phosphonate demethylation, which provided the target sodium phosphonates, was optimized for a preparative application avoiding acid promoted cationic rearrangements of the triterpenic core. Phosphonate disodium salts were obtained and characterized for the pentacyclic triterpenoids in the betulinic, oleanolic and ursolic acid series, including their 3-oxo-derivatives. All target compounds possess excellent aqueous solubility (3–26 mg/mL at pH 8.0–8.5), which was properly quantified by qNMR. Thus, this report stands out with the sample $^{1}$H NMR spectra of pentacyclic triterpenoid derivatives acquired in $D_2O$. The preliminary cytotoxicity evaluation of the target products revealed that the obtained PCT-derived sodium phosphonates do not possess significant cytotoxicity profile towards normal cells. This fact provides a promising possibility for future studies of these and similar phosphonate derivatives in those biological activity domains that require high selectivity between normal mammalian cells and external factors, such as viral, bacterial and fungal pathogens. Due to their non-toxic nature the title compounds classify also for further studies in the field of antidiabetic and anti-inflammatory agents.

## Methods

### Synthesis: general information

Solvents for the reactions were dried over standard drying agents and freshly distilled prior to use. All purchased chemicals (Fluka, Aldrich) were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 $F_{254}$ and visualized by using UV lamp. Column chromatography was performed on silica gel (60 Å, 40–63 μm, ROCC). Flash column chromatography was performed on a Büchi Sepacore system (Büchi-Labortechnik GmbH, Essen, Germany) with a Büchi Control Unit C-620, an UV detector Büchi UV photometer C-635, Büchi fraction collector C-660 and two Pump Modules C-605. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker 300 and 500 MHz, in $CDCl_3$ or [$D_4$]MeOD at 25 °C. Chemical shifts (δ) values are reported in ppm. The residual solvent peaks are used as internal reference ($CDCl_3$) 7.26 ppm, [$D_4$]MeOD 3.31 ppm for $^{1}$H NMR, $CDCl_3$ 77.16 ppm, [$D_4$]MeOD 49.00 ppm for $^{13}$C NMR), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); *J* in

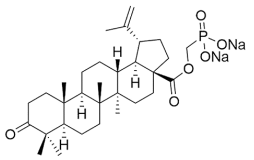
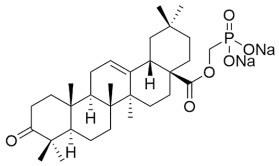
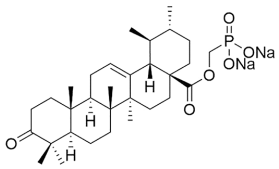
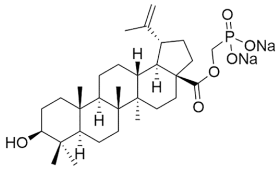
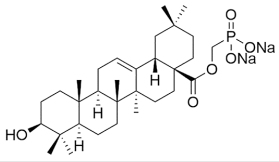
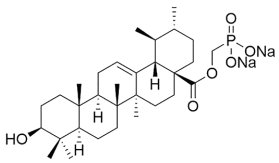
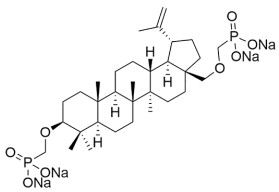
| Compound number | Structural formula | Aqueous solubility (mg/mL) in $D_2O$ at pH 8.0…8.5 |
|---|---|---|
| **7a** |  | 11 |
| **7b** |  | 8 |
| **7c** |  | 26 |
| **8a** |  | 3 |
| **8b** |  | 7 |
| **8c** |  | 7 |
| **12** |  | 3 |

**Table 3**. Aqueous solubility data of PCT-derived sodium phosphonates at pH 8.0…8.5.

hertz. $^{1}H$ and $^{13}C$ NMR peaks were assigned by analysis of multidimensional NMR (COSY, HSQC, HMBC). For $^{31}P$ NMR calibration, $Ph_3P$ was used as external reference (-6.00 ppm in $MeOD_{d4}$) in a coaxially inserted tube. High-resolution massspectra (ESI) were performed on Agilent 1290 Infinity series UPLC connected to Agilent 6230 TOF mass spectrometer (calibration at m/z 121.050873 and m/z 922.009798). Optical rotation was measured at 20 °C on Anton Paar MCP 500 polarimeter (1-cm cell) using multi-wavelength analysis (589 nm, 546 nm, 436 nm, 405 nm, 365 nm).

| Compound | Relative metabolic activity of MG-63 cells at given concentrations of PCTs | | | Relative metabolic activity of MC3T3-E1 cells at given concentrations of PCTs | | |
|---|---|---|---|---|---|---|
| | 50 µM | 25 µM | 10 µM | 50 µM | 25 µM | 10 µM |
| Betulinic acid | 1.12 ± 0.08 | 0.91 ± 0.14 | 0.74 ± 0.16 | 0.97 ± 0.07 | 0.56 ± 0.04 | 0.76 ± 0.07 |
| Betulonic acid (**2a**) | 0.88 ± 0.08 | 0.96 ± 0.04 | 1.14 ± 0.02 | 1.22 ± 0.01 | 1.70 ± 0.05 | 1.39 ± 0.06 |
| **7a** | 1.09 ± 0.04 | 1.30 ± 0.06 | 1.10 ± 0.04 | 1.13 ± 0.03 | 1.27 ± 0.05 | 1.41 ± 0.01 |
| **8a** | 1.59 ± 0.17 | 1.24 ± 0.25 | 1.58 ± 0.05 | 1.01 ± 0.05 | 1.19 ± 0.04 | 1.08 ± 0.05 |
| Oleanolic acid (**1b**) | 1.29 ± 0.11 | 1.58 ± 0.13 | 0.77 ± 0.14 | 0.96 ± 0.05 | 0.97 ± 0.08 | 1.04 ± 0.07 |
| Oleanonic acid (**2b**) | 1.03 ± 0.18 | 1.60 ± 0.03 | 1.51 ± 0.08 | 0.49 ± 0.12 | 0.99 ± 0.05 | 1.10 ± 0.01 |
| **7b** | 1.19 ± 0.05 | 1.32 ± 0.05 | 1.13 ± 0.08 | 1.04 ± 0.05 | 1.50 ± 0.04 | 1.31 ± 0.08 |
| **8b** | 0.73 ± 0.05 | 0.76 ± 0.04 | 0.84 ± 0.04 | 0.86 ± 0.08 | 0.97 ± 0.04 | 1.00 ± 0.03 |
| Ursolic acid (**1c**) | 0.28 ± 0.04 | 0.64 ± 0.03 | 0.66 ± 0.03 | 0.99 ± 0.08 | 0.83 ± 0.05 | 1.06 ± 0.05 |
| Ursonic acid (**2c**) | 0.67 ± 0.04 | 0.67 ± 0.04 | 0.76 ± 0.08 | 0.72 ± 0.09 | 1.07 ± 0.07 | 0.74 ± 0.02 |
| **7c** | 1.12 ± 0.03 | 0.98 ± 0.04 | 0.96 ± 0.04 | 0.94 ± 0.05 | 0.90 ± 0.03 | 0.91 ± 0.06 |
| **8c** | 1.26 ± 0.08 | 0.91 ± 0.05 | 1.22 ± 0.09 | 0.95 ± 0.03 | 0.89 ± 0.04 | 0.93 ± 0.09 |
| **12** | 0.94 ± 0.04 | 0.89 ± 0.05 | 0.97 ± 0.08 | 0.92 ± 0.04 | 0.93 ± 0.06 | 0.90 ± 0.07 |
| Doxorubicin | 0.16 ± 0.02 | 0.19 ± 0.01 | 0.41 ± 0.02 | 0.53 ± 0.03 | 0.60 ± 0.03 | 0.72 ± 0.07 |
| Positive control | 1.42 ± 0.03 | | | 1.10 ± 0.10 | | |
| Negative control | 0.16 ± 0.08 | | | 0.28 ± 0.12 | | |

**Table 4**. Cell metabolic activity data in the presence of the title phosphonates and their comparison to naturally occuring PCTs and doxorubicin.

## General procedure I for the synthesis of 3-oxo-triterpenic acid esters, process 2a-c → 3a-c

To solution of 3-oxo-triterpenic acid **2a-c** (500 mg, 1.099 mmol, 1 eq.) in anhydrous THF (5 mL) *t*BuOK (185 mg, 1.649 mmol, 1 eq.) is added portion wise at -5 °C. The resulting reaction mixture is stirred in ambient temperature for 30 min, then warmed up to room temperature and stirred for additional 60 min. The obtained mixture is re-cooled to -5 °C and a solution of previously prepared (dimethoxyphosphoryl)methyl trifluoromethanesulfonate (629 mg, 2.198 mmol, 2 eq.) in anhydrous THF (5 mL) is added dropwise. Then the resulting reaction mixture is warmed up to room temperature and stirred for 12 h. The reaction mixture is evaporated to dryness, redissolved in EtOAc (70 mL) and washed with brine (3 × 10 mL). Separated organic layer is dried over anhydrous $Na_2SO_4$. After filtration, the filtrate is concentrated *in vacuo* and purified by silica column chromatography (Hexanes-EtOAc 9:1 → 1:1) to yield carboxylic ester as a white amorphous solid: **3a** (78%, 495 mg); **3b** (61%, 387 mg), **3c** (71%, 450 mg).

### 3-oxo-(17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-28-norlup-20(29)-ene 3a

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.73 (s, 1H, $H_a$-C(29)), 4.60 (s, 1H, $H_b$-C(29)), 4.48 (dd, $^2J$ = 14.6, 8.3 Hz, 1H, $H_a$-C(28')), 4.39 (dd, $^2J$ = 14.6, 8.2 Hz, 1H, $H_b$-C(28')), 3.81 (d, $^3J$ = 10.9, 6 H, $(OMe)_2$), 2.98 (td, $^3J$ = 11.1, 4.8 Hz, 1H, H_C(19)), 2.48 (ddd, $^2J$ = 15.5 Hz, $^3J$ = 9.8, 7.5 Hz, 1H, $H_a$-C(2)), 2.39 (ddd, $^2J$ = 15.5 Hz, $^3J$ = 7.6, 4.4 Hz, 1H, $H_b$-C(2)), 2.31–2.19 (m, 2H, $H_a$-C(16), H-C(13)), 1.96–1.82 (m, 4 H, $H_a$-C(15), $H_a$-C(21), $H_a$-C(22), $H_a$-C(1)), 1.76–1.69 (m, 1H, $H_a$-C(12)), 1.68 (s, 3H, $H_3$-C(30)), 1.62 (t, $^3J$ = 11.4 Hz, 1H, H-C(18)), 1.54–1.34 (m, 9 H, $H_2$-C(6), $H_a$-C(11), $H_2$-C(7), $H_b$-C(21), $H_b$-C(1), H-C(9), $H_b$-C(16)), 1.34–1.14 (m, 4 H, $H_b$-C(11), $H_b$-C(15), $H_b$-C(22), H-C(5)), 1.06 (s, 3H, $H_3$-C(23)), 1.06–1.01 (m, 1H, $H_b$-C(12)), 1.01 (s, 3H, $H_3$-C(24)), 0.97 (s, 3H, $H_3$-C(27)), 0.96 (s, 3H, $H_3$-C(26)), 0.92 (s, 3H, $H_3$-C(25)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 218.25 (C3), 174.91 (d, $^3J$ = 6.4 Hz, (C28)), 150.34 (C20), 109.96 (C29), 56.90 (C17), 55.18 (d, $^1J$ = 167.4 Hz), 55.10 (C5), 53.20 (d, $^2J$ = 6.2 Hz, MeO), 53.18 (d, $^2J$ = 6.2 Hz, MeO), 50.04 (C9), 49.49 (C18), 47.46 (C4), 46.90 (C19), 42.61 (C14), 40.77 (C10), 39.77 (C1), 38.44 (C13), 37.04 (C21), 37.00 (C10), 34.26 (C2), 33.75 (C7), 32.03 (C16), 30.53 (C22), 29.65 (C15), 26.74 (C23), 25.65 (C12), 21.54 (C11), 21.15 (C24), 19.76 (C30), 19.47 (C6), 16.10 (C25), 15.85 (C26), 14.74 (C27). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.77. HRMS: [$C_{33}H_{53}O_6P$ + $H^+$] 577.3653; found 577.3626 (4.7 ppm). $[\alpha]_D^{20} = +0.19$; $[\alpha]_{546}^{20} = +0.23$; $[\alpha]_{436}^{20} = +0.50$; $[\alpha]_{405}^{20} = +0.66$; $[\alpha]_{365}^{20} = +1.02$ (c = 1.00, MeOH).

### 3-oxo-(17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-28-norolean-12(13)-ene 3b

$^1$H NMR (500 MHz, $CDCl_3$): δ 5.32 (t, $^3J$ = 3.6 Hz, 1H, H-C(12)), 4.42 (dd, $^2J$ = 14.0, 8.6 Hz, 1H, $H_a$-C(28`)), 4.32 (dd, $^2J$ = 14.0, 8.6 Hz, 1H, $H_b$-C(28`)), 3.81 (d, $^2J$ = 10.8 Hz, 6 H, $(MeO)_2$), 2.88 (dd, $^3J$ = 14.0, 4.3 Hz, 1H, H-C(18)), 2.55 (ddd, $^2J$ = 15.9 Hz, $^3J$ = 11.2, 7.2 Hz, 1H, $H_a$-C(2)), 2.36 (ddd, $^2J$ = 15.9 Hz, $^3J$ = 6.8, 3.6 Hz, 1H, $H_b$-C(2)), 2.01 (dt, $^2J$ = 14.0 Hz, $^3J$ = 4.3 Hz, 1H, $H_a$-C(16)), 2.00–1.90 (m, 2H, $H_2$-C(11)), 1.88 (ddd, $^2J$ = 13.2 Hz, $^3J$ = 7, 3.6 Hz, 1H, $H_a$-C(1)), 1.72 (dt, 1H, $^2J$ = 13.6 Hz, $^3J$ = 4.1 Hz, $H_a$-C(22)), 1.69–1.53 (m, 5 H, $H_b$-C(16), $H_a$-C(19), H-C(9), $H_a$-C(7), $H_a$-C(15)), 1.52–1.47 (m, 3H, $H_2$-C(6), $H_b$-C(7)), 1.40 (dt, $^2J$ = 12.3 Hz, $^3J$ = 6.0 Hz, 1H, $H_b$-C(1)), 1.35–1.28 (m, 4 H, $H_b$-C(22), $H_a$-C(21), H-C(5), $H_b$-C(6)), 1.26–1.08 (m, 3H, $H_b$-C(21), $H_b$-C(19), $H_b$-C(15)), 1.14 (s, 3H, $H_3$-C(27)), 1.08 (s, 3H, $H_3$-C(23)), 1.04 (s, 6 H, $H_3$-C(24), $H_3$-C(25)), 0.92 (s,

3H, $H_3$-C(29)), 0.90 (s, 3H, $H_3$-C(30)), 0.78 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 217.90 (C(3)), 176.77 (d, $^3J$= 8.0 Hz, (C28)), 143.55 (C13), 122.65 (C12), 55.82 (d, $^1J$ = 168.7 Hz, (C28`)), 55.47 (C5), 53.24 (d, $^2J$= 6.4 Hz, $(MeO)_2$), 47.60 (C4), 47.25 (C17), 46.98 (C9), 45.90 (C19), 41.96 (C14), 41.54 (C18), 39.40 (C8), 39.29 (C1), 36.89 (C10), 34.31 (C2), 33.91 (C21), 33.16 (C30), 32.37 (C7), 32.32 (C22), 30.81 (C20), 27.75 (C15), 26.56 (C23), 25.87 (C27), 23.66 (C29), 23.65 (C11), 23.19 (C16), 21.63 (C24), 19.72 (C6), 16.95 (C26), 15.18 (C25). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.74. HRMS: $[C_{33}H_{53}O_6P+H^+]$ 577.3653; found 577.3626 (4.7 ppm). $[\alpha]_D^{20} = +0.66$; $[\alpha]_{546}^{20} = +0.79$; $[\alpha]_{436}^{20} = +1.38$; $[\alpha]_{405}^{20} = +1.70$; $[\alpha]_{365}^{20} = +2.28$ (c = 1.00, MeOH).

## 3-oxo-(17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-28-norurs-12(13)-ene 3c

$^1$H NMR (500 MHz, $CDCl_3$) δ 5.29 (d, $^3J$ = 3.8 Hz, 1H, H-C(12)), 4.33 (d, $^2J$ = 8.5 Hz, 2H, $H_2$-C(28')), 3.80 (d, $^3J$ = 10.8 Hz, 6 H, $(OMe)_2$), 2.55 (ddd, $^2J$ = 16.0 Hz, $^3J$ = 10.8, 7.5 Hz, 1H, $H_a$-C(2)), 2.37 (ddd, $^2J$ = 16.0 Hz, $^3J$ = 6.9, 3.6 Hz, 1H, $H_b$-C(2)), 2.25 (d, $^3J$ = 11.3 Hz, 1H, H-C(18)), 2.04 (td, $^2J$ = 14.4, $^3J$ = 6.5 Hz, 1H, $H_a$-C(16)), 1.99–1.92 (m, 2H, $H_2$-C(11)), 1.90 (ddd, $^2J$ = 12.0 Hz, $^3J$ = 7.4, 3.6 Hz, 1H, $H_a$-C(1)), 1.80–1.68 (m, 3H, $H_b$-C(16), $H_a$-C(15), $H_a$-C(21)), 1.65–1.55 (m, 2H, $H_b$-C(21), H-C(9)), 1.55–1.39 (m, 5 H, $H_2$-C(6), $H_a$-C(15), $H_a$-C(7), $H_b$-C(1)), 1.39–1.23 (m, 4 H, $H_b$-C(22), $H_b$-C(7), H-C(19, H-C(5)), 1.17–1.11 (m, 1H, $H_b$-C(15)), 1.09 (s, 3H, $H_3$-C(27)), 1.08 (s, 3H, $H_3$-C(28)), 1.04 (s, 6 H, $H_3$-C(24), $H_3$-C(25)), 1.04–0.98 (m, 1H, H-C(20)), 0.94 (d, $^3J$ = 6.3 Hz, 3H, $H_3$-C(30)), 0.86 (d, $^3J$ = 6.4 Hz, 3H, $H_3$-C(29)), 0.79 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 217.95 (C3), 176.62 (d, $^3J$ = 8.2 Hz, (C28)), 138.02 (C13), 125.83 (C12), 55.81 (d, $^1J$ = 168.9 Hz, (C28')), 55.13 (C5), 53,24 (d, $^2J$ = 6.1 Hz, (OMe)), 53.21 (d, $^2J$ = 6.1 Hz, (OMe)), 53.07 (C18), 48.64 (C17), 47.55 (C4), 46.86 (C9), 42.28 (C14), 39.60 (C8), 39.44 (C1), 39.17 (C19), 38.91 (C20), 36.79 (C10), 36.58 (C21), 34.31 (C2), 32.65 (C7), 30.68 (C22), 28.08 (C15), 26.67 (C23), 24.32 (C16), 23.59 (C27), 23.58 (C11), 21.63 (C24), 21.24 (C30), 19.71 (C6), 17.12 (C29), 17.05 (C26), 15.37 (C25). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.85. HRMS: $[C_{33}H_{53}O_6P+H^+]$ 577.3653; found 577.3623 (5.2 ppm). $[\alpha]_D^{20} = +0.50$; $[\alpha]_{546}^{20} = +0.58$; $[\alpha]_{436}^{20} = +0.97$; $[\alpha]_{405}^{20} = +1.23$; $[\alpha]_{365}^{20} = +1.62$ (c = 1.00, MeOH).

### General procedure II for synthesis of 3-hydroxy-triterpenic acid esters, process 3a-c → 4a-c

To solution of 3-oxo-triterpenoic acid ester **3a-c** (200 mg, 0.347, 1 eq.) in MeOH (4 mL) $NaBH_4$ (53 mg, 1.388 mmol, 4 eq.) is added portion wise at 0 °C. The resulting reaction mixture is stirred at ambient temperature for 5 h. Then the reaction mixture is quenched by $NH_4Cl$ saturated aqueous solution (2 mL), evaporated to dryness, redissolved in EtOAc (25 mL) and washed with brine (3 × 10 mL). The combined organic layer is dried over anhydrous $Na_2SO_4$. After filtration, the filtrate is concentrated *in vacuo* and purified by silica column chromatography (Hexanes-EtOAc 9:1 → 1:1) to yield product as a white amorphous solid: **4a** (99%, 198 mg); **4b** (96%, 193 mg); **4c** (92%, 185 mg).

## (17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-3β-hydroxy-28-norlup-20(29)-ene 4a

$^1$H NMR (500 MHz, $CDCl_3$) δ 6.02 (bs, 1H, OH), 4.73 (s, 1H, $H_a$-C(29)), 4.61 (s, 1H, $H_b$-C(29)), 4.48 (dd, $^2J$ = 14.7, 8.2 Hz, 1H, $H_a$-C(28')), 4.39 (dd, $^2J$ = 14.7, 8.2 Hz, 1H, $H_b$-C(28')), 3.81 (d, $^3J$ = 10.8 Hz, 6 H, $(OMe)_2$), 3.18 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H-C(3)), 2.98 (td, $^3J$ = 11.2, 4.7 Hz, 1H, H-C(19)), 2.30–2.34 (m, 1H, $H_a$-C(16)), 2.24–2.15 (m, 1H, H-C(13)), 1.98–1.83 (m, 2H, $H_a$-C(21), $H_a$-C(22)), 1.74–1.31 (m, 17 H, $H_a$-C(15), $H_3$-C(C30), $H_a$-C(12), H-C(18), $H_2$-C(6), $H_a$-C(11), $H_2$-C(7), $H_b$-C(21), $H_a$-C(1), H-C(9), $H_b$-C(16), $H_2$-C(2)), 1.31–1.13 (m, 3H, $H_b$-C(11), $H_b$-C(15), $H_b$-C(22)), 1.08–0.99 (m, 1H, $H_b$-C(12)), 0.96 (s, 6 H, $H_3$-C(27), $H_3$-C(26)), 0.92 (s, 3H, $H_3$-C(23)), 0.90–0.85 (m, 1H, $H_b$-C(1)), 0.82 (s, 3H, $H_3$-C(25)), 0.75 (s, 3H, $H_3$-C(24)), 0.68 (d, $^3J$ = 9,4 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.97 (d, $^3J$ = 6.4 Hz, (C28)), 150.46 (C20), 109.91 (C29), 79.12 (C3), 56.96 (C17), 55.0 (C5), 55.17 (d, $^1J$ = 167.4 Hz, C(28')), 53.20 (d, $^2J$ = 6.1 Hz, (MeO)), 53.17 (d, $^2J$ = 6.1 Hz, (MeO)), 50.70 (C9), 49.58 (C18), 46.96 (C19), 42.58 (C14), 40.85 (C8), 39.01 (C4), 38.88 (C1), 38.39 (C13), 37.35 (10), 37.05 (C21), 34.48 (C7), 32.12 (C16), 30.57 (C22), 29.70 (C15), 28.13 (C23), 27.55 (C2), 25.67 (C12), 21.03 (C11), 19.49 (C30), 18.44 (C6), 16.30 (C25), 16.07 (C26), 15.50 (C24), 14.85 (C27). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.88. HRMS: $[C_{33}H_{55}O_6P+H^+]$ 579.3809; found 579.3782 (4.7 ppm). $[\alpha]_D^{20} = -0.01$; $[\alpha]_{546}^{20} = -0.01$; $[\alpha]_{436}^{20} = +0.01$; $[\alpha]_{405}^{20} = +0.02$; $[\alpha]_{365}^{20} = +0.02$ (c = 1.00, MeOH).

## (17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-3β-hydroxy − 28-norolean-12(13)-ene 4b

$^1$H NMR (500 MHz, $CDCl_3$) δ 5.30 (t, $^3J$ = 3.6 Hz, 1H, H-C(13)), 4.41 (dd, $^2J$ = 14.6, 8.7 Hz, 1H, $H_a$-C(28')), 4.31 (dd, $^2J$ = 14.6, 8.3 Hz, 1H, $H_b$-C(28')), 3.80 (d, $^3J$ = 10.9 Hz, 6 H, $(OMe)_2$), 3.25–3.17 (m, 1H, H-C(3)), 2.90–2.81 (m, 1H, H-C(18)), 2.07–1.95 (m, 1H, $H_a$-C(16)), 1.91–1.85 (m, 2H, $H_2$-C(11)), 1.77–1.16 (m, 16 H, $H_2$-C(6), $H_b$-C(16), $H_2$-C(2), $H_a$-C(15), $H_2$-C(22), $H_2$-C(7), $H_2$-C(21), H-C(9), $H_a$-C(1), $H_2$-C(19)), 1.13 (s, 3H, $H_3$-C(27)), 1.09 (d, $^2J$ = 14.0 Hz, 1H, $H_b$-C(15)), 0.98 (s, 3H, $H_3$-C(23)), 0.98–0.92 (m, 1H, $H_b$-C(1)), 0.92 (s, 3H, $H_3$-C(29)), 0.90 (s, 6 H, $H_3$-C(30), $H_3$-C(25)), 0.78 (s, 3H, $H_3$-C(24)), 0.77–0.72 (m, 1H, H-C(5)), 0.72 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.81 (d, $^3J$ = 7.8 Hz, (C28)), 143.49 (C12), 122.89 (C12), 79.16 (C3), 55.92 (d, $^1J$ = 169.5 Hz, (C28')), 55.13 (C5)), 53.23 (d, $^2J$ = 6.3 Hz, (OMe)), 53.23 (d, $^2J$ = 6.3 Hz, (OMe)), 47.73 (C9), 47.24 (C17), 45.97 (C19), 41.85 (C14), 41.48 (C18), 39.43 (C8), 38.90 (C4), 38.60 (C1), 37.18 (C10), 33.93 (C21), 33.18 (C30), 32.86 (C7), 32.38 (C22), 30.81 (C20), 28.25 (C23), 27.77 (C15), 27.34 (C2), 25.99 (C27), 23.69 (C29), 23.57 (C11), 23.21 (C16), 18.48 (C6), 17.02 (C26), 15.72 (C24), 15.48 (C25). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.77. HRMS: $[C_{33}H_{55}O_6P+NH_4^+]$ 596.4075; found 596.4042 (5.5 ppm). $[\alpha]_D^{20} = +0.38$; $[\alpha]_{546}^{20} = +0.46$; $[\alpha]_{436}^{20} = +0.79$; $[\alpha]_{405}^{20} = +0.97$; $[\alpha]_{365}^{20} = +1.27$ (c = 1.00, MeOH).

**(17 S)-17-(((dimethoxyphosphoryl)methoxy)carbonyl)-3β-hydroxy-28-norurs-12(13)-ene 4c**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 5.26 (bs, 1H, H-C(13)), 4.33 (d, $^{2}J$ = 8.4 Hz, 2H, $H_2$-C(28')), 3.80 (d, $^{3}J$ = 10.8 Hz, 6 H, $(OMe)_2$), 3.21 (dd, $^{3}J$ = 11.3, 4.6 Hz, 1H, H-C(3)), 2.23 (d, $^{3}J$ = 11.3 Hz, 1H, H-C(18)), 2.10–1.99 (m, 1H, $H_a$-C(16)), 1.95–1.84 (m, 2H, $H_2$-C(11)), 1.79–1.68 (m, 3H, $H_b$-C(16), $H_a$-C(15), $H_a$-C(21)), 1.67–1.22 (m, 12 H, $H_b$-C(21), $H_a$-C(1), $H_2$-C(2), $H_2$-C(6), $H_2$-C(7), $H_2$-C(22), H-C(9), H-C(19)), 1.13–1.08 (m, 1H, $H_b$-C(15)), 1.08 (s, 3H, $H_3$-C(27)), 1.04–0.99 (m, 1H, H-C(20)), 0.99 (s, 3H, $H_3$-C(23)), 0.99–0.94 (m, 1H, $H_b$-C(1)), 0.94 (d, $^{3}J$ = 6,3 Hz, 3H, $H_3$-C(30)), 0.92 (s, 3H, $H_3$-C(25)), 0.86 (d, $^{3}J$ = 6.6 Hz, 3H, $H_3$-C(29)), 0.78 (s, 3H, $H_3$-C(24)), 0.73 (s, 3H, $H_3$-C(26)), 0.73–0.69 (m, 1H, H-C(5)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.66 (d, $^{3}J$ = 8.3 Hz, (C28)), 137.93 (C12), 126.08 (C13), 79.18 (C3), 55.81 (d, $^{1}J$ = 168.9 Hz, (C28')), 55.36 (C5), 53.25 (d, $^{2}J$ = 6.4 Hz, (MeO)), 53.25 (d, $^{2}J$ = 6.4 Hz, (MeO)), 53.03 (C18), 48.63 (C17), 47.67 (C9), 42.18 (C14), 39.65 (C8), 39.19 (C19), 38.95 (C20), 38.90 (C4), 38.77 (C1), 37.11 (C10), 36.64 (C21), 33.15 (C7), 30.72 (C22), 28.28 (C23), 28.12 (C25), 27.37 (C2), 24.37 (C16), 23.70 (C27), 23.45 (C11), 21.28 (C30), 18.46 (C6), 17.13 (C26), 17.09 (C29), 15.76 (C24), 15.62 (C25). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 21.77. HRMS: $[C_{33}H_{55}O_6P+H^+]$ 579.3809; found 579.3781 (4.8 ppm). $[\alpha]_D^{20} = +0.36$; $[\alpha]_{546}^{20} = +0.43$; $[[\alpha]_{436}^{20} = +0.76$; $[\alpha]_{405}^{20} = +0.92$; $[\alpha]_{365}^{20} = +1.20$ (c = 1.00, MeOH).

**General procedure III for demethylation of phosphonic esters, processes 3a-b → 7a-c and 4a-c → 8a-c**

To solution of 3-oxo-triterpenic acid ester **3a-c** or 3-hydroxy-triterpenoic acid ester **4a-c** (0.4 mmol, 1 eq.) in anhydrous DCM (5 mL) TMSI (171 µL 1.2 mmol, 3 eq.) is added dropwise at -40 °C and the resulting reaction mixture is stirred at -40 °C for 5 h. Then MeOH (2.5 mL) is added dropwise at -40 °C. The obtained mixture is stirred for additional 30 min at the same temperature and solution of $NaHCO_3$ (101 mg, 1.2 mmol, 3 eq.) in $H_2O$ (4 mL) is added dropwise at -40 °C. The resulting reaction mixture is warmed up to room temperature and the organic solvents are evaporated *in vacuo*. The obtained aqueous suspension is centrifuged and the supernatant is removed and discarded. The precipitate is re-suspended in deionized water (1 mL) and the centrifugation – supernatant removal procedure is repeated additional two times (in total: washing with water 3 × 1mL). The obtained precipitated is dried at ambient temperature *in vacuo*: **7a** ( 97%, 230 mg); **7b** (90%, 214 mg); **7c** (51%, 121 mg); **8a** (91%, 217 mg); **8b** (78%, 186 mg); **8c** (93%, 222 mg).

**Sodium (3-oxo-(17R)-17-28-norlup-20(29)-en)-2-oxoethyl-phosphonate 7a**

$^{1}$H NMR (500 MHz, $MeOD_{d4}$) δ 4.72 (s, 1H, $H_a$-C(29)), 4.58 (s, 1H, $H_b$-C(29)), 4.16 (dd, $^{2}J$ = 13.1, 8.7 Hz, 1H, $H_a$-C(28')), 3.90 (dd, $^{2}J$ = 13.1, 8.4 Hz, 1H, $H_b$-C(29)), 3.02 (td, $^{3}J$ = 11.2, 4.4 Hz, 1H, H-C(19)), 2.58–2.36 (m, 4 H, $H_2$-C(2), H-C(13), $H_a$-C(16)), 2.24 (dd, $^{3}J$ = 11.7, 8.1 Hz, 1H, $H_a$-C(21)), 2.00–1.86 (m, 2H, $H_a$-C(21), $H_b$-C(22)), 1.76 (d, $^{3}J$ = 13.0 Hz, 1H, $H_a$-C(12)), 1.69 (s, 3H, $H_3$-C(30)), 1.63 (t, $^{3}J$ = 11.3 Hz, 1H, H-C(18)), 1.57–1.27 (m, 13H, $H_2$-C(6), $H_2$-C(11), $H_a$-C(7), $H_a$-C(15), $H_b$-C(22), $H_b$-C(16), $H_b$-C(1), H-C(9), $H_b$-C(21), H-C(5)), 1.23–1.15 (m, 1H, $H_b$-C(22)), 1.13–1.06 (m, 1H, $H_b$-C(12)), 1.06 (s, 3H, $H_3$-C(23)), 1.02 (s, 3H, $H_3$-C(24)), 1.01 (s, 3H, $H_3$-C(27)), 1.00 (s, 3H, $H_3$-C(26)), 0.95 (s, 3H, $H_3$-C(25)). $^{13}$C NMR (126 MHz, $MeOD_{d4}$) δ 221.02 (C3), 176.99 (d, $^{3}J$ = 8.4 Hz, (C28)), 151.94 (C20), 110.22 (C29), 59.92 (d, $^{1}J$ = 162.6 Hz, (C28')), 57.99 (C17), 56.11 (C5), 51.23 (C9), 50.68 (C18), 48.31 (C19), 43.61 (C14), 41.87 (C8), 40.70 (C4), 39.60 (C11), 38.06 (C13), 37.79 (C10), 35.05 (C21), 34.74 (C7), 34.72 (C16), 32.92 (C2), 31.61 (C22), 30.88 (C15), 27.17 (C23), 26.89 (C12), 22.62 (C11), 21.43 (C24), 20.76 (C6), 19.55 (C30), 16.54 (C26), 16.35 (C25), 15.03 (C27). $^{31}$P NMR (121 MHz, $MeOD_{d4}$) δ 14.20. HRMS: $[C_{31}H_{49}O_6P\text{-}H^+]$ 547.3194; found 547.3198 (0.7 ppm). $[\alpha]_D^{20} = +0.16$; $[\alpha]_{546}^{20} = +0.19$; $[[\alpha]_{436}^{20} = +0.38$; $[\alpha]_{405}^{20} = +0.51$; $[\alpha]_{365}^{20} = +0.80$ (c = 1.00, MeOH).

**Sodium (3-oxo-(17R)-17-28-norolean-12(13)-en)-2-oxoethyl-phosphonate 7b**

$^{1}$H NMR (500 MHz, $MeOD_{d4}$) δ 5.30 (d, $^{3}J$ = 3.7 Hz, 1H, H-C(13)), 4.21–4.09 (m, 2H, $H_2$-C(28')), 2.92 (dd, $^{3}J$ = 14.1, 4.5 Hz, 1H, H-C(18)), 2.57 (ddd, $^{2}J$ = 16.1 Hz, $^{3}J$ = 10.8, 7.4 Hz, 1H, $H_a$-C(2)), 2.37 (ddd, $^{2}J$ = 16.1 Hz, $^{3}J$ = 7.1, 3.6 Hz, 1H, $H_b$-C(2)), 2.09–1.86 (m, 4 H, $H_a$-C(16), $H_2$-C(11), $H_a$-C(1)), 1.84–1.60 (m, 6 H, $H_b$-C(16), $H_a$-C(15), $H_2$-C(22), $H_a$-C(19), H-C(9)), 1.59–1.32 (m, 7 H, $H_2$-C(6), $H_2$-C(7), $H_a$-C(21), $H_b$-C(1), H-C(5)), 1.21 (d, $^{2}J$ = 13.2 Hz, 1H, $H_b$-C(21)), 1.18 (s, 3H, $H_3$-C(27)), 1.16–1.09 (m, 2H, $H_b$-C(15), $H_b$-C(19)), 1.08 (s, 6 H, $H_3$-C(23), $H_3$-C(25)), 1.05 (s, 3H, $H_3$-C(24)), 0.95 (s, 3H, $H_3$-C(29)), 0.91 (s, 3H, $H_3$-C(30)), 0.83 (s, 3H, $H_3$-C(25)). $^{13}$C NMR (126 MHz, $MeOD_{d4}$) δ 220.52 (C3), 180.23 (d, $^{3}J$ = 9.0 Hz, (C28)), 145.38 (C12), 123.35 (C13), 60.43 (d, $^{1}J$ = 162.8 Hz, (C28')), 56.60 (C5), 48.83 (C4), 48.53 (C17), 48.26 (C9), 47.32 (C19), 42.98 (C14), 42.93 (C18), 40.56 (C8), 40.27 (C1), 37.92 (C10), 35.11 (C2), 35.00 (C21), 33.64 (C30), 33.38 (C7), 33.10 (C22), 31.58 (C20), 29.14 (C15), 26.96 (C23), 26.30 (C27), 24.59 (C11), 24.15 (C29), 23.78 (C16), 21.90 (C24), 20.73 (C6), 17.54 (C26), 15.53 (C25). $^{31}$P NMR (121 MHz, $MeOD_{d4}$) δ 11.54. HRMS: $[C_{31}H_{49}O_6P\text{-}H^+]$ 547.3194; found 547.3194 (0 ppm). $[\alpha]_D^{20} = +0.47$; $[\alpha]_{546}^{20} = +0.56$; $[[\alpha]_{436}^{20} = +0.98$; $[\alpha]_{405}^{20} = +1.22$; $[\alpha]_{365}^{20} = +1.65$ (c = 1.00, MeOH).

**Sodium (3-oxo-(17R)-17-28-norurs-12(13)-en)-2-oxoethyl-phosphonate 7c**

$^{1}$H NMR (500 MHz, $MeOD_{d4}$) δ 5.30 (d, $^{3}J$ = 3.7 Hz, 1H, H-C(12)), 4.08 (d, $^{2}J$ = 13.2 Hz, 1H, $H_a$-C(28')), 4.00 (d, $^{2}J$ = 13.2 Hz, 1H, $H_b$-C(28')), 2.57 (ddd, $^{2}J$ = 16.0 Hz, $^{3}J$ = 10.7, 7.4 Hz, 1H, $H_a$-C(2)), 2.39 (ddd, $^{2}J$ = 16.0 Hz, $^{3}J$ = 7.1, 3.7 Hz, 1H, $H_b$-C(2)), 2.32 (d, $^{3}J$ = 11,3 Hz, 1H, H-C(18)), 2.10–1.90 (m, 5 H, $H_2$-C(11), $H_a$-C(16), $H_a$-C(15), $H_a$-C(1)), 1.90–1.81 (m, 2H, $H_b$-C(16), $H_a$-C(21)), 1.72 (dt, $^{2}J$ = 13.8 Hz, $^{3}J$ = 4.0 Hz, 1H, $H_b$-C(21)), 1.67 (dd, $^{3}J$ = 11.0, 5.7 Hz, 1H, H-C(9)), 1.62–1.44 (m, 5 H, $H_2$-C(6), $H_a$-C(22), $H_a$-C(7), $H_b$-C(1)), 1.44–1.28 (m, 4 H, $H_b$-C(22), $H_b$-C(7), H-C(5), H-C(19)), 1.12 (s, 3H, $H_3$-C(27)), 1.12–1.08 (m, 1H, $H_b$-C(15)), 1.08 (s, 6 H, $H_3$-C(23), $H_3$-C(25)), 1.05 (s, 3H, $H_3$-C(24)), 1.03–0.99 (m, 1H, H-C(20)), 0.95 (d, $^{3}J$ = 6.2 Hz, 3H, $H_3$-C(30)), 0.89 (d, $^{3}J$ = 6.4 Hz, 3H, $H_3$-C(29)), 0.86 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $MeOD_{d4}$) δ 220.64 (C3), 179.92 (d, $^{3}J$ = 8.8 Hz, (C28)), 139.68 (C13), 126.80 (C12), 62.93 (d, $^{1}J$ = 153.5 Hz, (C28')), 56.50 (C5), 54.32 (C18), 49.49 (C17), 48.15 (C9), 43.30 (C14), 40.80 (C8), 40.46 (C19), 40.41 (C1), 40.23 (C20), 37.82 (C10), 37.44 (C21), 35.14 (C7), 33.68 (C2), 31.84 (C22), 29.39 (C15), 27.07 (C23), 25.07 (C16), 24.51 (C11), 24.07 (C27), 21.92

(C24), 21.60 (C30), 20.72 (C6), 17.67 (C29), 17.63 (C26), 15.72 (C25). $^{31}$P NMR (121 MHz, MeOD$_{d4}$) δ 11.53. HRMS: [$C_{31}H_{49}O_6P$-H$^+$] 547.3194; found 547.3195 (0.2 ppm). $[\alpha]_D^{20} = +0.49$; $[\alpha]_{546}^{20} = +0.58$; [ $[\alpha]_{436}^{20} = +0.97$ ; $[\alpha]_{405}^{20} = +1.23$; $[\alpha]_{365}^{20} = +1.62$ (c = 1.00, MeOH).

### Sodium (3β-hydroxy-(17R)-17-28-norlup-20(29)-en)-2-oxoethyl-phosphonate 8a

$^1$H NMR (500 MHz, MeOD$_{d4}$) δ 4.62 (s, 1H, H$_a$-C(29)), 4.48 (s, 1H, H$_b$-C(29)), 4.08 (dd, $^2J$ = 13.5, 8.9 Hz, 1H, H$_a$-C(28')), 3.95 (dd, $^2J$ = 13.5, 8.9 Hz, 1H, H$_b$-C(28')), 3.02 (dd, $^3J$ = 11.4, 4.6 Hz, 1H, H-C(3)), 2.93 (td, $^3J$ = 11.3, 4.5 Hz, 1H, H-C(19)), 2.32 (d, $^2J$ = 12.3 Hz, 1H, H$_a$-C(16)), 2.27–2.19 (m, 1H, H-C(13)), 1.99 (dd, $^2J$ = 12.1 Hz, $^3J$ = 8.1 Hz, 1H, H$_a$-C(21)), 1.88–1.80 (m, 1H, H$_a$-C(22)), 1.66–1.57 (m, 1H, H$_a$-C(12)), 1.59 (s, 3H, H$_3$-C(30)), 1.57–1.11 (m, 15 H, H$_2$-C(6), H$_2$-C(11), H$_2$-C(7), H$_2$-C(2), H$_b$-C(22), H$_b$-C(21), H$_b$-C(16), H$_a$-C(1), H-C(9), H-C(18), H$_a$-C(15)), 1.11–0.91 (m, 2H, H$_b$-C(15), H$_b$-C(12)), 0.89 (s, 3H, H$_3$-C(27)), 0.87–0.82 (m, 7 H, H$_3$-C(23), H-C(1), H$_3$-C(26)), 0.76 (s, 3H, H$_3$-C(25)), 0.65 (s, 3H, H$_3$-C(24)), 0.63–0.57 (m, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD$_{d4}$) δ 177.50 (d, $^3J$ = 8.8 Hz, (C28)), 152.07 (C20), 110.11 (C29), 79.69 (C3), 61,13 (d, $^1J$ = 159.5 Hz, (C28')), 57.95 (C17), 56.90 (C5), 52.05 (C9), 50.81 (C18), 48.32 (C19), 43.52 (C14), 41.95 (C8), 40.11 (C4), 39.96 (C1), 39.42 (C13), 38.33 (C10), 37.83 (C21), 35.55 (C7), 32.99 (C16), 31.67 (C22), 30.95 (C15), 28.61 (C23), 28.05 (C2), 26.90 (C12), 22.08 (C11), 19.57 (C30), 19.45 (C6), 16.74 (C25), 16.62 (C26), 16.11 (C24), 15.11 (C27). $^{31}$P NMR (121 MHz, MeOD$_{d4}$) δ 11.47. HRMS: [$C_{31}H_{51}O_6P$-H$^+$] 549.3350; found 549.3351 (0.2 ppm). $[\alpha]_D^{20} = -0.07$; $[\alpha]_{546}^{20} = -0.08$; [ $[\alpha]_{436}^{20} = -0.10$; $[\alpha]_{405}^{20} = -0.10$; $[\alpha]_{365}^{20} = -0.11$ (c = 1.00, MeOH).

### Sodium (3β-hydroxy-(17R)-17-28-norurs-12(13)-en)-2-oxoethyl-phosphonate 8b

$^1$H NMR (500 MHz, MeOD$_{d4}$) δ 5.27 (d, $^3J$ = 3.9 Hz, 1H, H-C(13)), 4.06 (dd, $^2J$ = 10.3, 5.1 Hz, 1H, H$_a$-C(28')), 4.02 (dd, $^2J$ = 10.3, 5.1 Hz, 1H, H$_b$-C(28')), 3.15 (dd, $^3J$ = 11.4, 4.6 Hz, 1H, H, H-C(3)), 2.31 (d, $^3J$ = 11.3 Hz, 1H, H-C(18)), 2.04 (td, $^2J$ = 13.3 Hz, $^3J$ = 4.3 Hz, 1H, H$_a$-C(16)), 1.96–1.85 (m, 3H, H$_2$-C(11), H$_a$-C(15)), 1.84–1.73 (m, 2H, H$_b$-C(16), H$_a$-C(21)), 1.73–1.61 (m, 3H, H$_a$-C(2), H$_b$-C(21), H$_a$-C(1)), 1.61–1.46 (m, 5 H, H$_a$-C(6), H$_b$-C(2), H$_a$-C(22), H$_a$-C(7), H-C(9)), 1.45–1.26 (m, 4 H, H$_b$-C(6), H$_b$-C(22), H$_b$-C(7), H-C(19)), 1.11 (s, 3H, H$_3$-C(27)), 1.07 (d, $^2J$ = 13.4 Hz, 1H, H$_b$-C(15)), 1.04–0.98 (m, 2H, H-C(20), H$_b$-C(1)), 0.97 (s, 3H, H$_3$-C(23)), 0.96 (d, $^3J$ = 6.3 Hz, 3H, H$_3$-C(30)), 0.95 (s, 3H, H$_3$-C(25)), 0.89 (d, $^3J$ = 6.4 Hz, 3H, H$_3$-C(25)), 0.79 (s, 3H, H$_3$-C(24)), 0.78 (s, 3H, H$_3$-C(26)), 0.74 (d, $^3J$ = 11.4 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD$_{d4}$) δ 179.47 (d, $^3J$ = 9.2 Hz, C(28)), 139.44 (C13), 127.13 (C12), 79.72 (C3), 61.63 (d, $^1J$ = 158.8 Hz, C(28')), 56.75 (C5), 54.19 (C18), 49.49 (C17), 49.03 (C9), 43.12 (C14), 40.83 (C8), 40.39 (C19), 40.21 (C20), 40.01 (C1), 39.84 (C4), 38.09 (C10), 37.51 (C21), 34.20 (C7), 31.77 (C22), 29.29 (C15), 28.76 (C23), 27.90 (C2), 25.09 (C16), 24.36 (C11), 24.18 (C27), 21.59 (C30), 19.47 (C6), 17.70 (C24), 17.62 (C29), 16.37 (C26), 16.03 (C25). $^{31}$P NMR (121 MHz, MeOD$_{d4}$) δ 12.17. HRMS: [$C_{31}H_{51}O_6P$-H$^+$] 549.3350; found 549.3349 (0.2 ppm). $[\alpha]_D^{20} = +0.33$; $[\alpha]_{546}^{20} = +0.40$ ; [ $[\alpha]_{436}^{20} = +0.71$; $[\alpha]_{405}^{20} = +0.88$; $[\alpha]_{365}^{20} = +1.12$ (c = 1.00, MeOH).

### Sodium (3β-hydroxy-(17R)-17-28-norolean-12(13)-en)-2-oxoethyl-phosphonate 8c

$^1$H NMR (500 MHz, MeOD$_{d4}$) δ 5.25 (t, $^3J$ = 3.6 Hz, 1H, H-C(13)), 4.16 (dd, $^2J$ = 13.2, 8.8 Hz, 1H, H$_a$-C(28')), 3.96 (dd, $^2J$ = 13.3, 8.6 Hz, 1H, H$_b$-C(28')), 3.14 (dd, $^3J$ = 11.4, 4.5 Hz, 1H, C(3)), 2.88 (dd, $^3J$ = 14.2, 4.4 Hz, 1H, H-C(18)), 1.99 (dt, $^2J$ = 13.8 Hz, $^3J$ = 7,7 Hz, 1H, H$_a$-C(16)), 1.96–1.79 (m, 3H, H$_b$-C(16), H-C(11)), 1.79–1.27 (m, 13H, H$_2$-C(6), H$_2$-C(2), H$_a$-C(15), H$_2$-C(22), H$_2$-C(7), H$_a$-C(21), H$_a$-C(1), H$_a$-C(19), H-C(9)), 1.19 (d, $^2J$ = 14.9 Hz, 1H, H$_b$-C(21)), 1.15 (s, 3H, H$_3$-C(27)), 1.13–1.00 (m, 2H, H$_b$-C(19), H$_b$-C(15)), 1.00–0.95 (m, 4 H, H$_3$-C(23), H$_b$-C(1)), 0.94 (s, 6 H, H$_3$-C(29), H$_3$-C(25)), 0.90 (s, 3H, H$_3$-C(30)), 0.78 (s, 6 H, H$_3$-C(26), H$_3$-C(24)), 0.77–0.72 (m, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD$_{d4}$) δ 180.03 (d, $^3J$ = 8.9 Hz, C(28)), 145.27 (C12), 123.59 (C13), 79.77 (C3), 62.76 (d, $^1J$ = 154.7 Hz, (C28')), 56.80 (C5), 49.17 (C9), 48.11 (C17), 47.34 (C19), 42.85 (C18), 40.60 (C14), 39.88 (C8), 39.85 (C1), 38.17 (C4), 38.17 (C10), 34.99 (C21), 33.94 (C7), 33.64 (C30), 33.17 (C22), 31.58 (C20), 29.11 (C15), 28.74 (C23), 27.88 (C2), 26.41 (C27), 24.53 (C11), 24.16 (C29), 23.80 (C16), 19.50 (C6), 17.67 (C26), 16.30 (C24), 15.91 (C25). $^{31}$P NMR (121 MHz, MeOD$_{d4}$) δ 11.59. HRMS: [$C_{31}H_{51}O_6P$-H$^+$] 549.3350; found 549.3348 (0.4 ppm). $[\alpha]_D^{20} = +0.31$; $[\alpha]_{546}^{20} = +0.43$; [ $[\alpha]_{436}^{20} = +0.76$ ; $[\alpha]_{405}^{20} = +0.91$; $[\alpha]_{365}^{20} = +1.21$ (c = 1.00, MeOH).

### Synthesis of a mixture of products 9, 10 and 11

To solution of betulin (**1a**) (500 mg, 1.131 mmol, 1 eq.) in anhydrous THF (5mL) freshly prepared 1 M LDA solution in THF (2.37 mL, 2.37 mmol, 2.1 eq.) is added dropwise at -78 °C. The resulting reaction mixture is warmed up to 0 °C and stirred at ambient temperature for 40 min. Then the solution of previously prepared (dimethoxyphosphoryl)methyl trifluoromethanesulfonate (712 mg, 2.49 mmol, 2.2 eq.) in anhydrous THF (3 mL) is added dropwise to the suspension of lithium alkoxide at 0 °C. The obtained reaction mixture is warmed up to room temperature and stirred for 3 h. Then the reaction mixture is quenched by MeOH (2 mL ), evaporated to dryness, redissolved in EtOAc (50 mL) and subsequently washed with $H_2O$ (30 mL) and brine (2 × 30 mL). The combined organic layer is dried over anhydrous $Na_2SO_4$. After filtration, the filtrate is concentrated *in vacuo* and purified by silica column chromatography (Hexanes-EtOAc 4:1–1:9) to yield bis-ether **9** as a white amorphous solid (29%, 226 mg). R*f* = 0.31 (100% EtOAc). Side product **11** was isolated with preparative HPLC on C18 reverse phase column by gradient A/B (60/40) → A/B 0/100)*. However, the presence of monoester **10** was detected by HPLC and NMR, yet the product **10** was not isolated in pure form.

* A: 95 parts of 0.1% aqueous solution of trifluoroacetic acid and 5 parts of acetonitrile;
B: acetonitrile.

### (3 S)-3,28-di((dimethoxyphosphoryl)methyloxy)-lup-20(29)ene 9

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.67 (s, 1H, H$_a$-C(29)), 4.57 (s, 1H, H$_b$-C(29)), 3.99 (dd, $^2J$ = 13.6 Hz, $^3J$ = 8.7 Hz, 1H, H$_a$-C(28')), 3.87–3.76 (m, 14 H, H$_2$-C(3'), (H$_3$-CO)$_4$), 3.70 (d, $^2J$ = 8.7 Hz, 1H, H$_a$-C(28)), 3.68 (dd,

$^2J$ = 13.6 Hz, $^3J$ = 9.7 Hz, 1H, $H_b$-C(28')), 3.24 (d, $^2J$ = 8.7 Hz, 1H, $H_b$-C(28)), 2.83 (dd, $^3J$ = 11.8, 4.3 Hz, 1H, H-C(3)), 2.38 (td, $^3J$ = 10.8, 5.5 Hz, 1H, H-C(19)), 2.01–1.86 (m, 3H, $H_a$-C(16), $H_a$-C(21), $H_a$-C(22)), 1.78–1.68 (m, 3H, $H_a$-C(1), $H_a$-C(15), $H_a$-C(2)), 1.67 (s, 3H, $H_3$-C(30)), 1.65–1.57 (m, 2H, $H_a$-C(12), $H_a$-C(13)), 1.56–1.43 (m, 3H, $H_a$-C(6), $H_b$-C(2), H-C(18)), 1.43–1.33 (m, 5 H, $H_a$-C(11), $H_b$-C(6), $H_b$-C(16), $H_2$-C(7)), 1.28–1.13 (m, 3H, $H_b$-C(11), $H_b$-C(22), H-C(9)), 1.08–0.99 (m, 6 H, $H_3$-C(26), $H_b$-C(12), $H_b$-C(15), $H_b$-C(21)), 0.98 (s, 3H, $H_3$-C(23)), 0.95 (s, 3H, $H_3$-C(27)), 0.85–0.78 (m, 4 H, $H_3$-C(25)), 0.76 (s, 3H, $H_3$-C(26)), 0.67 (d, $^3J$ = 9.5 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.61 (C20), 109.82 (C29), 90.08 (d, $^3J$ = 12.2 Hz, (C3)), 72.41 (d, $^3J$ = 9.5 Hz (C28)), 65.40 (d, $^1J$ = 164.5 Hz, (C3')), 63.18 (d, $^1J$ = 166.5 Hz, (C28')), 55.81 (C5), 53.29 (d, $^2J$ = 6.6 Hz, (MeO)) 53.14 (d, $^2J$ = 6.8 Hz, (MeO)), 53.12 (d, $^2J$ = 6.5 Hz, (MeO)), 53.09 (d, $^2J$ = 6.9 Hz, (MeO)), 50.46 (C9), 48.98 (C18), 48.03 (C19), 47.56 (C17), 42.81 (C14), 41.06 (C8), 39.10 (C4), 38.52 (C1), 37.66 (C13), 37.26 (C10), 34.65 (C21), 34.31 (C7), 29.96 (C22), 29.86 (C16), 28.15 (C23), 27.20 (C15), 25.30 (C12), 22.35 (C2), 20.97 (C11), 19.25 (C30), 18.27 (C6), 16.25 (C24), 16.20 (C25), 16.10 (C26), 14.89 (C27). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 23.96, 23.73. HRMS: $[C_{36}H_{64}O_8P_2 + H^+]$ 687.4149; found 687.4141 (1.1 ppm). $[\alpha]_D^{20} = +0.21$; $[\alpha]_{546}^{20} = +0.26$; $[\alpha]_{436}^{20} = +0.47$; $[\alpha]_{405}^{20} = +0.57$; $[\alpha]_{365}^{20} = +0.74$ (c = 1.00, MeOH).

### (((3 S)-3-((dimethoxyphosphoryl)methyloxy)-28-lup-20(29)enyloxy)(methoxy)phosphoryl) methyl trifluoromethanesulfonate 11

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 1H, $H_a$-C(29)), 4.59 (s, 1H, $H_b$-C(29)), 4.27 (dd, $^2J$ = 9.3 Hz, $^3J$ = 5.2 Hz, 1H, $H_a$-C(28)), 4.00 (dd, $^2J$ = 13.7 Hz, $^3J$ = 8.8 Hz, 1H, H-C(3)), 3.88–3.78 (m, 9H, ($H_3$-COP)$_2$, $H_2$-C(28'), $H_b$-C(28)), 3.70 (dd, $^2J$ = 13.7 Hz, $^3J$ = 9.7 Hz, 1H, H-C(3')), 3.47 (m, 3H, OMe), 2.83 (dd, $^3J$ = 11.8, 4.3 Hz, 1H, H-C(3)), 2.38 (ddd, $^3J$ = 10.6, 10.1, 5.6 Hz, 1H, H-C(19)), 2.01–1.86 (m, 3H, $H_a$-C(16), $H_a$-C(21), $H_a$-C(22)), 1.80–1.69 (m, 3H, $H_a$-C(2), $H_a$-C(15), $H_a$-C(1)), 1.66 (s, 3H, $H_3$-C(30)), 1.66–1.57 (m, 3H, $H_a$-C(12), H-C(13), H-C(18)), 1.57–1.32 (m, 7 H, $H_a$$H_2$-C(6), $H_a$-C(11), $H_b$-C(2), $H_b$-C(22), H-C(7)), 1.32–1.13 (m, 3H, $H_b$-C(11), $H_b$-C(16)), 1.13–1.03 (m, 3H, $H_b$-C(12), $H_b$-C(15), $H_b$-C(22)), 1.02 (s, 3H, $H_3$-C(26)), 0.98 (s, 3H, $H_3$-C(23)), 0.96 (s, 3H, $H_3$-C(27)), 0.82 (s, 3H, $H_3$-C(25)), 0.82–0.75 (m, 1H, $H_b$-C(1)), 0.75 (s, 3H, $H_3$-C(24)), 0.67 (d, $^3J$ = 9.6 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.13 (C20), 110.09 (C29), 90.11 (d, $^3J$ = 12.4 Hz, (H-C(3)), 66.33 (d, $^1J$ = 166.44, H-C(3')), 65.34 (d,$^2J$ = 7.6 Hz, C(28)), 63.10 (d, $^1J$ = 167.3 Hz, H-C(28')), 61.56 (d, $^2J$ = 13.1 Hz, MeO-P($H_2$C(28))), 55.81 (C5), 53.40 (d, $^2J$ = 6.5 Hz, (MeO)), 53.37 (d, $^2J$ = 6.6 Hz, (MeO)), 50.44 (C9), 48.76 (C18), 47.82 (C19), 47.37 (d, $^3J$ = 6.6 Hz, (C17)), 42.84 (C14), 41.04 (C8), 39.10 (C4), 38.52 (C1), 37.75 (C13), 37.26 (C10), 34.27 (C21), 34.20 (C7), 29.59 (C22), 29.30 (C16), 28.13 (C23), 26.95 (C15), 25.30 (C12), 22.33 (C2), 20.94 (C11), 19.24 (C30), 18.25 (C6), 16.23 (C24), 16.19 (C25), 16.08 (C26), 14.87 (C27). $^{31}$P NMR (121 MHz, $CDCl_3$) δ 24.02, 22.69. R*f* = 0.43 (100% EtOAc).

### Sodium (lup-20(29)-en-(3 S)-3,28-diylbis(oxymethylene))bis(phosphonate) 12, demethylation process 9 → 12

To a solution of compound **9** (275 mg, 0.4 mmol, 1 eq.) in anhydrous DCM (5 mL) TMSI (342 µL 2.4 mmol, 6 eq.) is added dropwise at -40 °C and the resulting reaction mixture is stirred at -40 °C for 5 h. Then MeOH (2 mL) is added dropwise at -40 °C. The obtained reaction mixture is stirred for additional 30 min and solution of $NaHCO_3$ (202 mg, 2.4 mmol, 6 eq.) in $H_2O$ (6 mL) is added dropwise at -40 °C, and the resulting mixture is warmed up to room temperature. The resulting reaction mixture is warmed up to room temperature and the organic solvents are evaporated *in vacuo*. The obtained aqueous suspension is centrifuged and the supernatant is removed and discarded. The precipitate is re-suspended in deionized water (1 mL) and the centrifugation – supernatant removal procedure is repeated additional two times (in total: washing with water 3 × 1mL). The obtained precipitate is then dried in vacuo to yield product **12** as a yellowish amorphous solid (78%, 225 mg).

$^1$H NMR (500 MHz, MeOD) δ 4.69 (s, 1H, $H_a$-C(29)), 4.57 (s, 1H, $H_b$-C(29)), 3.85 (dd, $^2J$ = 13.3, 9.1 Hz, 1H, $H_a$-C(28'), 3.74–3.68 (m, 3H, $H_a$-C(28), $H_2$-C(3')), 3.55 (dd, $^2J$ = 13.3, 10.2 Hz, 1H, $H_b$-C(28')), 3.32(d, $^2J$ = 11.4 Hz, 1H, $H_b$-C(28)), 2.89 (dd, $^3J$ = 11.7, 4.3 Hz, 1H, H-C(3)), 2.46 (td, $^3J$ = 11.0, 5.9 Hz, 1H, H-C(19)), 2.08–1.98 (m, 3H, H, $H_a$-C(16), $H_a$-C(21), $H_a$-C(22)), 1.90–1.70 (m, 5 H, $H_a$-C(15), $H_a$-C(1), H-C(13), $H_a$-C(12), $H_a$-C(2)), 1.69 (s, 3H, $H_3$-C(30)), 1.62–1.39 (m, 7 H, $H_2$-C(6), $H_a$-C(11), $H_b$-C(2), H-C(18), $H_2$-C(7)), 1.39–1.10 (m, 4 H, $H_b$-C(11), $H_b$-C(22), $H_b$-C(16), H-C(9)), 1.09 (s, 3H, $H_3$-C(26)), 1.09–1.03 (m, 1H, $H_b$-C(12)), 1.03 (s, 3H, $H_3$-C(23)), 1.02–0.95 (m, 5 H, $H_3$-C(27), $H_b$-C(21), $H_b$-C(15)), 0.95–0.89 (m, 1H, $H_b$-C(1)), 0.88 (s, 3H, $H_3$-C(25)), 0.80 (s, 3H, $H_3$-C(24)), 0.74 (d, $^3J$ = 9.6 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD) δ 150.51 (C20), 108.83 (C10), 89.45 (d,$^3J$ = 12.1 Hz, C(3)), 71.56 (d, $^3J$ = 10.6 Hz, (C28)), 66.93 (d, $^1J$ = 162.8 Hz, (C3')), 64.67 (d, $^1J$ = 164.8 Hz, C(28')), 55.77 (C5), 50.41 (C9), 48.79 (C18), 48.01 (C19), 42.40 (C14), 40.77 (C8), 38.69 (C1), 38.33 (C4), 37.51 (C13), 36.90 (C10), 34.30 (C21), 34.05 (C7), 29.58 (C22), 29.49 (C16), 27.19 (C23), 26.97 (C15), 25.20 (C12), 21.92 (C2), 20.60 (C11), 17.98 (C30), 17.89 (C6), 15.34 (C25), 15.32 (C24), 15.22 (C26), 13.85 (C27). $^{31}$P NMR (121 MHz, MeOD) δ 19.72, 19.07. $[\alpha]_D^{20} = +0.11$; $[\alpha]_{546}^{20} = +0.17$; $[\alpha]_{436}^{20} = +0.33$; $[\alpha]_{405}^{20} = +0.37$; $[\alpha]_{365}^{20} = +0.46$ (c = 1.00, MeOH).

### Cytotoxicity evaluation

Cytotoxicity of betulinic acid, ursolic acid and oleanolic acid derivatives was evaluated using human-derived osteosarcoma cell line MG63 (ATCC, CRL-1427) and mouse-derived preosteoblast cell line MC3T3-E1 (ATCC CRL-2593). Before conducting the experiments, both cell lines were continuously cultured according to the ATCC product sheet instructions. Briefly, both cell lines were expanded in α-MEM medium supplemented with 10% FBS and 1% pen-strep and maintained at 37 °C in a humidified atmosphere with 5% $CO_2$.

Each cell line was plated at a concentration of $1 \times 10^4$ cells/well in 96-well plate. The plates were incubated for 24 h to allow cell attachment and growth. Bioactive substances were solubilized in methanol prior further dilution in cell culture media. Following the cell incubation period, the culture media was removed and the dilutions of active substance (10, 25 and 50 µM) in cell culture media were added. The culture medium only

and its dilutions with methanol solution respective to the bioactive substance concentrations were used as the controls. The final concentration of methanol did not exceed 1%. Cells were treated with bioactive substance solutions for 24 h. After 24 h incubation, relative cell metabolic activity was assessed using CellTiter-Blue® (CTB) analysis (Promega, JAV). Absorbance was measured at 590 nm using microplate reader (Infinite® 200 PRO, Tecan, USA). The relative cell metabolic activity was calculated for each bioactive substance concentration as well as for the controls. All results were presented as the mean ± standard deviation of at least 5 replicates. Statistically significant differences between sample groups are assessed using a one-way ANOVA test and then corrected using the Šídák multiple comparison test. Statistically significant differences were considered to be those with a P-values less than 0.05 ($p < 0.05$). Numerical values of the cell relative metabolic activity are summarized in Table 4 and the corresponding graphical representation can be found in supporting information (Figures S1-S4).

## Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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## Author contributions

Concept, study design, data analysis (J.L, M.T.). Manuscript preparation (V.K., A.D., M.T.) and revison (M.T., D.L.). Chemical synthesis and purification (J.L., V.K., R.L., E.F.). Solubility tests (V.K.). Cytotoxicity tests and evaluation (Ö.D., A.D., D.L.). NMR, quality control and characterization (V.K., J.L.). All authors reviewed the manuscript.

## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

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Pielikums II

Appendix II

Lugiņina, J., Kroškins, V., Lācis, R., Fedorovska, E., Turks, M

Ūdenī šķīstoši triterpenoīdu fosfonāti un to sintēzes metode

Water-soluble triterpenoid phosphonates and synthesis method thereof

*Latvijas patents / Latvian Patent*

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(54) Izgudrojuma nosaukums: ŪDENĪ ŠĶĪSTOŠI TRITERPENOĪDU FOSFONĀTI UN TO IEGŪŠANAS PAŅĒMIENS
WATER-SOLUBLE TRITERPENOID PHOSPHONATES AND SYNTHESIS METHOD THEREOF

(57) Kopsavilkums:

Izgudrojums attiecas uz organiskās ķīmijas tehnoloģijas nozari, konkrēti, uz ūdenī šķīstošu fosfonāta grupu saistītu triterpenoīdu (5a-c) un (6a-c) un to izveidošanas paņēmienu.

# IZGUDROJUMA APRAKSTS

[001] Izgudrojums attiecas uz organiskās ķīmijas tehnoloģijas nozari, konkrēti, uz ūdenī šķīstošu fosfonāta grupu saistītu triterpenoīdu un to iegūšanas paņēmienu.

## Zināmais tehnikas līmenis

[002] Pentacikliskie triterpenoīdi (PTs) ir zināma savienojumu klase, kas dabā sastopama vairāk nekā 200 dažādos augos sekundāro metabolītu veidā. Tādi PTs kā betulīns, betulīnskābe, oleānolskābe un ursolskābe ir plaši izmantoti rūpniecībā, pateicoties to plaša spektra augstai bioloģiskajai aktivitātei [1]. Tomēr šo savienojumu un to pussintētisko atvasinājumu medicīniskais lietojums ir apgrūtināts zemas ūdens šķīdības dēļ [2]. Viens no iespējamajiem veidiem, kā uzlabot savienojuma šķīdību ūdenī, ir ievadīt savienojumos hidrofīlos centrus kā, piemēram, tādas anjonās grupas kā karboksilātgrupas ($RCOO^-$), sulfātgrupas ($ROSO_3^-$) un fosfātgrupas ($ROPO_3^{2-}$).

[003] Zināmas metodes PTs karboksilātu iegūšanai paredz apstrādāt PTs karbonskābes ar sārmu, sārmzemju metālu vai ceturtējiem amonija hidroksīdiem spirtā [3]. Iespējams iegūt karboksilātus, kas satur tādus katjonus kā $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$, $NR_4^+$. Tomēr karboksilātu atvasinājumu šķīdības pētījumi neuzrādīja apmierinošus rezultātus, kā arī pie savienojumu koncentrācijas, kas pārsniedz 2 mg/g tie veido koloīdus ar šķīdinātāju, tādējādi būtiski apgrūtinot šķīdības noteikšanu.

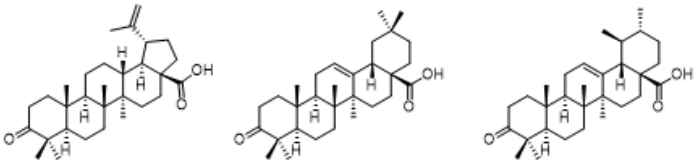
[004] Viens no zināmiem PTs sulfatēšanas paņēmieniem balstās uz PTs mijiedarbību ar $SO_3$-amīna kompleksu, kuru iegūst no sērskābes un etiķskābes anhidrīda polārā šķīdinātājā (Py, DMF, DMA) [4]. Citas alternatīvas sulfatēšanas metodes pamatā ir sulfamīnskābes dononakceptorā kompleksa izveide ar tādiem akceptējošiem aktivātoriem kā 1,4-dioksāns, urīnviela, DMF, morfolīns, piperidīns un piridīns [5]. PTs difosfātus iegūst PTs dioliem reaģējot ar fosforilhlorīdu absolutizētajā piridīnā, kam seko hidrolīze neitrālajā vidē 1,4-dioksāna/ūdens maisījumā [6]. Gan PTs sulfātu, gan PTs fosfātu būtisks izmantošanas ierobežojums medicīnā ir to salīdzinoši zema hidrolītiskā stabilitāte.

[005] Ir zināmi PTs fosfonātu ($R^1OP(OR^2)$ piemēri, kur fosfonāta grupu ievada caur estersaiti [7], amīdsaiti [8] vai C-C saiti [9], taču to pārvēršana par anjono fosfonskābi vai fosfonskābes sāļiem nav aprakstīta pieejamos informācijas avotos.

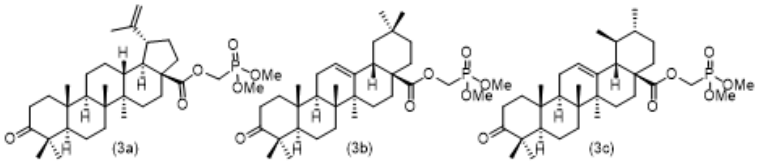
Izgudrojuma mērķis un būtība

[006] Izgudrojuma mērķis ir izstrādāt jaunu paņēmienu ūdenī šķīstošu triterpenoīdu fosfonātu atvasinājumu iegūšanai.

[007] Izgudrojuma mērķis ir sasniegts šādi: tika atklāts, ka triterpenoīdu karbonskābes: betulonkābes, oleanonskābe un ursonskābe ar formulām (1a), (1b) un (1c):

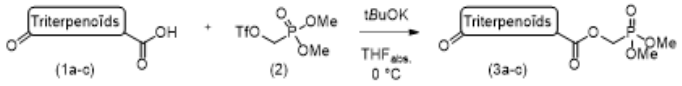



absolutizētā tetrahidrofurānā (THF) kā šķīdinātājā 0 °C temperatūrā izcili reaģē ar reakcijas vidē esošu alkilējošu reaģentu: (dimetoksifosforil)metiltrifluorometānsulfonātu (2), lietojot tBuOK kā papildu piedevu, veidojot caur estera saiti saistītus modificētus triterpenoīdu fosfonātu konjugātus ar formulām (3a), (3b) un (3c):

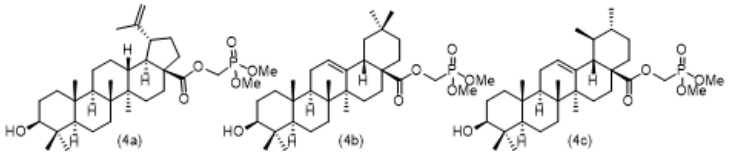



[008] Estera saites veidošanas reakciju atspoguļo 1. shēma:

1. shēma

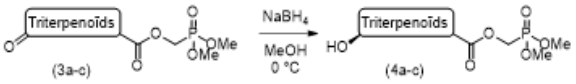



[009] Tālāk, ar nolūku uzlabot atvasinājuma hidrofīlās īpašības, no atvasinājumiem (3a) līdz (3c) reducējošos apstākļos saskaņā ar informācijas avotā [10] aprakstīto metodi iegūst spirta funkcionālo grupu saturošus atvasinājumus (4a), (4b) un (4c):



[010] Reducēšanas reakcijas atspoguļo 2. shēma:

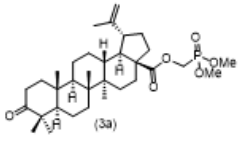
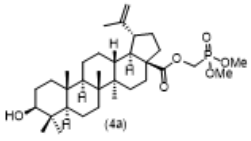
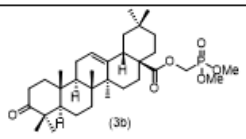
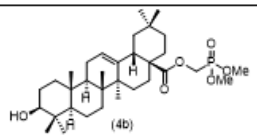
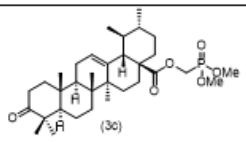
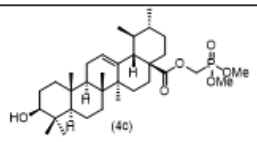
2. shēma



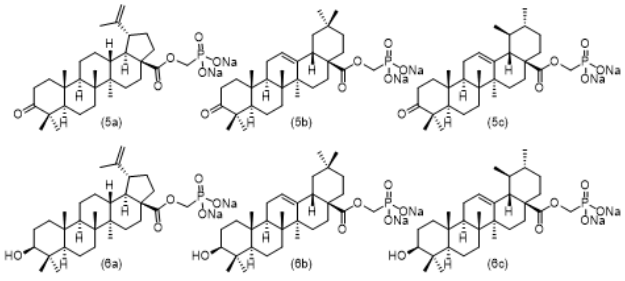

[011] Iegūtie produkti ar formulu (3a) līdz (3c) un (4a) līdz (4c) un to iegūšanas reakciju iznākumi ir apkopoti 1. tabulā.

1. tabula

Triterpenoīdu esteri (3a-c) un (4a-c)

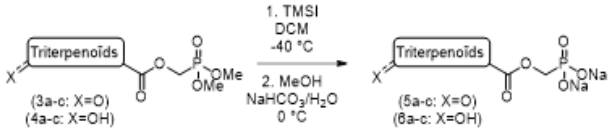
| Produkts, (Nr.) | Iznākums, (%) | Produkts, (Nr.) | Iznākums, (%) |
|---|---|---|---|
|  (3a) | 78 |  (4a) | >99 |
|  (3b) | 61 |  (4b) | 96 |
|  (3c) | 71 |  (4c) | 92 |

[012] Pēdējā stadija izgudrojuma mērķa sasniegšanai paredz veikt hidrolīzes reakcijas metilgrupu noņemšanu atvasinājumiem (3a) līdz (3c) un (4a) līdz (4c), veidojot fosfonātu konjugātus ar formulām (5a) līdz (5c) un (6a) līdz (6c):



[013] Demetilēšanas reakcijas atspoguļo 3. shēma:

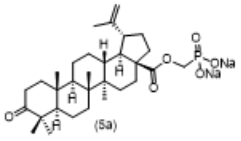
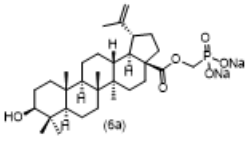
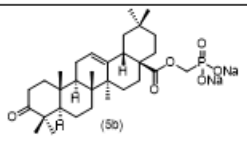
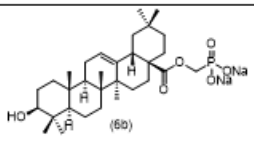
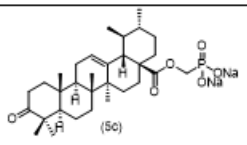
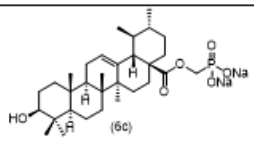
3. shēma




[014] Iegūtie produkti ar formulām (5a) līdz (5c) un (6a) līdz (6c) un to iegūšanas reakciju iznākumi ir apkopoti 2. tabulā.

2. tabula

Triterpenoīdu fosfonāti (5a-c) un (6a-c)

| Produkts, (Nr.) | Iznākums, (%) | Produkts, (Nr.) | Iznākums, (%) |
|---|---|---|---|
|  | 97 |  | 91 |
|  | 90 |  | 78 |
|  | 51 |  | 93 |

[015] Izgudrojuma mērķa sasniegšanas pierādījumam tika pārbaudīta estera saites saturošu triterpenoīdu fosfonātu (5a) līdz (5c) un (6a) līdz (6c) šķīdība ūdens vidē. Iegūtie rezultāti apkopoti 3. tabulā. Analizējot datus tika secināts, ka visi iegūtie triterpenoīdi ir ūdenī šķīstoši un izvirzītais izgudrojuma mērķis ir sasniegts. Visaugstāko šķīdību $H_2O$ uzrādīja ursonksābes atvasinājums (5c): 26,2 mg/ml, kamēr, pēc literatūras datiem, dabīgās ursolskābes (1c) šķīdība ūdenī ir vien tikai 0,12 μg/l [11].

3. tabula

Triterpenoīdu fosfonātu šķīdība

| Produkts, (Nr.) | 5a | 5b | 5c | 6a | 6b | 6c |
|---|---|---|---|---|---|---|
| Šķīdība 1 ml $H_2O$ (pH=8) | 11,0 mg | 7,8 mg | 26,2 mg | 2,6 mg | 6,7 mg | 6,9 mg |

Izgudrojuma īstenošanas piemēri

[016] Vispārīgā metode I: iepriekš izkarsētā kolbā, kas aprīkota ar magnētisko maisītāju, iesver triterpenoīdu karbonskābi (1a-c) (1 ekviv.), to zem inertas gāzes ($N_2$ vai Ar) vides izšķīdina $THF_{abs.}$ (10 ml). Atdzesētam līdz -5 līdz -7 °C šķīdumam pievieno *t*BuOK (1,5 ekviv.), maisa 30 minūtes -5 °C temperatūrā un 1 stundu istabas temperatūrā. Atkārtoti atdzesē reakcijas maisījumu līdz -5 līdz -7 °C un lēni pilinot pievieno iepriekš sagatavotu triflāta (2) (2 ekviv.) šķīdumu $THF_{abs.}$ (5 ml), reakcijas maisījumam ļauj silt līdz istabas temperatūrai un turpina maisīšanu 12 stundas. Pēc tam reakcijas maisījumu iekoncentrē pazeminātā spiedienā uz rotācijas ietvaicētāja, pievieno EtOAc (70 ml) un secīgi mazgā ar piesātinātu NaCl ūdens šķīdumu (3×10 ml), organisko fāzi žāvē virs bezūdens $Na_2SO_4$, filtrē un ietvaicē ar rotācijas ietvaicētāja palīdzību. Atlikumu attīra hromatogrāfiski uz silikagela (Hex/EtOAc (10%→50% EtOAc)).

[017] Vispārīgā metode II: iepriekš izkarsētā kolbā, kas aprīkota ar magnētisko maisītāju, iesver triterpenoīdu ketonu (3a-c) (1 ekviv.), to MeOH (10 ml). Atdzesētam līdz 0 °C šķīdumam pakāpeniski pa porcijām pievieno $NaBH_4$ (4 ekviv.), maisa 5 stundas 0 °C temperatūrā. Pēc tam reakcijas maisījumam pievieno piesātinātu $NH_4Cl$ ūdens šķīdumu (5 ml) un iekoncentrē pazeminātā spiedienā uz rotācijas ietvaicētāja, pievieno EtOAc (70 ml) un secīgi mazgā ar piesātinātu NaCl ūdens šķīdumu (3×10 ml), organisko fāzi žāvē virs bezūdens $Na_2SO_4$, filtrē un ietvaicē ar rotācijas ietvaicētāja palīdzību.

[018] Vispārīgā metode III: iepriekš izkarsētā kolbā, kas aprīkota ar magnētisko maisītāju, iesver triterpenoīdu fosfonāta metilesteri (3a-c vai 4a-c) (1 ekviv.), to zem inertas gāzes ($N_2$ vai Ar) vides izšķīdina $DCM_{abs.}$ (10 ml). Atdzesētam līdz -40 °C šķīdumam lēni pa pilienam pievieno TMSI (3 ekviv.), maisa 5 stundas -40 °C temperatūrā. Tad pie atdzesēta reakcijas maisījuma lēni piepilina MeOH (5 ml), maisa reakcijas šķīdumu 30 minūtes. Tad reakcijas maisījumam pievieno izšķīdinātu $NaHCO_3$ (3 ekviv.) šķīdumu $H_2O$ (5–10 ml) reakcijas maisījuma, maisa reakcijas šķīdumu vēl 30 minūtes un iekoncentrē pazeminātā spiedienā uz

rotācijas ietvaicētāja. Cieto atlikumu no suspensijas atdala centrifugējot, cieto atlikumu mazgā ar $H_2O$ (3×2 ml) un žāvē vakuumā.

[019] 1. piemērs: savienojuma (3a) iegūšana:

Sintezēts pēc vispārīgās metodes I: betulonskābe (1a) (1 g, 2,199 mmol, 1 ekviv.), triflāts (2) (0,897 g, 3,298 mmol, 1,5 ekviv.), tBuOK (0,537 g, 4,398 mmol, 2 ekviv.), THF (30 ml). Reakcijas laiks 2 stundas, 0 °C un 12 stundas istabas temperatūrā. Iznākums: 992 mg, 78 %. Balta amorfa viela. $^1$H KMR (500 MHz, $CDCl_3$) δ 4,73 (s, 1H,), 4,60 (s, 1H), 4,48 (dd, $^2J$=14,6, $^3J$=8,3 Hz, 1H), 4,39 (dd, $^2J$=14,6, $^3J$=8,2 Hz, 1H), 3,81 (d, $^3J$=10,9, 6H), 2,98 (td, $^3J$=11,1, 4,8 Hz, 1H), 2,48 (ddd, $^2J$=15,5 Hz, $^3J$=9,8, 7,5 Hz, 1H), 2,39 (ddd, $^2J$=15,5 Hz, $^3J$=7,6, 4,4 Hz, 1H), 2,31–2,19 (m, 2H), 1,96–1,82 (m, 3H), 1,76–1,69 (m, 1H), 1,68 (s, 3H), 1,62 (t, $^3J$=11,4 Hz, 1H), 1,54–1,34 (m, 12H), 1,34–1,14 (m, 4H), 1,06 (s, 3H), 1,01 (s, 3H), 0,97 (s, 3H), 0.96 (s, 3H), 0,92 (s, 3H), 0,89–0,82 (m, 1H). $^{13}$C KMR (126 MHz, $CDCl_3$) δ 218,25, 174,91 (d, $^3J$=6,4 Hz) , 150,34, 109,96, 56,90, 55,18 (d, $^1J$=16,4 Hz), 55,10, 53,20 (d, $^2J$=6,2 Hz), 53,18 (d, $^2J$=6,2 Hz), 50,04, 49,49, 47,46, 46,90, 42,61, 40,77, 39,77, 38,44, 37,04, 37,00, 34,26, 33,75, 32,03, 30,53, 29,65, 26,74, 25,65, 21,54, 21,15, 19,76, 19,47, 16,10, 15,85, 14,74. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,87. AIMS: [$C_{33}H_{53}O_6P+H^+$] 577,3653; atrasts 577,3626 (4,7 ppm).

[020] 2. piemērs: savienojuma (3b) iegūšana:

Sintezēts pēc vispārīgās metodes I: oleanonskābe (1b) (0,780 g, 1,715 mmol, 1 ekviv.), triflāts (2) (0,934 g, 3,431 mmol, 1,5 ekviv.), tBuOK (0,290 g, 2,573 mmol, 2 ekviv.), THF (25 ml). Reakcijas laiks 2 stundas, 0 °C un 12 stundas istabas temperatūrā. Iznākums: 607 mg, 61 %. Balta amorfa viela. $^1$H KMR (500 MHz, $CDCl_3$) δ 5.33 (t, $^3J$=3,6 Hz, 1H), 4,42 (dd, $^2J$=14,6 Hz, $^3J$=8,6 Hz, 1H), 4,32 (dd, $^2J$=14,6 Hz, $^3J$=8,3 Hz, 1H), 3,81 (d, $^3J$=10,8 Hz, 6H), 2,93–2,84 (m, 1H), 2,54 (ddd, $^2J$=15,9 Hz, $^3J$=11,1, 7,3 Hz, 1H), 2,36 (ddd, $^2J$=15,9 Hz, $^3J$=6,8, 3,5 Hz, 1H), 2,06–1,83 (m, 4H), 1,76–1,61 (m, 5H), 1,52–1,17 (m, 10H), 1,15 (s, 3H), 1,15–1,09 (m, 1H), 1,08 (s, 3H), 1,04 (s, 6H), 0,92 (d, $J$=9,4 Hz, 6H), 0,78 (s, 3H). $^{13}$C KMR (126 MHz, $CDCl_3$) δ 217,91, 176,77 (d, $^3J$=7,8 Hz), 143,54, 122,65, 55,81 (d, $^1J$=168,8 Hz), 55,14, 53,24 (d, $^2J$=6,1 Hz), 53,24 (d, $^2J$=6,1 Hz), 47,59, 47,24, 46,97, 45,89, 41,95, 41,54, 39,39, 39,28, 36,88, 34,30, 33,90, 33,15, 32,36, 32,32, 30,80, 27,74, 26,55, 25,86, 23,65, 23,64, 23,18, 21,62, 19,72, 16,94, 15,17. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,74. AIMS: [$C_{33}H_{53}O_6P+H^+$] 577,3653; atrasts 577,3623 (5,2 ppm).

[021] 3. piemērs: savienojuma (3c) iegūšana:

Sintezēts pēc vispārīgās metodes I: ursonskābe (1c) (0,727 g, 1,599 mmol, 1 ekviv.), triflāts (2) (0,870 g, 3,198 mmol, 1,5 ekviv.), tBuOK (0,270 g, 2,398 mmol, 2 ekviv.), THF (18 ml).

Reakcijas laiks 2 stundas, 0 °C un 12 stundas istabas temperatūrā. Iznākums: 654 mg, 71 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, $CDCl_3$) δ 5,29 (d, $^{3}J$=3,8 Hz, 1H), 4,33 (d, $^{2}J$=8,5 Hz, 2H), 3,80 (d, $^{3}J$=10,8 Hz, 6H), 2,55 (ddd, $^{2}J$=16,0 Hz, $^{3}J$ = 10,8, 7,5 Hz, 1H), 2,37 (ddd, $^{2}J$=16,0 Hz, $^{3}J$=6,9, 3,6 Hz, 1H), 2,25 (d, $^{3}J$=11,3 Hz, 1H), 2,04 (td, $J$=14,4, 6,5 Hz, 1H), 1,99–1,92 (m, 2H), 1,90 (ddd, $^{2}J$=12,0 Hz, $^{3}J$=7,4, 3,6 Hz, 1H), 1,80–1,68 (m, 3H), 1,65–1,55 (m, 3H), 1,55–1,39 (m, 5H), 1,39–1,23 (m, 4H), 1,17–1,11 (m, 1H), 1,09 (s, 3H), 1,08 (s, 3H), 1,04 (s, 6H), 1,04–0,98 (m, 1H), 0,94 (d, $^{3}J$=6,3 Hz, 3H), 0,86 (d, $^{3}J$=6,4 Hz, 3H), 0,79 (s, 3H).$^{13}$C KMR (126 MHz, $CDCl_3$) δ 217,95, 176,62 (d, $^{3}J$=8,2 Hz), 138,02, 125,83, 55,81 (d, $^{1}J$=168,9 Hz), 55,13, 53,24 (d, $^{2}J$=6,1 Hz), 53,21 (d, $^{2}J$=6,1 Hz), 53,07, 48,64, 47,55, 46,86, 42,28, 39,60, 39,44, 39,17, 38,91, 36,79, 36,58, 34,31, 32,65, 30.,68, 28,08, 26,67, 24,32, 23,59, 23,58, 21,63, 21,24, 19,71, 17,12, 17,05, 15,37. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,85. AIMS: [$C_{33}H_{53}O_6P+H^+$] 577,3653; atrasts 577,3623 (5,2 ppm).

[022] 4. piemērs: savienojuma (4a) iegūšana:

Sintezēts pēc vispārīgās metodes II: savienojums (3a) (0,310 g, 0,537 mmol, 1 ekviv.), $NaBH_4$ (0,081 g, 2,150 mmol, 4 ekviv.), MeOH (8 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 312 mg, kvant. Balta amorfa viela. $^{1}$H KMR (500 MHz, $CDCl_3$) δ 6,02 (bs, 1H), 4,73 (s, 1H), 4,61 (s, 1H), 4,48 (dd, $^{2}J$=14,7 Hz, $^{3}J$=8,3 Hz, 1H), 4,39 (dd, $^{2}J$=14,7 Hz, $^{3}J$=8,2 Hz, 1H), 3,81 (d, $^{3}J$=10,8 Hz, 6H), 3,18 (dd, $^{3}J$=11,4, 4,7 Hz, 1H), 2,98 (td, $^{3}J$=11,2, 4,7 Hz, 1H), 2,30–2,34 (m, 1H), 2,24–2,15 (m, 1H), 1,98–1,83 (m, 2H), 1,74–1,31 (m, 17H), 1,31–1,13 (m, 4H), 1,08–0,99 (m, 1H), 1,00–0,95 (m, 6H), 0,92 (s, 3H), 0,82 (s, 3H), 0,75 (s, 3H), 0,68 (d, $J$=9,4 Hz, 1H). $^{13}$C KMR (126 MHz, $CDCl_3$) δ 174,97 (d, $^{3}J$=6,4 Hz), 150,46, 109,91, 79,12, 56,96, 55,50, 55,17 (d, $^{1}J$=167,4 Hz), 53,20 (d, $^{2}J$=6,1 Hz), 53,17 (d, $^{2}J$=6,1 Hz), 50,70, 49,58, 46,96, 42,58, 40,85, 39,01, 38,88, 38,39, 37,35, 37,05, 34,48, 32,12, 30,57, 29,70, 28,13, 27,55, 25,67, 21,03, 19,49, 18,44, 16,30, 16,07, 15,50, 14,85. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,88. AIMS: [$C_{33}H_{55}O_6P+H^+$] 579,3809; atrasts 579,3782 (4,7 ppm).

[023] 5. piemērs: savienojuma (4b) iegūšana:

Sintezēts pēc vispārīgās metodes II: savienojums (3b) (0,815 g, 1,413 mmol, 1 ekviv.), $NaBH_4$ (0,213 g, 5,652 mmol, 4 ekviv.), MeOH (20 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 804 mg, 96 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, $CDCl_3$) δ 5,30 (t, $^{3}J$=3,6 Hz, 1H), 4,41 (dd, $^{2}J$=14,6 Hz, 8,7 Hz, 1H), 4,31 (dd, $^{2}J$=14,6 Hz, $^{3}J$=8,3 Hz, 1H), 3,80 (d, $^{3}J$=10,9 Hz, 6H), 3,25–3,17 (m, 1H), 2,90–2.81 (m, 1H), 2,07–1,95 (m, 1H), 1,91–1,85 (m, 2H), 1,77–1,16 (m, 17H), 1,13 (s, 3H), 1,09 (d, $^{2}J$=14,0 Hz, 1H), 0,98 (s, 3H), 0,98–0,92 (m, 1H), 0,92 (s, 3H), 0,90 (s, 6H), 0,78 (s, 3H), 0,72 (s, 3H). $^{13}$C KMR (126 MHz, $CDCl_3$) δ 176,81 (d, $^{3}J$=7,8 Hz), 143,49, 122,89, 79,16, 55,92 (d, $^{1}J$=169,5 Hz), 55,13, 53,23 (d, $^{2}J$=6,3 Hz), 53,23 (d,

$^{2}J$=6,3 Hz), 47,73, 47,24, 45,97, 41,85, 41,48, 39,43, 38,90, 38,60, 37,18, 33,93, 33,18, 32,86, 32,38, 30,81, 28,25, 27,77, 27,34, 25,99, 23,69, 23,57, 23,21, 18,48, 17,02, 15,72, 15,48. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,77. AIMS: [$C_{33}H_{55}O_6P+NH_4^+$] 596,4075; atrasts 596,4042 (5,5 ppm).

[024] 6. piemērs: savienojuma (4c) iegūšana:

Sintezēts pēc vispārīgās metodes II: savienojums (3c) (0,403 g, 0,699 mmol, 1 ekviv.), $NaBH_4$ (0,106 g, 2,795 mmol, 4 ekviv.), MeOH (8 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 382 mg, 92 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, $CDCl_3$) δ 5,26 (bs, 1H), 4,33 (d, $^{2}J$=8,4 Hz, 2H), 3,80 (d, $^{3}J$=10,8 Hz, 6H), 3,21 (dd, $^{3}J$=11,3, 4,6 Hz, 1H), 2,23 (d, $^{3}J$=11,3 Hz, 1H), 2,10–1,99 (m, 1H), 1,95–1,84 (m, 2H), 1,79–1,68 (m, 3H), 1,67–1,22 (m, 12H), 1,13–1,08 (m, 1H), 1.08 (s, 3H), 1,04–0,99 (m, 1H), 0,99 (s, 3H), 0,99–0,94 (m, 1H), 0,94 (d, $^{3}J$=6,3 Hz, 3H), 0,92 (s, 3H), 0,86 (d, $^{3}J$=6,6 Hz, 3H), 0,78 (s, 3H), 0,73 (s, 3H), 0,73–0,69 (m, 1H). $^{13}$C KMR (126 MHz, $CDCl_3$) δ 176,66 (d, $^{3}J$=8,3 Hz), 137,93, 126,08, 79,18, 56,48, 55,81 (d, $^{1}J$=168,9 Hz), 53,25 (d, $^{2}J$=6,4 Hz), 53,25 (d, $^{2}J$=6,4 Hz), 53,03, 48,63, 47,67, 42,18, 39,65, 39,19, 38,95, 38,90, 38,77, 37,11, 36,64, 33,15, 30,72, 28,28, 28,12, 27,37, 24,37, 23,70, 23,45, 21,28, 18,46, 17,13, 17,09, 15,76, 15,62. $^{31}$P KMR (121 MHz, $CDCl_3$) δ 21,91. AIMS: [$C_{33}H_{55}O_6P+H^+$] 579,3809; atrasts 579,3781 (4,8 ppm).

[025] 7. piemērs: savienojuma (5a) iegūšana:

Sintezēts pēc vispārīgās metodes III: savienojums (3a) (0,582 g, 1,009 mmol, 1 ekviv.), TMSI (430 µl, 3,027 mmol, 3 ekviv.), DCM (10 ml), $NaHCO_3$ (0,254 g, 3,027 mmol, 3 ekviv.), $H_2O$ (5 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 569 mg, 97 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, $MeOD_{d4}$) δ 4,72 (s, 1H), 4,58 (s, 1H), 4,16 (dd, $^{2}J$=13,1 Hz, $^{3}J$=8,7 Hz, 1H), 3,90 (dd, $^{2}J$=13,1 Hz, $^{3}J$=8,4 Hz, 1H), 3,02 (td, $^{3}J$=11,2, 4,4 Hz, 1H), 2,58–2,36 (m, 4H), 2,24 (dd, $^{3}J$=11,7, 8,1 Hz, 1H), 2,00–1,86 (m, 2H), 1,76 (d, $^{3}J$=13,0 Hz, 1H), 1,69 (s, 3H), 1,63 (t, $^{3}J$=11,3 Hz, 1H), 1,57–1,27 (m, 13H), 1,19 (t, $^{3}J$=11,7 Hz, 1H), 1,13–1,06 (m, 1H), 1,06 (s, 3H), 1,04–0,98 (m, 9H), 0,95 (s, 3H). $^{13}$C KMR (126 MHz, $MeOD_{d4}$) δ 221,02, 176,99 (d, $^{3}J$=8,4 Hz), 151,94, 110,22, 59,92 (d, $^{1}J$=162,6 Hz), 57,99, 56,11, 51,23, 50,68, 48,31, 43,61, 41,87, 40,75, 39,60, 38,06, 37,79, 35,05, 34,74, 34,74, 32,92, 31,61, 30,88, 27,17, 26,89, 22,62, 21,43, 20,76, 19,55, 16,54, 16,35, 15,03. $^{31}$P KMR (121 MHz, $MeOD_{d4}$) δ 14,20. AIMS: [$C_{31}H_{49}O_6P-H^+$] 547,3194; atrasts 547,3198 (0,7 ppm).

[026] 8. piemērs: savienojuma (5b) iegūšana:

Sintezēts pēc vispārīgās metodes III: savienojums (3b) (0,343 g, 0,595 mmol, 1 ekviv.), TMSI (260 µl, 1,787 mmol, 3 ekviv.), DCM (7 ml), $NaHCO_3$ (0,151 g, 1,787 mmol, 3 ekviv.), $H_2O$ (6 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 317 mg, 90 %. Balta amorfa viela.

$^{1}$H KMR (500 MHz, MeOD$_{d4}$) δ 5,30 (d, $^{3}J$=3,7 Hz, 1H), 4,21–4,09 (m, 2H), 2,92 (dd, $^{2}J$=14,1 Hz, $^{3}J$=4,5 Hz, 1H), 2,57 (ddd, $^{2}J$=16,1 Hz, $^{3}J$=10,8, 7,4 Hz, 1H), 2,37 (ddd, $^{2}J$=16,1 Hz, $^{3}J$=7,1, 3,6 Hz, 1H), 2,09–1,86 (m, 4H), 1,84–1,60 (m, 6H), 1,59–1,32 (m, 7H), 1,21 (d, $^{2}J$=13,2 Hz, 1H), 1,18 (s, 3H), 1,16–1,09 (m, 2H), 1,08 (s, 6H), 1,05 (s, 3H), 0,95 (s, 3H), 0,91 (s, 3H), 0,83 (s, 3H). $^{13}$C KMR (126 MHz, MeOD$_{d4}$) δ 220,52, 179,04 (d, $^{3}J$=9,0 Hz), 144,96, 124,09, 123,75, 90,51, 60,43 (d, $^{1}J$=162,8 Hz), 56,64, 48,23, 48,22, 47,12, 42,97, 42,90, 40,59, 40,22, 37,90, 34,88, 33,56, 33,39, 33,31, 31,59, 28,95, 26,89, 26,31, 24,61, 24,06, 23,89, 21,90, 20,71, 17,51, 15,54. $^{31}$P KMR (121 MHz, MeOD$_{d4}$) δ 11,53. AIMS: [$C_{31}H_{49}O_6P$-$H^+$] 547,3194; atrasts 547,3194 (0 ppm).

[027] 9. piemērs: savienojuma (5c) iegūšana:

Sintezēts pēc vispārīgās metodes III: Sintezēts pēc vispārīgās metodes III: savienojums (3c) (0,450 g, 0,780 mmol, 1 ekviv.), TMSI (340 µl, 2,341 mmol, 3 ekviv.), DCM (5 ml), $NaHCO_3$ (0,250 g, 2,341 mmol, 3 ekviv.), $H_2O$ (4 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 237 mg, 51 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, MeOD$_{d4}$) δ 5,30 (d, $^{3}J$=3,7 Hz, 1H), 4,08 (d, $^{2}J$=13,2 Hz, 1H), 4,00 (d, $^{2}J$=13,2 Hz, 1H), 2,57 (ddd, $^{2}J$=16,0 Hz, $^{3}J$=10,7, 7,4 Hz, 1H), 2,39 (ddd, $^{2}J$=16,0 Hz, $^{3}J$=7,1, 3,7 Hz, 1H), 2,32 (d, $^{3}J$=11,3 Hz, 1H), 2,10–1,90 (m, 4H), 1,90–1,81 (m, 2H), 1,72 (dt, $^{2}J$=13,8 Hz, $^{3}J$=4,0 Hz, 1H), 1,67 (dd, $^{3}J$=11,0, 5,7 Hz, 1H), 1,62–1,44 (m, 5H), 1,44–1,28 (m, 4H), 1,12 (s, 3H), 1,12–1,08 (m, 1H), 1,08 (s, 6H), 1,05 (s, 3H), 1,03–0,99 (m, 1H), 0,95 (d, $^{3}J$=6,2 Hz, 4H), 0,89 (d, $^{3}J$=6,4 Hz, 3H), 0,86 (s, 3H). $^{13}$C KMR (126 MHz, MeOD$_{d4}$) δ 220,64, 179,92 (d, $^{3}J$=8,8 Hz), 139,68, 126,80, 62,93 (d, $^{1}J$=153,5 Hz), 56,50, 54,32, 49,49, 48,15, 43,30, 40,80, 40,46, 40,41, 40,23, 37,82, 37,82, 37,44, 35,14, 33,68, 31,84, 29,39, 27,07, 25,07, 24,51, 24,07, 21,92, 21,60, 20,72, 17,67, 17,63, 15,72. $^{31}$P KMR (121 MHz, MeOD$_{d4}$) δ 11,53. AIMS: [$C_{31}H_{49}O_6P$-$H^+$] 547,3194; atrasts 547,3195 (0,2 ppm).

[028] 10. piemērs: savienojuma (6a) iegūšana:

Sintezēts pēc vispārīgās metodes III: savienojums (4a) (0,280 g, 0,359 mmol, 1 ekviv.), TMSI (150 µl, 1,078 mmol, 3 ekviv.), DCM (6 ml), $NaHCO_3$ (0,091 g, 1,078 mmol, 3 ekviv.), $H_2O$ (3 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 194 mg, 91 %. Balta amorfa viela. $^{1}$H KMR (500 MHz, MeOD$_{d4}$) δ 4,62 (s, 1H), 4,48 (s, 1H), 4,08 (dd, $^{2}J$=13,5 Hz, $^{3}J$=8,9 Hz, 1H), 3,95 (dd, $^{2}J$=13,5 Hz, $^{3}J$=8,9 Hz, 1H), 3,02 (dd, $^{3}J$=11,4, 4,6 Hz, 1H), 2,93 (td, $^{3}J$=11,3, 4,5 Hz, 1H), 2,32 (d, $^{2}J$=12,3 Hz, 1H), 2,27–2,19 (m, 1H), 1,99 (dd, $^{2}J$=12,1, $^{3}J$=8,1 Hz, 1H), 1,88–1,80 (m, 1H), 1,66–1,57 (m, 1H), 1,59 (s, 3H), 1,57–1,11 (m, 15H), 1,11–0,91 (m, 2H), 0,89 (s, 3H), 0,87–0,82 (m, 7H), 0,76 (s, 3H), 0,65 (s, 3H), 0,63–0,57 (m, 1H). $^{13}$C KMR (126 MHz, MeOD$_{d4}$) δ 177,50 (d, $^{3}J$=8,8 Hz), 152,07, 110,11, 79,69, 61,13 (d, $^{1}J$=159,5 Hz), 57,95,

56,90, 52,05, 50,81, 48,32, 43,52, 41,95, 40,11, 39,96, 39,42, 38,33, 37,83, 35,55, 32,99, 31,67, 30,95, 28,61, 28,05, 26,90, 22,08, 19,57, 19,45, 16,74, 16,62, 16,11, 15,11. $^{31}$P KMR (121 MHz, MeOD$_{d4}$) δ 11,47. AIMS: [$C_{31}H_{51}O_6P$-$H^+$] 549,3350; atrasts 549,3351 (0,2 ppm).

[029] 11. piemērs: savienojuma (6b) iegūšana:

Sintezēts pēc vispārīgās metodes III: savienojums (4b) (0,600 g, 1,037 mmol, 1 ekviv.), TMSI (440 µl, 3,110 mmol, 3 ekviv.), DCM (10 ml), $NaHCO_3$ (0,260 g, 3.110 mmol, 3 ekviv.), $H_2O$ (5 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 481 mg, 78 %. Balta amorfa viela. $^1$H KMR (500 MHz, MeOD$_{d4}$) δ 5,25 (t, $^3J$=3,6 Hz, 1H), 4.16 (dd, $^2J$=13,2 Hz, $^3J$=8,8 Hz, 1H), 3,96 (dd, $^2J$=13,3 Hz, $^3J$=8,6 Hz, 1H), 3,14 (dd, $^3J$=11,4, 4,5 Hz, 1H), 2,88 (dd, $^3J$=14,2, 4,4 Hz, 1H), 1,99 (dt, $^2J$=13,8 Hz, $^3J$=7,7 Hz, 1H), 1,96–1,79 (m, 3H), 1,79–1,27 (m, 14H), 119 (d, $^2J$=14,9 Hz, 1H), 1,15 (s, 3H), 1,13–1,00 (m, 2H), 0,97 (s, 3H), 0,94 (s, 6H), 0,90 (s, 3H), 0,78 (s, 6H), 0,77–0,72 (m, 1H). $^{13}$C KMR (126 MHz, MeOD$_{d4}$) δ 180.03 (d, $^3J$=8.9 Hz), 145.27, 123.59, 79.77, 62.76 (d, $^1J$=154.7 Hz), 56.80, 49.17, 48.11, 47.34, 42.85, 40.60, 39.88, 39.85, 38.17, 38.17, 34.99, 33.94, 33.64, 33.17, 31.58, 29.11, 28.74, 27.88, 26.41, 24.53, 24.16, 23.80, 19.50, 17.67, 16.30, 15.91. $^{31}$P KMR (121 MHz, MeOD$_{d4}$) δ 11,59. AIMS: [$C_{31}H_{51}O_6P$-$H^+$] 549,3350; atrasts 549,3348 (0,4 ppm).

[030] 12. piemērs: savienojuma (6c) iegūšana:

Sintezēts pēc vispārīgās metodes III: savienojums (4c) (0,445 g, 0,769 mmol, 1 ekviv.), TMSI (330 µl, 2,307 mmol, 3 ekviv.), DCM (5 ml), $NaHCO_3$ (0,195 g, 3.110 mmol, 3 ekviv.), $H_2O$ (4 ml). Reakcijas laiks 5 stundas, 0 °C temperatūrā. Iznākums: 426 mg, 93 %. Balta amorfa viela. $^1$H KMR (500 MHz, MeOD$_{d4}$) δ 5,27 (d, $^3J$=3,9 Hz, 1H), 4,03 (dt, $^2J$=10,3 Hz, $^3J$=5,1 Hz, 2H), 3,15 (dd, $^3J$=11,4, 4,6 Hz, 1H), 2,31 (d, $^3J$=11,3 Hz, 1H), 2,04 (td, $^2J$=13,3 Hz, $^3J$=4,3 Hz, 1H), 1,96–1,85 (qd, $^2J$=12,1 Hz, $^3J$=4,0 Hz, 3H), 1,84–1,73 (m, 2H), 1,73–1,61 (m, 3H), 1,61–1,46 (m, 5H), 1,45–1,26 (m, 4H), 1,11 (s, 3H), 1,07 (d, $^2J$=13,4 Hz, 1H), 1,04–0,98 (m, 2H), 0,98–0,93 (m, 9H), 0,89 (d, $^3J$=6,4 Hz, 3H), 0,79 (s, 3H), 0,78 (s, 3H), 0,74 (d, $^3J$=11,4 Hz, 1H). $^{13}$C KMR (126 MHz, MeOD$_{d4}$) δ 179,47 (d, $^3J$=9,2 Hz), 139,44, 127,13, 79,72, 61,63 (d, $^1J$=158,8 Hz), 56,75, 54,19, 49,49, 49,03, 43,12, 40,83, 40,39, 40,21, 40,01, 39,84, 38,09, 37,51, 34,20, 31,77, 29,29, 28,76, 27,90, 25,09, 24,36, 24,18, 21,59, 19,47, 17,70, 17,62, 16,37, 16,03. $^{31}$P KMR (121 MHz, MeOD$_{d4}$) δ 12,17. AIMS: [$C_{31}H_{51}O_6P$-$H^+$] 549,3350; atrasts 549,3349 (0,2 ppm).

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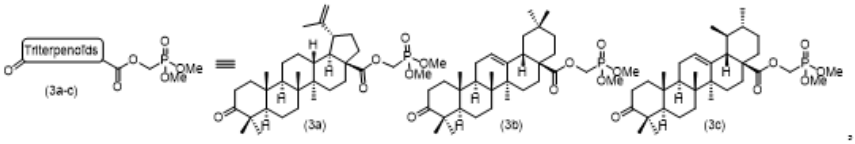
# PRETENZIJAS

1. Triterpenoīdu dabas savienojumu ar vispārīgo formulu (3a-c) iegūšanas paņēmiens, kas raksturīgs ar to, ka triterpenoīdu karbonskābes (1a-c) un triflāts (2) reaģē absolutizētā THF šķīdumā tBuOK klātienē un veido mērķa produktus (3a-c), ko izdala ar vispārpieņemtām metodēm.

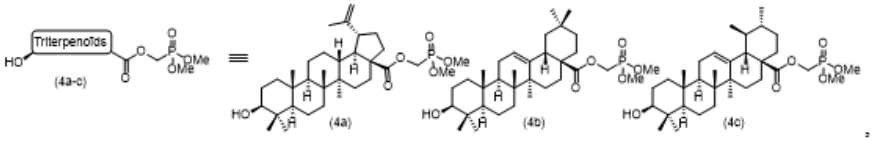
2. Triterpenoīdu dabas savienojumi ar vispārīgo formulu (3a-c):




kuri iegūti ar paņēmienu saskaņā ar 1. pretenziju.

3. Triterpenoīdu dabas savienojumu ar vispārīgo formulu (4a-c) iegūšanas paņēmiens, kas raksturīgs ar to, ka ketona funkcionālās grupas saturoši atvasinājumi (3a-c) viegli pakļaujas reducēšanai ar $NaBH_4$ atdzesētā līdz 0 °C MeOH šķīdumā un veido atbilstošus spirta funkcionālo grupu saturošus produktus, kurus izdala ar vispārpieņemtām metodēm.

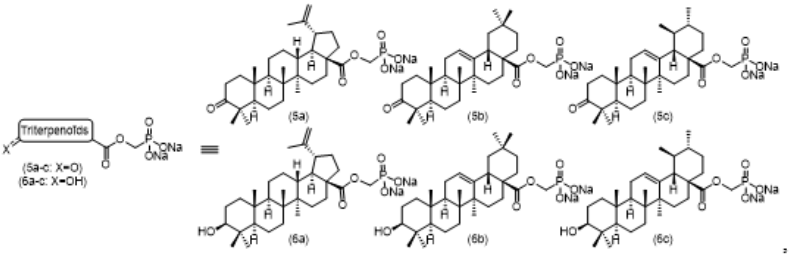
4. Triterpenoīdu dabas savienojumi ar vispārīgo formulu (4a-c):




kuri iegūti ar paņēmienu saskaņā ar 3. pretenziju.

5. Ūdens vidē šķīstošu triterpenoīdu dabas savienojumu ar vispārīgo formulu (5a-c) un (6a-c) iegūšanas paņēmiens, kas raksturīgs ar to, ka estera saiti saturoši savienojumi (3a-c) un (4a-c) tiek pakļauti demetilēšanas reakcijai ar TMSI atdzesētā līdz -40 °C dihlormetāna šķīdumā 4 stundās, veido produktus, kurus izdala ar vienkāršām un vispārpieņemtām metodēm.

6. Ūdens vidē šķīstoši triterpenoīdu dabas savienojumi ar vispārīgo formulu (5a-c) un (6a-c):




kuri iegūti ar paņēmienu saskaņā ar 5. pretenziju.

Pielikums III

Appendix III

# C(3)-Phosphonate derivatives of pentacyclic triterpenoids (unpublished results)

**Synthesis: general information**

Solvents for the reactions were dried over standard drying agents and freshly distilled prior to use. All purchased chemicals (Fluka, Aldrich) were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 $F_{254}$ and visualized by using UV lamp. Column chromatography was performed on silica gel (60 Å, Upasil® 60 35-70μm). Flash column chromatography was performed on a Büchi Sepacore system (Büchi-Labortechnik GmbH, Essen, Germany) with a Büchi Control Unit C-620, an UV detector Büchi UV photometer C-635, Büchi fraction collector C-660 and two Pump Modules C-605. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 300 and 500 MHz, in $CDCl_3$ or [$D_4$]MeOD at 25 °C. Chemical shifts (δ) values are reported in ppm. The residual solvent peaks are used as internal reference ($CDCl_3$) 7.26 ppm, [$D_4$]MeOD 3.31 ppm for $^{1}H$ NMR, $CDCl_3$ 77.16 ppm, [$D_4$]MeOD 49.00 ppm for $^{13}C$ NMR), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); *J* in hertz. $^{1}H$ and $^{13}C$ NMR peaks were assigned by analysis of multidimensional NMR (COSY, HSQC, HMBC). For $^{31}P$ NMR calibration, $Ph_3P$ was used as external reference (-6.00 ppm in $MeOD_{d4}$) in a coaxially inserted tube. High-resolution mass spectra (ESI) were performed on Thermo Fisher Scientific Orbitrap Exploris 120 mass spectrometer operating in Full Scan mode at the 120000 resolutions.

**General method for synthesis of triterpenic acid PMB esters**

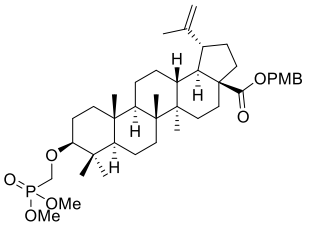
To a suspension of triterpenic acid (5.50 g, 12.0 mmol, 1.0 eq.) and $K_2CO_3$ (4.97 g, 36.0 mmol, 3.0 eq.) in DMF (50 mL) 4-methoxybenzyl bromide (2.90 g, 14.4 mmol, 1.2 eq.) was added dropwise at 0 °C. The resulting reaction mixture was stirred for 16 h at room temperature and DMF was evaporated at reduced pressure. Solid residue was dissolved in ethyl acetate (100 mL) and subsequently washed with water (3 × 50 mL) and brine (50 mL). Then it was dried over $Na_2SO_4$, filtered and evaporated do dryness to afford white amorphous solid which was directly used in the next step without additional purification.

**General method for synthesis of triterpenic phosphonate ethers 31a-c**

To solution of triterpenic acid PMB ester (470 mg, 0.81 mmol, 1 eq.) in THF (4.5 mL) freshly prepared solution of 0.5 M LDA (1.72 mL, 0.86 mmol, 1.05 eq) in THF was added dropwise at -78 °C and obtained mixture was stirred for 20 min at ambient temperature. Then a solution of (dimethoxyphosphoryl)methyl trifluoromethanesulfonate (277 mg, 1.02 mmol, 1.2 eq.) in THF (2mL) was added at -78 °C. The resulting mixture was left to warm up to room temperature during 1 h and then stirred for additional 2 h at room temperature. Then the reaction mixture was quenched with MeOH (1 mL) and evaporated to dryness, redissolved in EtOAc (25 mL) and subsequently washed with $H_2O$ (15 mL) and brine (2 × 15 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated *in vacuo* and purified by silica column chromatography (Hexanes-EtOAc 4:1–1:1) to yield the desired product as a white amorphous solid.

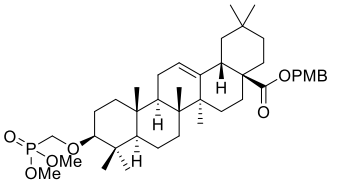
**General method for demethylation of triterpenic phosphonate ethers**

To a solution of compound **32a-c** (140 mg, 0.2 mmol, 1 eq.) in anhydrous DCM (2 mL) TMSI (171 µL 1.2 mmol, 6 eq.) is added dropwise at -40 °C and the resulting reaction mixture is stirred at -40 °C for 5 h. Then MeOH (1 mL) is added dropwise at -40 °C. The obtained reaction mixture is stirred for additional 30 min at the same temperature and solution of $NaHCO_3$ (101 mg, 1.2 mmol, 6 eq.) in $H_2O$ (3 mL) is added dropwise at -40 °C. The resulting reaction mixture is warmed up to room temperature and the organic solvents are evaporated *in vacuo*. The obtained aqueous suspension is centrifuged and the supernatant is removed and discarded. The precipitate is re-suspended in deionized water (1 mL) and the centrifugation – supernatant removal procedure is repeated additional two times (in total: washing with water 3 × 1 mL). The obtained precipitate is then suspended in MeCN (1 mL) and centrifuged and the supernatant is removed and discarded. The precipitate is re-suspended in MeCN (1 mL) and the centrifugation – supernatant removal procedure is repeated additional four times (in total: washing with MeCN 5 × 1 mL). The obtained precipitate is then dried in vacuo to yield product as a white amorphous solid.




**(3*S*)-3-((dimethoxyphosphoryl)methyloxy)-lup-20(29)en-28-oic acid 4-methoxybenzyl ester 31a**

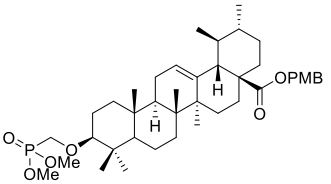
$^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 2H, 2H-Ar, $^3J$ = 8.6 Hz), 6.85 (d, 2H, 2H-Ar, $^3J$ = 8.6 Hz), 5.07 (d, $^2J$ = 12.0 Hz, 1H, $H_a$-C-Ar), 5.02 (d, $^2J$ = 12.0 Hz, 1H, $H_b$-C-Ar), 4.72 (s, 1H, $H_a$-C(29)), 4.58 (s, 1H, $H_b$-C(29)), 3.98 (dd, $^2J$ = 13.6, 8.7 Hz, 1H, $H_a$-C(3')), 3.81 (s, 3H, P-OMe), 3.80 (s, 3H, P-OMe), 3.79 (s, 3H, Ar-OMe), 3.67 (dd, $^2J$ = 13.6, 9.7 Hz, 1H, $H_b$-C(3')), 3.00 (ddd, $^3J$ = 11.4, 10.2, 4.5 Hz, 1H, H-C(19)), 2.82 (dd, $^3J$ = 11.8, 4.3 Hz, 1H, H-C(3)), 2.24 (dt, $^2J$ = 12.2, $^3J$ = 3.1 Hz, 1H, $H_a$-C(16)), 2.15 (td, $^3J$ = 12.3, 3.6 Hz, 1H, H-C(13)), 1.90 – 1.82 (m, 2H, $H_a$-C(21), $H_a$-C(22)), 1.78 – 1.67 (m, 2H, $H_a$-C(1), $H_a$-C(2)), 1.69 – 1.64 (m, 4H, $H_3$-C(30), $H_a$-C(12)), 1.56 (dd, $^3J$ = 12.3, 11.4 Hz, 1H, H-C(18)), 1.50 – 1.15 (m, 12H, $H_2$-C(6), $H_2$-C(11), $H_b$-C(12), $H_a$-C(15), $H_b$-C(16), $H_b$-C(21), $H_2$-C(7), $H_b$-C(22), H-C(6)), 1.07 (dt, $^2J$ = 13.4, $^3J$ = 3.1 Hz, 1H, $H_b$-C(15)), 1.00 – 0.95 (m, 4H, $H_b$-C(15), $H_3$-C(23)), 0.92 (s, 3H, $H_3$-C(27)), 0.84 – 0.80 (m, 1H, $H_b$-C(1)), 0.79 (s, 3H, $H_3$-C(25)), 0.75 (s, 3H, $H_3$-C(24)), 0.74 (s, 3H, $H_3$-C(26)), 0.67 – 0.61 (m, 1H, H-C(5)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.02 (C28), 159.60 (C-OMe), 150.78 (C20), 130.18 (2C-H(Ar)), 128.82 (C-O-C=O), 113.97 (2C-H(Ar)), 109.70 (C29), 90.06 (d, $^3J$ = 12.1 Hz, C(3)), 65.59 ($CH_2$-Ar), 63.21 (d,$^1J$ = 167.1 Hz, (C3')), 56.62 (C17), 55.87 (C5), 55.44 (OMe), 53.27 (d, $^3J$ = 6.5 Hz, MeOP), 53.13 (d, $^3J$ = 6.5 Hz, MeOP), 50.64 (C9), 49.56 (C18), 47.10 (C19) , 42.51 (C14), 40.80 (C8), 39.10 (C4), 38.55 (C1), 38.31 (C13), 37.29 (C10), 37.07 (C21), 34.40 (C7), 32.25 (C16), 30.73 (C22), 29.66 (C15), 28.15 (C23), 25.66 (C12), 22.36 (C2), 21.04 (C11), 19.51 (C30), 18.27 (C6), 16.26 (C24), 16.23 (C25), 15.97 (C26), 14.76 (C27). $^1$P NMR (121 MHz, $CDCl_3$) δ 23.85. HRMS: [$C_{41}H_{63}O_7P + H^+$] 699.4384; found 699.4402 (2.6 ppm).




**(3*S*)-3-((dimethoxyphosphoryl)methyloxy)-olean-12(13)en-28-oic acid 4-methoxybenzyl ester 31b**

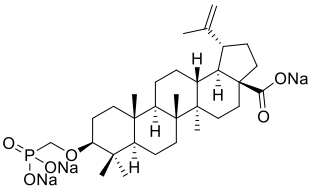
$^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $^3J$ = 8.6 Hz, 2H, 2H-Ar), 6.88 (d, $^3J$ = 8.6 Hz, 2H, 2H-Ar), 5.26 (t, $^3J$ = 3.7 Hz, 1H, H-C(12)), 5.03 (d, $^2J$ = 12.1 Hz, $H_a$-C-Ar), 4.97 (d, $^2J$ = 12.1 Hz, 1H, $H_a$-C-Ar), 3.99 (dd, $^2J$ = 13.6 Hz, $^3J$ = 8.7 Hz, 1H, $H_a$-C(3')), 3.82 (s, 3H, MeO-P), 3.81 (s, 3H, MeO-Ar), 3.79 (s, 3H, MeO-P), 3.68 (dd, $^2J$ = 13.6 Hz, $^3J$ = 9.6 Hz, 1H, $H_b$-C(3')), 2.90 –

2.83 (m, 2H, H-C(3), H-C(18)), 1.95 (td, $^{2}J$ = 13.2 Hz, $^{3}J$ = 4.0 Hz, 1H, $H_a$-C(16)), 1.86 – 1.80 (m, 2H, $H_2$-C(11)), 1.75 (ddd, $^{2}J$ = 12.4 Hz, $^{3}J$ = 12.3, 3.9 Hz, 1H, $H_a$-C(2)), 1.69 – 1.56 (m, 5H, $H_b$-C(16), $H_a$-C(15), $H_a$-C(21), $H_a$-C(1), $H_a$-C(19)), 1.56 – 1.37 (m, 5H, $H_a$-C(6), $H_b$-C(2), $H_b$-C(21), $H_a$-C(22), H-C(9)), 1.37 – 1.11 (m, 5H, $H_b$-C(6), $H_b$-C(22), $H_2$-C(7), $H_b$-C(19)), 1.10 (s, 3H, $H_3$-C(27)), 1.04 – 1.00 (m, 1H, $H_b$-C(15)), 1.00 (s, 3H, $H_3$-C(23)), 0.90 (s, 3H, C(29)), 0.88 (s, 3H, $H_3$-C(30)), 0.87 (s, 3H, $H_3$-C(25)), 0.87 – 0.82 (m, 1H, H-C(1)), 0.77 (s, 3H, $H_3$-C(24)), 0.72 – 0.67 (m, 1H, H-C(5)), 0.59 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 177.64 (C28), 159.52 (C-OMe), 143.90 (C13), 129.95 (2C-H(Ar)), 128.73 (C-O-C=O), 122.51 (C12), 113.90 (2C-H(Ar)), 90.06 (d, $^{3}J$ = 12.1 Hz, C(3)), 65.86 ($CH_2$-Ar), 63.23 (d,$^{1}J$ = 167.3 Hz, (C3')), 55.73 (C5), 55.42 (OMe) , 53.30 (d, $^{3}J$ = 6.5 Hz, MeOP), 53.13 (d, $^{3}J$ = 6.5 Hz, MeOP), 47.71 (C9), 46.80 (C17), 46.00 (C19), 41.81 (C14), 41.50 (C18), 39.44 (C8), 39.00 (C4), 38.29 (C1), 37.11 (C10), 33.98 (C7), 33.25 (C30), 32.82 (C22), 32.47 (C21), 30.84 (C20), 28.27 (C23), 27.72 (C15), 25.99 (C27), 23.80 (C29), 23.56 (C11), 23.14 (C16), 22.15 (C2), 18.30 (C6), 17.03 (C26), 16.47 (C24), 15.41 (C25). $^{1}$P NMR (121 MHz, $CDCl_3$) δ 23.81. HRMS: [$C_{41}H_{63}O_7P + H^+$] 699.4384; found 699.4395 (1.6 ppm).




**(3*S*)-3-((dimethoxyphosphoryl)methyloxy)-urs-12(13)en-28-oic acid 4-methoxybenzyl ester 31c**

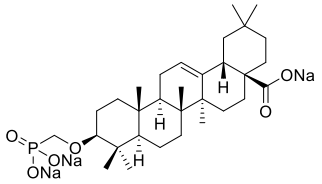
$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, $^{3}J$ = 8.6 Hz, 2H, 2H-Ar), 6.87 (d, $^{3}J$ = 8.6 Hz, 2H, 2H-Ar), 5.21 (t, $^{3}J$ = 3.6 Hz, 1H, H-C(12)), 5.04 (d, $^{2}J$ = 12.1 Hz, 1H, $H_a$-C-Ar), 4.90 (d, $^{2}J$ = 12.1 Hz, 1H, $H_b$-C-Ar), 3.99 (dd, $^{2}J$ = 13.6 Hz, $^{3}J$ = 8.7 Hz, 1H, $H_a$-C(3')), 3.82 (s, 3H, MeO-P), 3.81 (s, 3H, MeO-Ar), 3.80 (s, 3H, MeO-P), 3.68 (dd, $^{2}J$ = 13.6 Hz, $^{3}J$ = 9.7 Hz, 1H, $H_b$-C(3')), 2.86 (dd, $^{3}J$ = 11.7, 4.2 Hz, 1H, H-C(3)), 2.24 (d, $^{3}J$ = 11.0 Hz, 1H, H-C(18)), 1.98 (td, $^{2}J$ = 13.2 Hz, 4.4 Hz, 1H, $H_a$-C(16)), 1.92 – 1.81 (m, 2H, $H_2$-C(11)), 1.81 – 1.73 (m, 2H, $H_a$-C(2), $H_a$-C(15)), 1.71 – 1.63 (m, 3H, $H_b$-C(16), $H_a$-C(21), $H_a$-C(1)), 1.61 – 1.53 (m, 1H, $H_b$-C(21)), 1.53 – 1.41 (m, 5H, $H_a$-C(16), $H_b$-C(2), $H_a$-C(22), $H_a$-C(7), H-C(9)), 1.37 – 1.23 (m, 4H, $H_b$-C(6), $H_b$-C(22), $H_b$-C(7), H-C(19)), 1.05 (s, 3H, $H_3$-C(27)), 1.04 – 0.99 (m, 5H, $H_3$-C(23), H-C(20), $H_b$-C(15)), 0.94 – 0.90 (m, 4H, $H_3$-C(30), $H_b$-C(1)), 0.89 (s, 3H, $H_3$-C(25)), 0.84 (d, $^{3}J$ = 6.4 Hz, 3H, $H_3$-C(29)), 0.77 (s, 3H, $H_3$-C(24)), 0.69 (d, $^{3}J$ = 11.7 Hz, 1H, H-C(5)), 0.62 (s, 3H, $H_3$-C(26)). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 177.49 (C28), 159.54 (C-OMe), 138.28 (C13), 130.11 (2C-H(Ar)), 128.66 (C-O-C=O), 125.73 (C12), 113.89 (2C-H(Ar)), 90.12 (d, $^{3}J$ = 12.1 Hz, C(3)), 65.90 ($CH_2$-Ar), 63.26 (d,$^{1}J$ = 167.1 Hz, (C3')) 55.75 (C5), 55.42 (OMe), 53.30 (d, $^{3}J$ = 6.5 Hz, MeOP), 53.13 (d, $^{3}J$ = 6.5 Hz, MeOP), 53.00 (C18), 48.17 (C17), 47.66 (C18), 42.16 (C14), 39.68 (C8), 39.22 (C19), 38.99 (C4), 38.95 (C20), 38.48 (C1), 37.05 (C10), 36.73 (C21), 33.14 (C7), 30.79 (C22), 28.31 (C23), 28.05 (C15), 24.33 (C16), 23.66 (C11), 23.44 (C27), 22.19 (C2), 21.32 (C30), 18.29 (C6), 17.17 (C29), 17.14 (C26), 16.52 (C24), 15.55 (C25). $^{1}$P NMR (121 MHz, $CDCl_3$) δ 23.84. HRMS: [$C_{41}H_{63}O_7P + H^+$] 699.4384; found 699.4396 (1.7 ppm).




**Sodium (28-norlup-20(29)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32a**

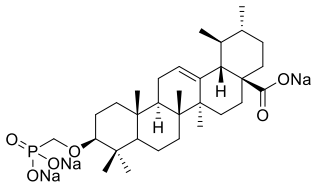
$^{1}$H NMR (500 MHz, MeOD) δ 4.71 (s, 1H, $H_a$-C(29)), 4.59 (s, 1H, $H_b$-C(29)), 3.86 (dd, $^{2}J$ = 13.3 Hz, $^{3}J$ = 9.0 Hz, 1H, $H_a$-C(3')), 3.56 (dd, $^{2}J$ = 13.3 Hz, $^{3}J$ = 10.2 Hz, 1H, $H_b$-C(3')), 3.02 (td, $^{3}J$ = 10.9, 4.7 Hz, 1H, H-C(19)), 2.89 (dd, $^{3}J$ = 11.8, 4.3 Hz, 1H, H-C(3)), 2.30 (td, $^{3}J$ =

12.0, 3.6 Hz, 1H, H-C(13)), 2.23 (dt, $^2J$ = 12.8 Hz, $^3J$ = 3.3 Hz, 1H, $H_a$-C(16)), 1.99 – 1.87 (m, 2H, $H_a$-C(21), $H_a$-C(22)), 1.82 (dt, $^2J$ = 12.6 Hz, $^3J$ = 4.3 Hz, 1H, $H_a$-C(2)), 1.79 – 1.70 (m, 2H, $H_a$-C(12), $H_a$-C(1)), 1.70 (s, 3H, $H_3$-C(30)), 1.63 (dd, $^3J$ = 12.0, 10.9 Hz, 1H, H-C(18)), 1.58 – 1.48 (m, 3H, $H_a$-C(6), $H_b$-C(2), $H_a$-C(15)), 1.48 – 1.34 (m, 7H, $H_b$-C(6), $H_a$-C(11), $H_b$-C(22), $H_b$-C(21), $H_2$-C(7), $H_b$-C(16)), 1.34 – 1.21 (m, 2H, $H_b$-C(11), H-C(9)), 1.18 (dt, $^2J$ = 13.3 Hz, $^3J$ = 3.3 Hz, 1H, $H_b$-C(15)), 1.08 – 1.01 (m, 1H, $H_b$-C(12)), 1.02 (s, 3H, $H_3$-C(23)), 1.01 (s, 3H, $H_3$-C(27)), 0.94(s, 3H, $H_3$-C(26)), 0.93 – 0.88 (m, 1H, $H_a$-C(1)), 0.87 (s, 3H, $H_3$-C(25)), 0.79 (s, 3H, $H_3$-C(24)), 0.73 (d, $^3J$ = 9.7 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD) δ 179.99 (C28), 151.98 (C20), 110.19 (C29), 90.88 (d, $^3J$ = 12.5 Hz, C(3)), 66.83 (d, $^1J$ = 165.5 Hz, C(3')), 57.46 (C17), 57.21 (C5), 51.96 (C9), 50.42 (C18), 48.48 (C19), 43.58 (C14), 41.96 (C8), 40.09 (C4), 39.74 (C1), 39.65 (C13), 38.34 (C10), 38.13 (C21), 35.57 (C7), 33.32 (C16), 31.69 (C21), 30.83 (C15), 28.57 (C23), 26.87 (C12), 23.31 (C2), 22.12 (C11), 19.54 (C30), 19.27 (C6), 16.76 (C25), 16.69 (C24), 16.64 (C26), 15.10 (C27). $^1$P NMR (121 MHz, MeOD$_{d4}$) δ 20.13. HRMS: [$C_{31}H_{51}O_6P$-H$^+$] 549.3350; found 549.3345 (0.9 ppm).



**Sodium (28-norolean-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32b**

$^1$H NMR (500 MHz, MeOD) δ 5.24 (t, $^3J$ = 3.7 Hz, 1H, H-C(12)), 3.84 (dd, $^2J$ = 13.2 Hz, $^3J$ = 9.0 Hz, 1H, $H_a$-C(3')), 3.55 (dd, $^2J$ = 13.2 Hz, $^3J$ = 10.2 Hz, 1H, $H_b$-C(3')), 2.91 (dd, $^3J$ = 11.8, 4.2 Hz, 1H, H-C(3)), 2.85 (dd, $^3J$ = 13.3, 4.6 Hz, 1H, H-C(18)), 2.02 (td, $^2J$ = 13.6 Hz, $^3J$ = 4.0 Hz, 1H, $H_a$-C(16)), 1.94 – 1.88 (m, 2H, $H_2$-C(11)), 1.85 – 1.80 (m, 1H, $H_a$-C(2)), 1.79 – 1.65 (m, 4H, $H_a$-C(15), $H_a$-C(21), $H_a$-C(1), $H_a$-C(19)), 1.63 – 1.47 (m, 6H, $H_a$-C(6), $H_b$-C(16), $H_b$-C(2), $H_2$-C(7), H-C(9)), 1.46 – 1.35 (m, 2H, $H_b$-C(6), $H_a$-C(22)), 1.33 – 1.28 (m, 1H, $H_b$-C(21)), 1.23 – 1.18 (m, 1H, $H_b$-C(22)), 1.16 (s, 3H, $H_3$-C(27)), 1.14 – 1.07 (m, 2H, $H_b$-C(15), $H_b$-C(19)), 1.04 (s, 3H, $H_3$-C(23)), 0.95 (s, 3H, $H_3$-C(25)), 0.94 (s, 3H, $H_3$-C(29)), 0.94 – 0.91 (m, 1H, $H_b$-C(1)), 0.91 (s, 3H, $H_3$-C(30)), 0.81 (s, 6H, $H_3$-C(24), $H_3$-C(25)), 0.78 (d, $^3J$ = 11.5 Hz, 1H, H-C(5)). $^{13}$C NMR (126 MHz, MeOD) δ 181.82 (C28), 145.21 (C13), 123.65 (C12), 90.85 (d, $^3J$ = 12.1 Hz, C(3)), 66.23 (d, $^1J$ = 164.7 Hz, C(3')), 57.12 (C5), 49.01 (C9), 47.63 (C17), 47.23 (C19), 42.89 (C14), 42.73 (C18), 40.59 (C8), 39.98 (C4), 39.52 (C1), 38.18 (C10), 34.89 (C22), 34.00 (C21), 33.82 (C7), 33.56 (C30), 31.62 (C20), 28.83 (C15), 28.72 (C23), 26.39 (C27), 24.55 (C11), 24.05 (C16), 23.97 (C29), 23.14 (C2), 19.34 (C6), 17.73 (C26), 16.91 (C24), 15.93 (C25). $^1$P NMR (121 MHz, MeOD$_{d4}$) δ 19.58. HRMS: [$C_{31}H_{51}O_6P$-H$^+$] 549.3350; found 549.3342 (1.5 ppm).

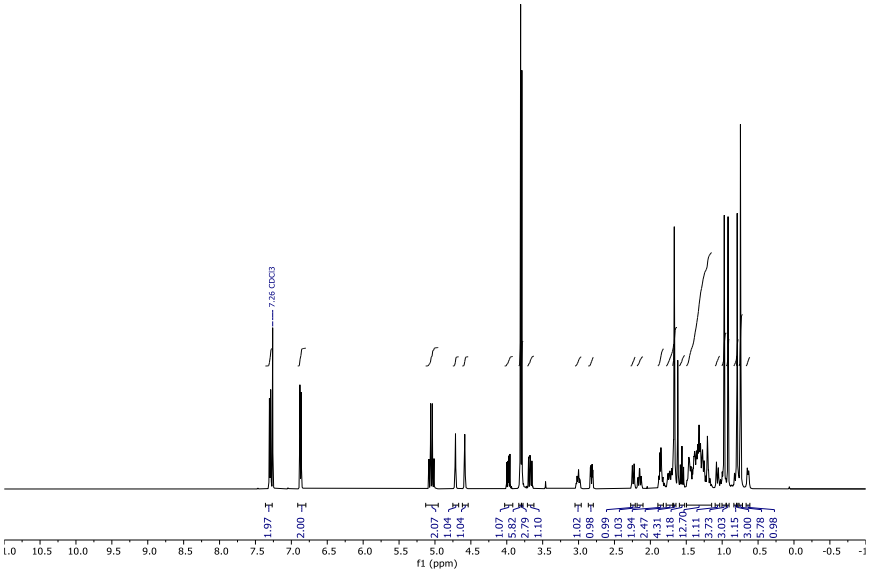


**Sodium (28-norurs-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32c**

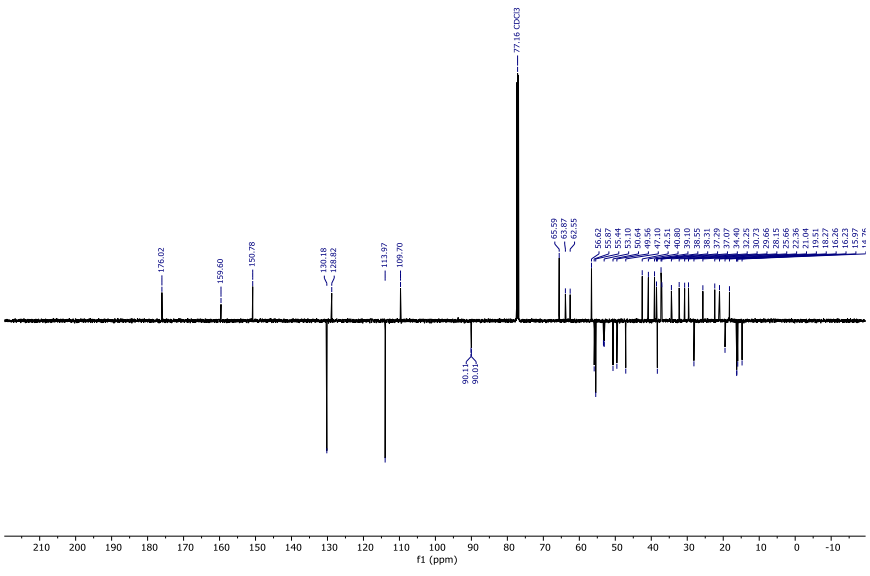
$^1$H NMR (500 MHz, MeOD) δ 5.23 (t, $^3J$ = 3.7 Hz, 1H, H-C(12)), 3.85 (dd, $^2J$ = 13.2 Hz, $^3J$ = 9.0 Hz, 1H, $H_a$-C(3')), 3.55 (dd, $^3J$ = 13.2 Hz, $^3J$ = 10.1 Hz, 1H, $H_b$-C(3')), 2.92 (dd, $^3J$ = 11.8, 4.3 Hz, 1H, H-C(3)), 2.20 (d, $^3J$ = 11.3 Hz, 1H, H-C(18)), 2.05 (td, $^2J$ = 13.4 Hz, $^3J$ = 4.2 Hz, 1H, $H_a$-C(16)), 1.97 – 1.88 (m, 3H, $H_2$-C(11), $H_a$-C(15)), 1.84 (dd, $^2J$ = 13.7 Hz, $^3J$ = 4.3 Hz, 1H, $H_a$-C(2)), 1.75 – 1.59 (m, 4H, $H_b$-C(16), $H_2$-C(21), $H_a$-C(1)), 1.59 – 1.25 (m, 9H, $H_2$-C(6), $H_b$-C(11), $H_2$-C(22), $H_2$-C(7), H-C(9), H-C(19)), 1.12 (s, 3H, $H_3$-C(27)), 1.11 – 1.06 (m, 1H, $H_b$-C(15)), 1.05 (s, 3H, $H_3$-C(23)), 1.01 – 0.95 (m, 8H, $H_b$-C(1), H-C(20), $H_3$-C(25), $H_3$-C(30)), 0.97 (d, $^3J$ = 6.4 Hz, 3H, $H_3$-C(29)), 0.85 (s, 3H, $H_3$-C(26)), 0.82 (s, 3H, $H_3$-C(27)), 0.78 (d, $^3J$ = 11.4 Hz, 1H, H-C(5)).$^{13}$C NMR (126 MHz,

MeOD) δ 181.62 (C28), 139.64 (C13), 126.90 (C12), 90.85 (d, $^{3}J$ = 12.3 Hz, (C3)), 66.20 (d, $^{1}J$ = 164.7 Hz, C(3')), 57.10 (C5), 54.36 (C18),49.00 (C17), 48.86 (C9), 43.24 (C14), 40.81 (C8), 40.42 (C20+C19), 39.97 (C4), 39.68 (C1), 38.11 (C21+C10), 34.31 (C7), 31.77 (C22), 29.20 (C15), 28.75 (C23), 25.31 (C16), 24.39 (C2), 24.09 (C27), 23.17 (C11), 21.57 (C30), 19.31 (C6), 17.81 (C26), 17.65 (C29), 16.98 (C24), 16.07 (C25). $^{1}$P NMR (121 MHz, MeOD$_{d4}$) δ 19.49. HRMS: [$C_{31}H_{51}O_6P$-$H^+$] 549.3350; found 549.3341 (1.6 ppm).

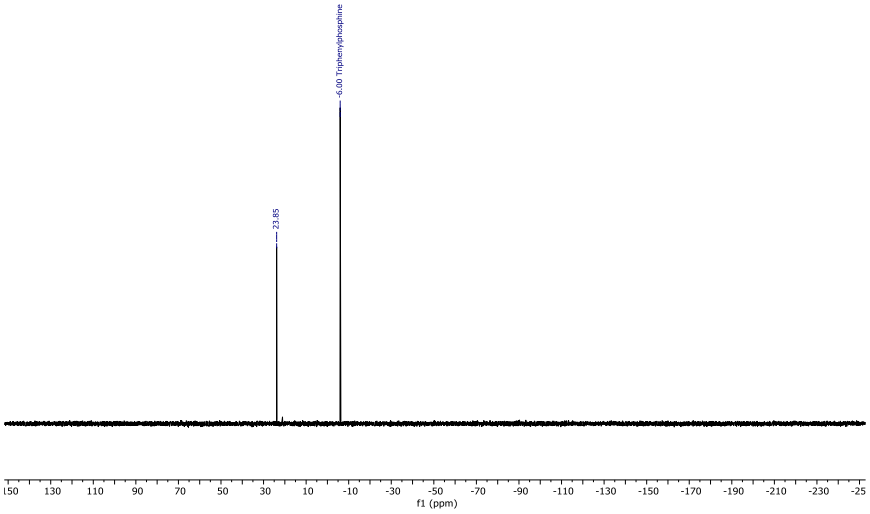
**$^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-lup-20(29)en-28-oic acid 4-methoxybenzyl ester 31a**



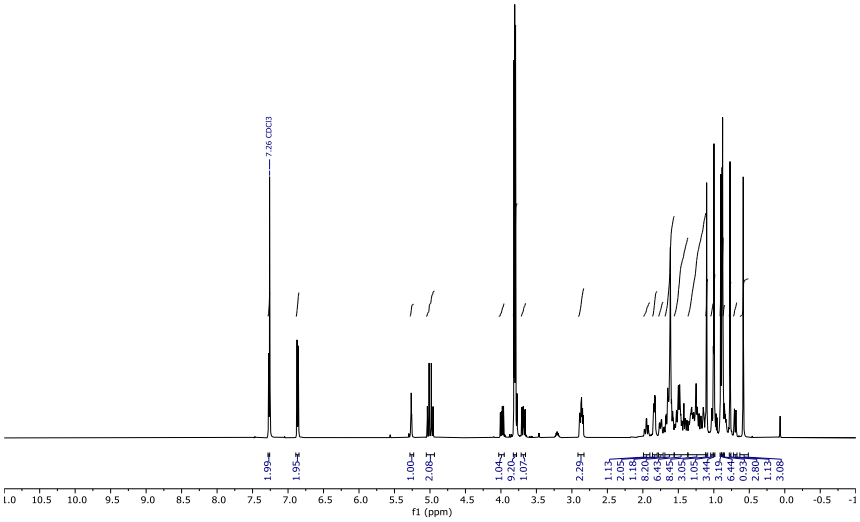

**$^{13}$C NMR (126 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-lup-20(29)en-28-oic acid 4-methoxybenzyl ester 31a**



**$^{31}$P NMR (121 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-lup-20(29)en-28-oic acid 4-methoxybenzyl ester 31a**




**$^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-olean-12(13)en-28-oic acid 4-methoxybenzyl ester 31b**



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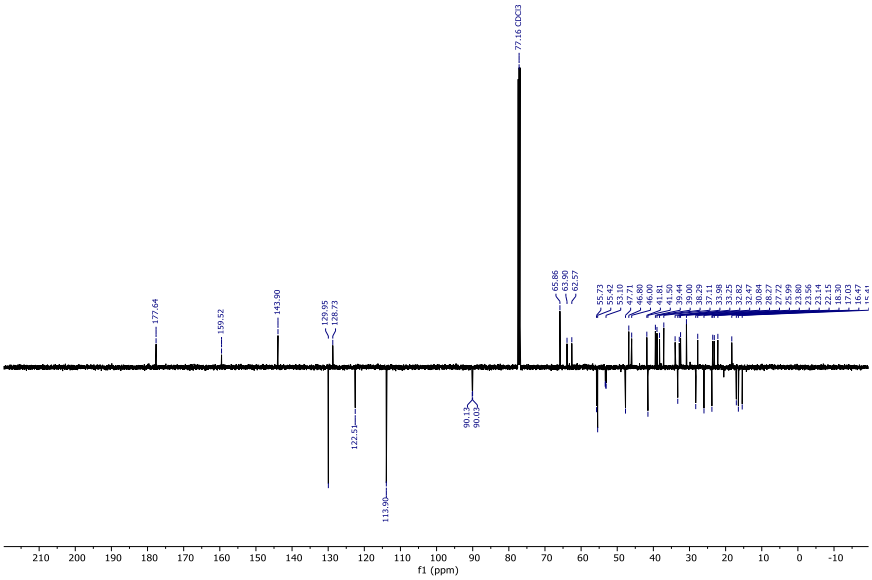
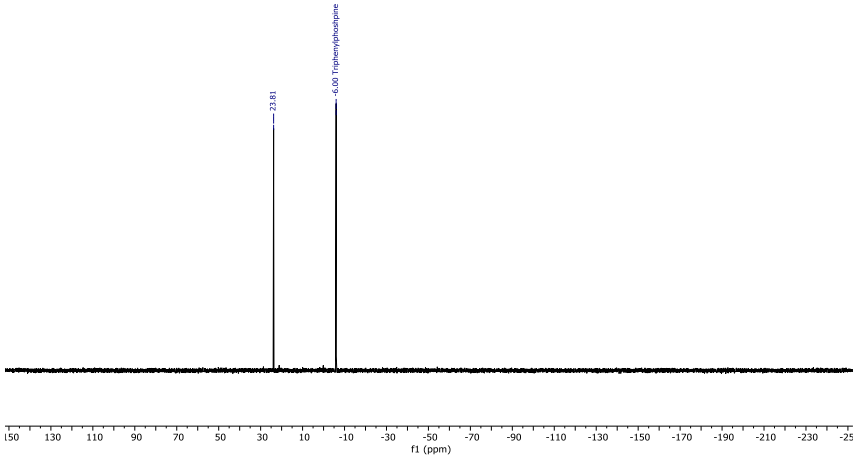
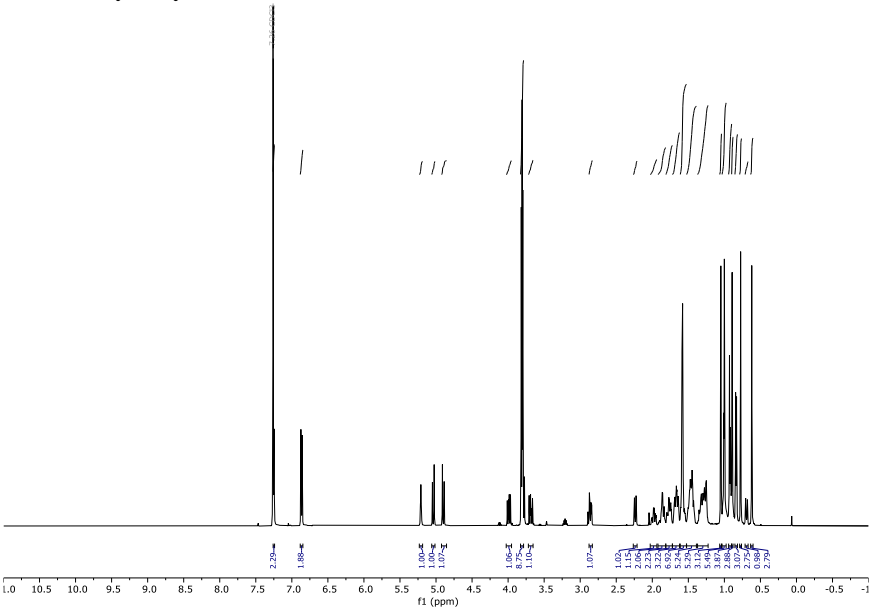


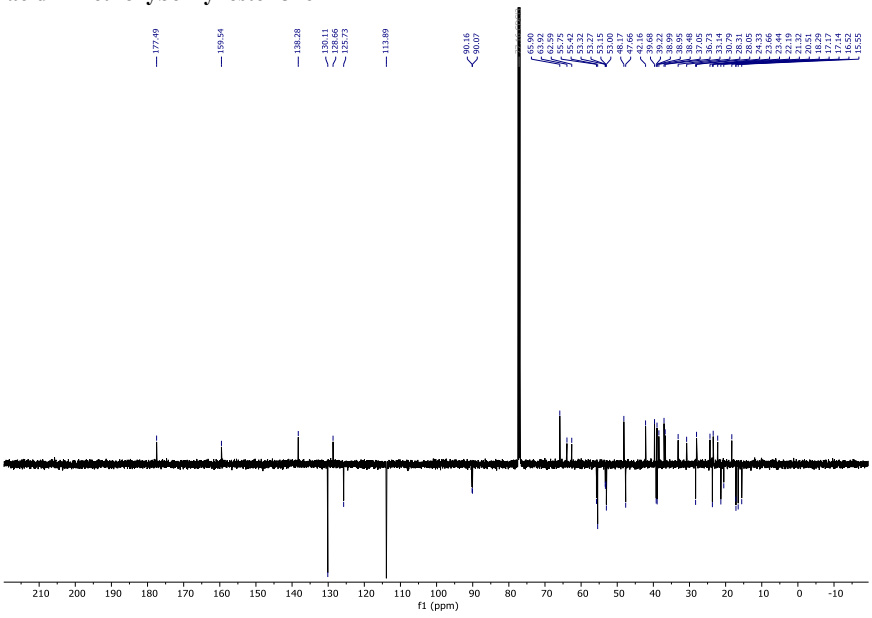

**$^{31}$P NMR (121 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-olean-12(13)en-28-oic acid 4-methoxybenzyl ester 31b**



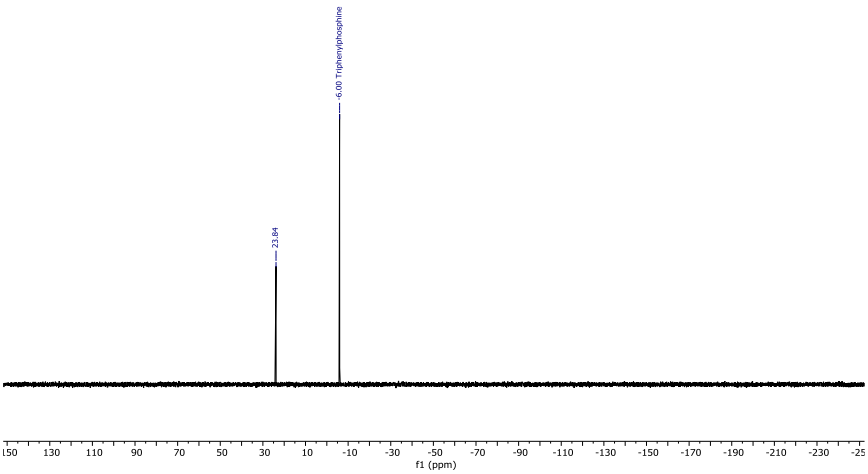
**$^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-urs-12(13)en-28-oic acid 4-methoxybenzyl ester 31c**



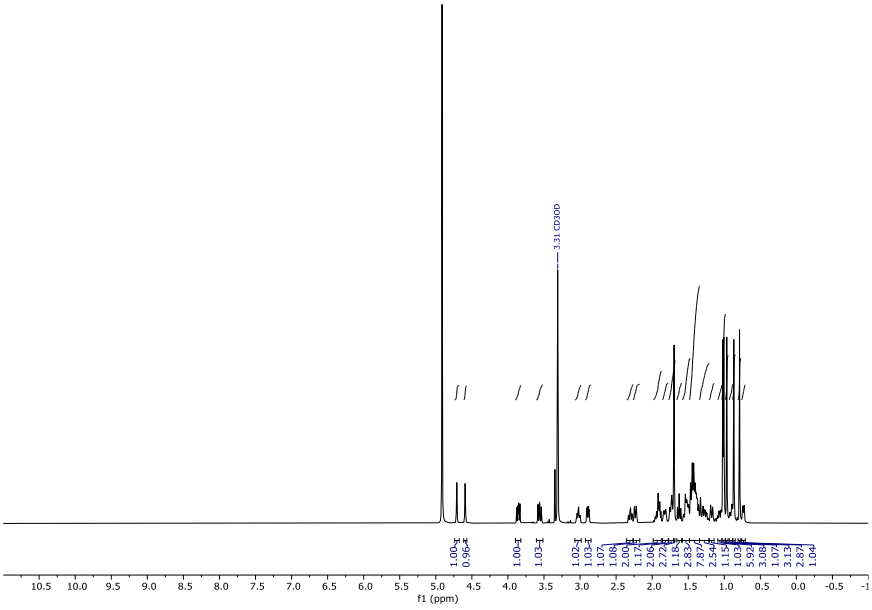

**$^{13}$C NMR (126 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-urs-12(13)en-28-oic acid 4-methoxybenzyl ester 31c**



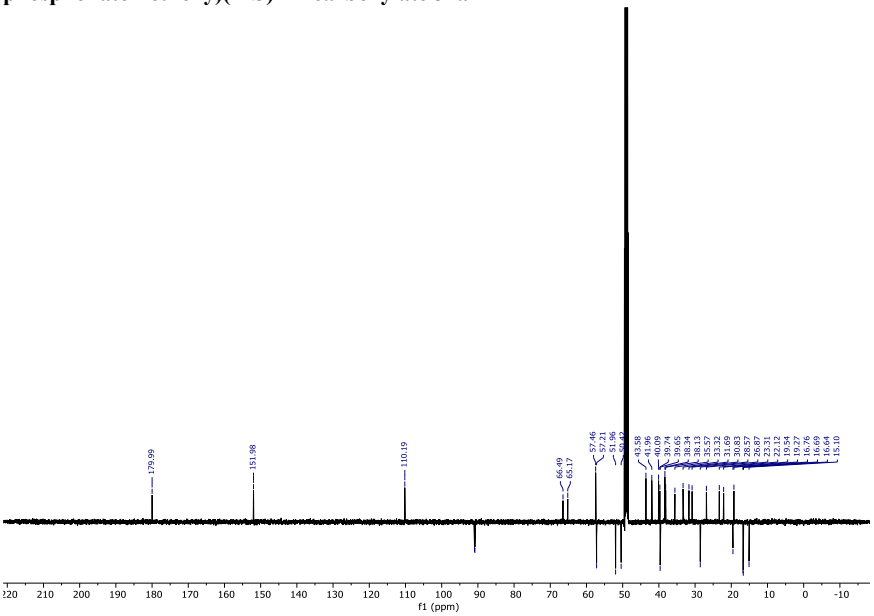
**$^{31}$P NMR (121 MHz, $CDCl_3$) spectrum of (3*S*)-3-((dimethoxyphosphoryl)methyloxy)-urs-12(13)en-28-oic acid 4-methoxybenzyl ester 31c**



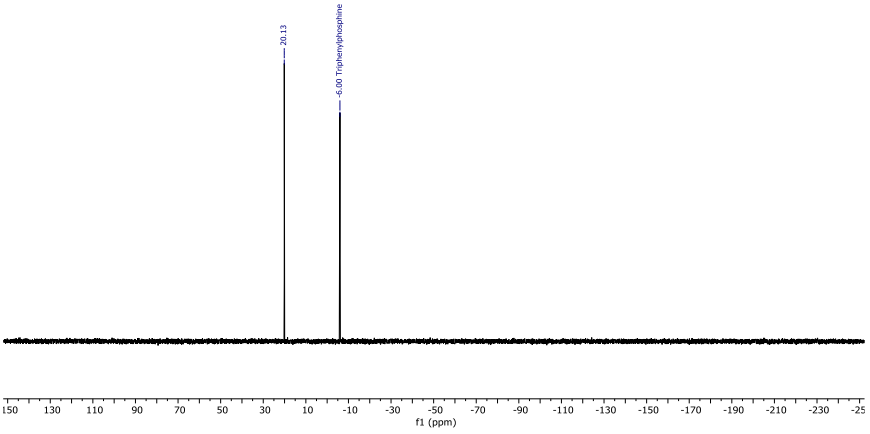

**$^{1}$H NMR (500 MHz, MeOD$_{d4}$) spectrum of sodium (28-norlup-20(29)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32a**



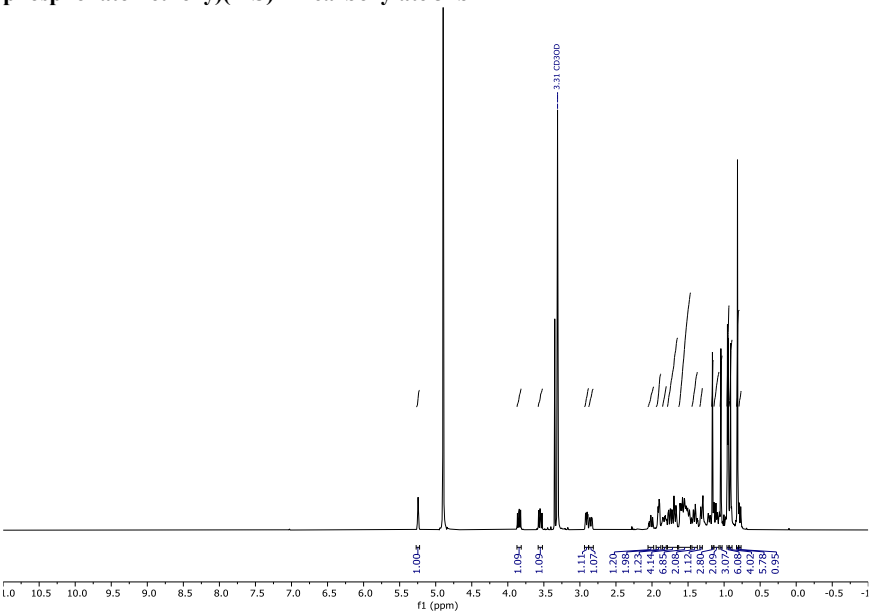
**$^{13}$C NMR (126 MHz, MeOD$_{d4}$) spectrum of sodium (28-norlup-20(29)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32a**



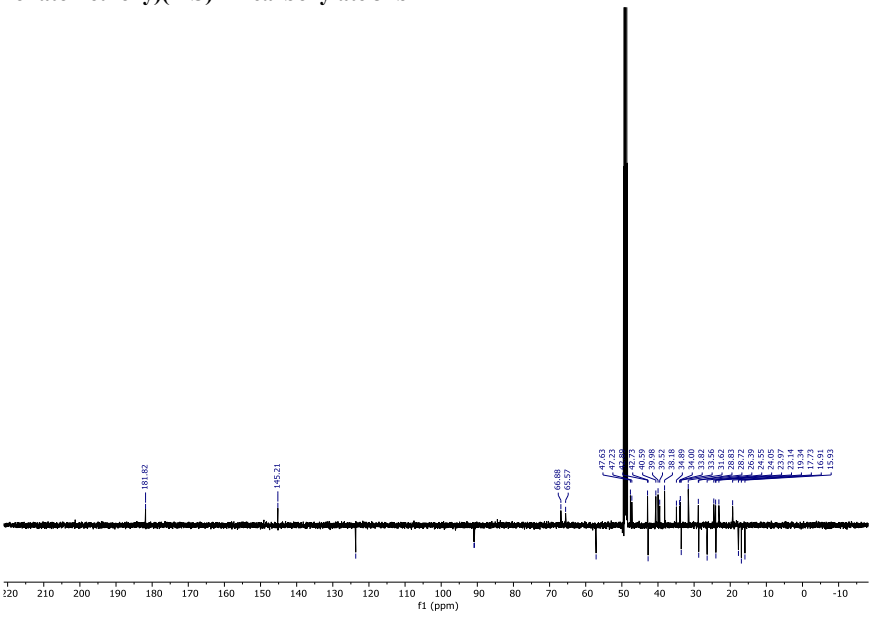

**$^{31}$P NMR (121 MHz, MeOD$_{d4}$) spectrum of sodium (28-norlup-20(29)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32a**



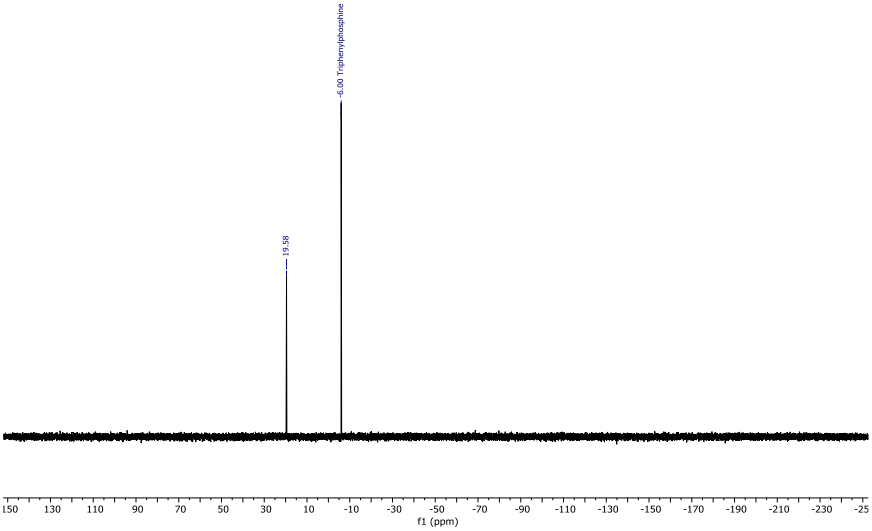
**$^{1}$H NMR (500 MHz, MeOD$_{d4}$) spectrum of sodium (28-norolean-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32b**




**$^{13}$C NMR (126 MHz, MeOD$_{d4}$) spectrum of sodium (28-norolean-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32b**



**$^{31}$P NMR (121 MHz, MeOD$_{d4}$) spectrum of sodium (28-norolean-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32b**

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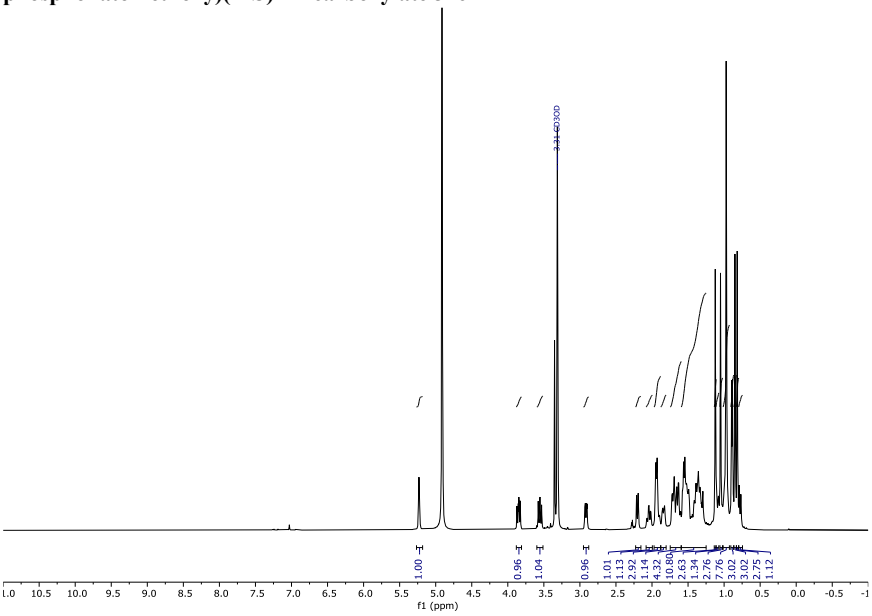

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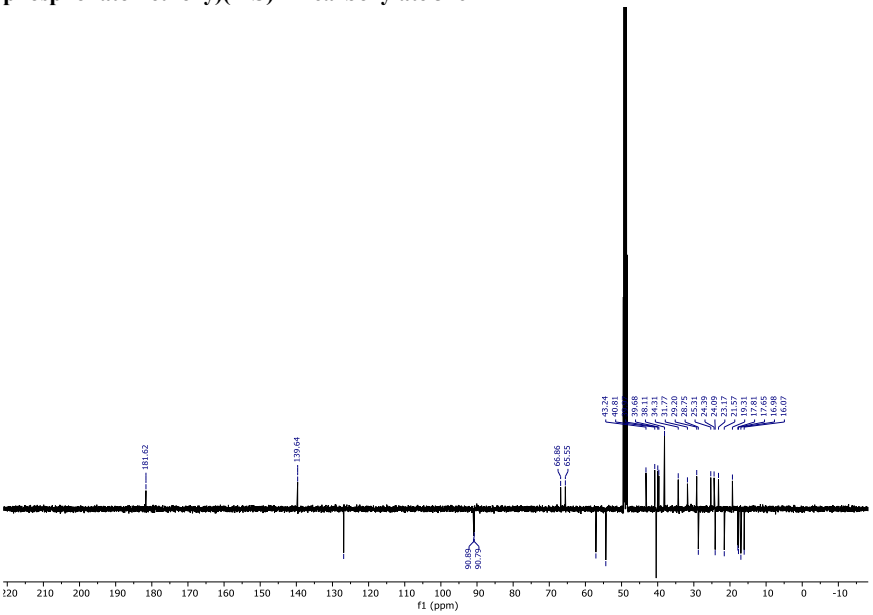
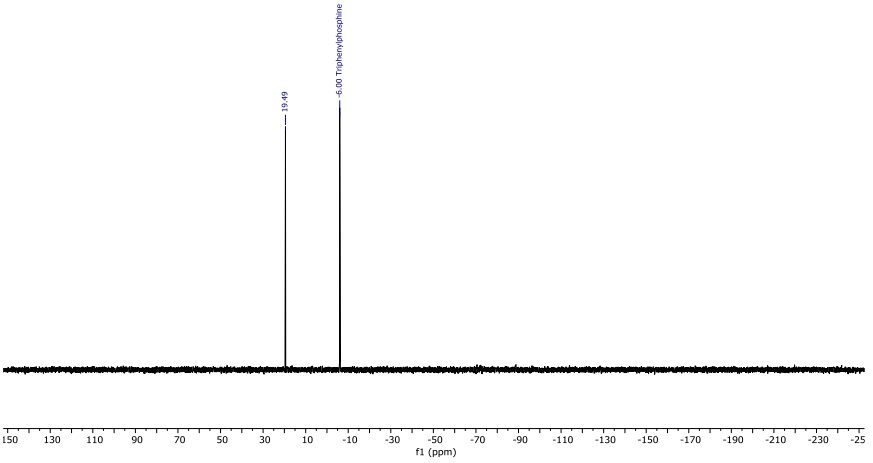



**$^{31}$P NMR (121 MHz, MeOD$_{d4}$) spectrum of sodium (28-norurs-12(13)-en-(3*S*)-3-phosphonatomethoxy)(17*S*)-17-carboxylate 32c**



Pielikums IV

Appendix IV

Kroškins, V., Turks, M

# Recent investigations in synthesis of oxathiazinanes by sulfamate estercyclization (microreview)

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*Химия гетероциклических соединений* **2023**, *59*(9/10), 637–639

ГЕТЕРОЦИКЛЫ В ФОКУСЕ

Химия гетероциклических соединений

# Recent investigations in synthesis of oxathiazinanes by sulfamate ester cyclization (microreview)

**Vladislavs Kroškins[1]*, Māris Turks[1]**

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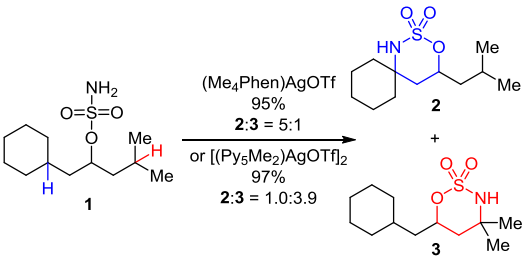
Recent investigations of intramolecular C–H bond amination reaction of sulfamate ester derivatives forming 1,2,3-oxathiazine-2,2-diones and 5,6-dihydro-1,2,3-oxathiazinane-2,2-diones from 2017 to 2021 are summarized.

## Introduction

In early 2000's Du Bois and coworkers developed rhodium-catalyzed C–H bond amination approach toward synthesis of cyclic sulfamidates from acyclic sulfamate esters *via* formation of reactive iminoiodinane species.[1] This opened capacious research field, which was reviewed in 2017.[2] In the past five years, several novel catalytic systems and conditions for transformation of omnipresent C–H bonds into valuable C–N bonds by exploiting sulfamate ester moiety have been described. Treatment of alcohols with sulfamoyl chloride is the most common way to obtain sulfamate esters.[3] Cyclic sulfamidates as the cyclization products of the latter have revealed themselves as versatile precursors for the synthesis of various N-heterocycles. The cyclic sulfamidate moiety is masked 1,3-amino alcohol, a significant motif from synthetic and biological point of view.

## Reactions with transition metal stabilized nitrenes

Schomaker group expanded the utility of metal-catalyzed nitrene transfer to enclose tunable amination of competing tertiary C–H bonds in similar steric and/or electronic environments[4] and site selective amination of α-conjugated C–H bonds over tertiary alkyl C($sp^3$)–H bonds[5] using ligand-controlled Ag(I) catalysis. Treatment of sulfamate ester **1** bearing cyclohexyl and isopropyl C–H bonds with $(Me_4Phen)AgOTf$ leads to the formation of oxathiazinanes **2** and **3** in 5:1 ratio. However, application of $[(Py_5Me)_2AgOTf]_2$ results in the formation of mixture of the same products, albeit in 1.0:3.9 ratio.

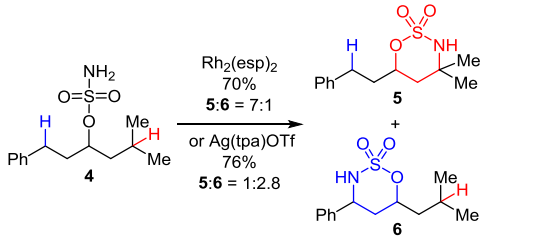



**Vladislavs Kroškins** obtained his MSc in chemical engineering in 2021 from the Riga Technical University (RTU). He is currently working toward his PhD under supervision of Professor Māris Turks at RTU. His research focuses on modification and C–H bond activation of different pentacyclic triterpenoids.

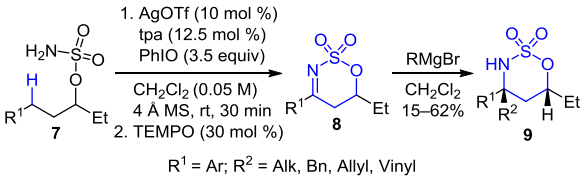
**Māris Turks** obtained his Dr. ès sc. degree in 2005 from the Swiss Federal Institute of Technology, Lausanne, under the guidance of Professor P. Vogel. He spent a year as Postdoctoral Fellow at Stanford University with Professor B. M. Trost. Currently he is a Full Professor and head of the Institute of Technology of Organic Chemistry of RTU. His research interests involve carbohydrate and nucleoside chemistry, functionalized heterocycles, organosilicon chemistry, and applications of liquid sulfur dioxide in organic synthesis.

**Reactions with transition metal stabilized nitrenes** (continued)

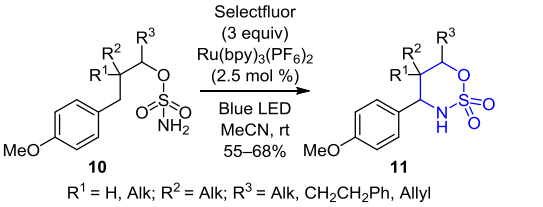
On the other hand, nitrene transfer reaction for compound **4** in the presence of $Rh(II)_2L_n$ displayed higher selectivity for the formation of compound **5**, as the bridging equatorial ligands on the Rh increased in size, but the reaction with Ag(tpa)OTf was found to be influenced by weak non-covalent interactions between the substrate and the catalyst showing better selectivity for compound **6**. Schomaker and coworkers also investigated silver-catalyzed nitrene transfer reactions in $H_2O$.[6] It was observed that $H_2O$ does not occupy the coordination site on the silver catalyst and has little effect on the coordination geometry of the nitrene intermediate.



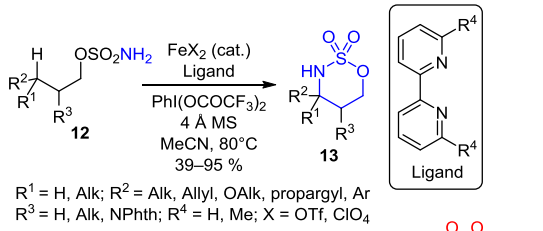

Tandem Ag(I)-catalyzed C–H bond amination of sulfamate esters **7** and following oxidation of cyclic sulfimidate to the corresponding imine adduct have been reported by Schomaker group.[7] The obtained imines **8** can be used as important intermediates that can undergo diastereoselective nucleophilic attack. Nitrene transfer into benzylic and allylic C–H bonds in the presence of catalytic amount of AgOTf and excess of PhIO was followed by TEMPO-mediated oxidation of cyclic sulfimidate to a cyclic imine. After subsequent reaction with the Grignard reagents, *syn*-amino alcohols **9** bearing an α-tertiary amine functionality were obtained in *dr* >19:1.



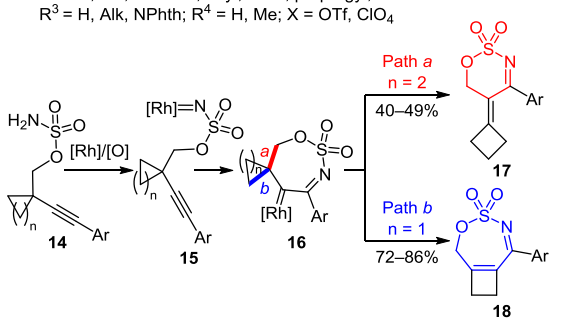

Mondal and coworkers have presented a novel method for intramolecular benzylic C–H bond amination of aromatic sulfamate esters **10** *via* photoredox catalysis.[8] Visible light irradiation of photoredox system $Ru(bpy)_3(PF_6)_2$/Selectfluor provides cyclic products **11**.



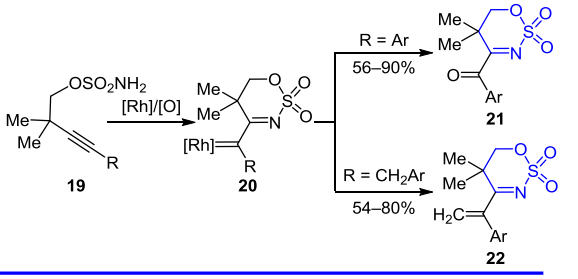

In 2019, Liu group disclosed an iron-catalyzed intramolecular C−H bond amination in substrates **12** and formation of 5,6-dihydro-1,2,3-oxathiazinanes **13** using cheap and commercially available 2,2'-bipyridine ligands and $Fe(OTf)_2$ or $Fe(ClO_4)$ in combination with $PhI(OCOCF_3)_2$.[9]




Recently, Shi and coworkers demonstrated protocol of Rh(II)-catalyzed conversion of 1-[(arylethynyl)cycloalkyl]-methyl sulfamates **14** into six- and seven-membered nitrogen heterocyles.[10] Transformation is based on generation of metallonitrene **15**, which then undergoes reaction with alkyne providing active species **16**. Termination of the process depends on size of the cycloalkyl substituent. Cyclobutyl intermediate (n = 2) undergoes alkoxyl moiety migration (path *a*), giving six-membered heterocyclic product **17**. In case of cyclopropyl intermediate (n = 1), the transformation terminates with ring expansion (path *b*) and products **18** are obtained.



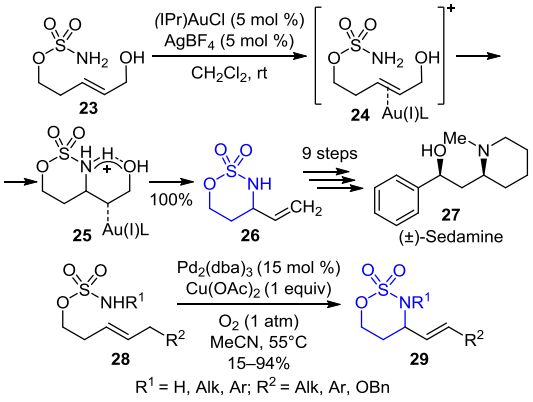

Later, *gem*-dimethyl-substituted sulfamates **19** were tested in a similar transformation.[11] Thus, aryl-substituted α-iminometal carbene intermediate **20** (R = Ar) was trapped by $H_2O$ and then oxidized by iodine(III) oxidants forming aroyl group containing heterocycles **21**. On the other hand, benzyl-substituted α-iminometal carbene intermediate **20** ($R = CH_2Ar$) inserted into neighboring benzyl C–C bond and yielded 2-styryl group containing heterocycles **22**.



## Transition-metal-catalyzed hydroamination reactions

Ryu group has described a catalytic system for allylic shift in allyl alcohols, which are tethered to sulfamate esters.[12] The reaction mechanism involves coordination of cationic Au(I) species to the double bond in allyl alcohols **23** and formation of metal–π-alkene complex **24**. The intramolecular cyclization of the latter proceeds *via anti* addition and leads to the formation of hydrogen-bonded metal–alkyl complex **25**. Further proton transfer and subsequent *anti* elimination of $H_2O$ yields oxathiazinane **26**, which is the key intermediate in synthesis of alkaloid (±)-sedamine (**27**).[13]

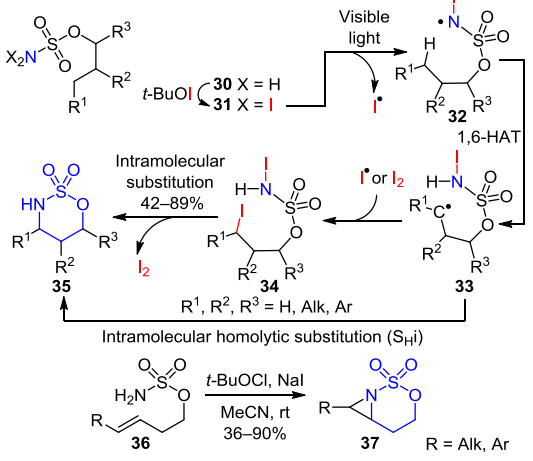
Sathyamoorthi and coworkers have disclosed aza-Wacker cyclization of sulfamate esters **28** that can be rapidly converted into alkenyl oxathiazinanes **29** in the presence of Pd(0) precatalyst and Cu(II) salts under oxygen atmosphere.[14] The procedure is compatible with both *N*-alkyl and *N*-aryl sulfamates and tolerates a variety of important functional groups.




## Transition-metal-free reactions of *N*-iodo derivatives

A variation of the Hofmann–Löffler–Freytag reaction, which proceeds with 1,6-hydrogen atom abstraction/transfer (1,6-HAT) in the case of sulfamate esters, was reported by Kiyokawa and coworkers.[15] The transformation starts with interaction of sulfamate ester **30** and 2.2 equiv of iodine oxidant – *tert*-butyl hypoiodite (*t*-BuOI)[16] or *N*-iodosuccinimide (NIS) in the presence of ambient light. Firstly, *N*,*N*-diiodosulfamate ester **31** is formed. The visible light irradiation then leads to the generation of nitrogen-centered radical **32**, which takes part in the 1,6-HAT process. The obtained carbon-centered radical intermediate **33** is trapped by iodine radical or $I_2$ and subsequent intramolecular substitution of alkyl iodide **34** results in the formation of oxathiazinane **35**. Alternatively, radical intermediate **33** can directly form final product **35** *via* intramolecular homolytic substitution ($S_Hi$) pathway.

In a similar fashion, alkenes **36** bearing sulfamate ester moiety undergo intramolecular aziridination in the presence of *in situ* generated *t*-BuOI forming bicyclic products **37**.[17]




## Conclusion

Numerous examples of sulfamate ester cyclizations based on metal-stabilized nitrene C–H bond insertion were described. The cyclization can also proceed *via* metal-free radical pathway by a variation of the Hofmann–Löffler–Freytag reaction as well as *via* π-selective Lewis acid catalyzed amine addition to unsaturated systems. Sulfamate ester can be a powerful tool for chemoselective synthesis of 1,2,3-oxathiazinanes and 5,6-dihydro-1,2,3-oxathiazinanes involving broad range of substrates.

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### References

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Pielikums V

Appendix V

Kroškins, V., Lugiņina, J., Lācis, R., Kumar, D., Kumpiņš, V., Rjabovs, V., Mishnev, A., Turks, M

# Palladium-catalyzed C-H arylation and azetidination of pentacyclic triterpenoids

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Article

# Palladium-Catalyzed C−H Arylation and Azetidination of Pentacyclic Triterpenoids

Vladislavs Kroškins,[#] Jevgeņija Lugiņina,[#] Rihards Lācis, Dinesh Kumar, Viktors Kumpiņš, Vitālijs Rjabovs, Anatoly Mishnev, and Māris Turks*

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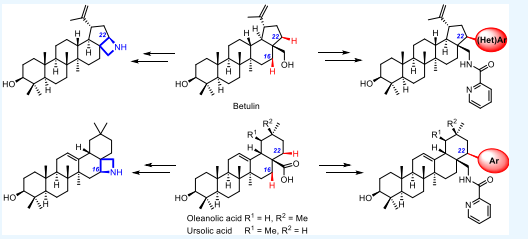
**ABSTRACT:** Synthetic protocols for site-selective palladium-catalyzed C−H arylation and azetidination of pentacyclic triterpenoids have been developed. Betulin, oleanolic, and ursolic acids were converted into primary amines C(28)-$NH_2$ that were further transformed into the corresponding picolinamides. The latter was found to be a suitable directing group for triterpenoid C($sp^3$)-H (het)arylation with iodo(het)arenes in the presence of $Pd(OAc)_2/CuBr_2/CsOAc$ system. C($sp^3$)-H (het)arylation provided yields from 29 to 83%, and the C(22)/C(16) selectivity from 9:1 in the lupane (betulin) series to 19:1 in the oleane and ursane series. The highest isolated yields of C($sp^3$)-H arylated products were achieved with iodoarenes bearing electron-donating groups, but the use of electron-deficient iodoarenes gave a significant proportion of *N*-picolinoyl azetidine side product. The latter were obtained with good selectivity as major products when 1-iodo-4-nitrobenzene was used as an additive. C($sp^3$)-H arylation revealed C(22)-selectivity in all tested triterpenoid series; however, the azetidination occurred at C(22) in lupane (betulin) series and at C(16) in oleane series. C($sp^3$)-H (het)arylation and azetidination is a new entry in the derivatization of natural triterpenoids and can be regarded as a useful tool for further exploration in terms of medicinal chemistry.






## INTRODUCTION

Naturally abundant pentacyclic triterpenoids (PCT) are plant secondary metabolites, which have aroused significant interest due to a wide range of their biological activities such as antitumor[1,2] antidiabetic,[3−5] anti-inflammatory,[6−8] and antiviral properties.[9,10] Betulin and oleanolic, ursolic, and betulinic acids are the most naturally abundant and therefore most notorious compounds of this type.[11−13] Development of semisynthetic derivatives of PCTs by chemical modifications is known to ameliorate certain designed properties, among others: cytotoxic selectivity toward cancer cells, enhanced aqueous solubility,[14] and bioavailability.[15]

The vast majority of synthetic methods for the decoration of PCT core involve the use of C(3) and C(28) C−O functionalities and the available olefin moiety.[16] On the other hand, the transition metal catalyzed functionalization of C($sp^3$)-H bonds, which is considered a powerful synthetic tool,[17] has been far less applied to the triterpenoid skeletons. Literature analysis on C($sp^3$)-H activation in the PCT core has shown only a few examples (Figure 1). Thus, the Yu group[18] has reported site-selective C−H hydroxylation of different pentacyclic triterpenoids using Schönecker and Baran's Cu-mediated aerobic conditions ($Cu(OTf)_2$, $O_2$). In this case, the site-selectivity has been controlled by the transient pyridine-imino directing group, which was introduced using C(28) aldehyde. Baldwin's method[19] was successfully applied to introduce and modify a hydroxyl group on a nonactivated C(23) methyl group by several research groups.[20] Selective oxygenation of oleanolic C(23) using iridium catalyzed hydroxyl group-directed silylation/Tamao-Fleming oxidation sequence was explored by Hartwig.[21] Maulide group reported an approach for functionalization of the B ring in oleanane triterpenoids using a hydroxylated C(23) group as the key functionality for further linear reaction sequence.[22] Lu group developed an Ir-catalyzed C($sp^3$)-H amination reaction using $TrocN_3$ as an easily transformable amine source at C(23) of oleanolic triterpenoid as an example of a topologically and functionally complex natural product substrate.[23] The betulin scaffold was also investigated in intramolecular metallonitrene-based C($sp^3$)-H amination of sulfamate esters. White group discovered that [Mn(*t*BuPc)]$SbF_6$ catalyst preferentially forms C−N bond at the γ-C−H bond of the equatorial C(23) methyl group and provided oxathiazinane with high site- and

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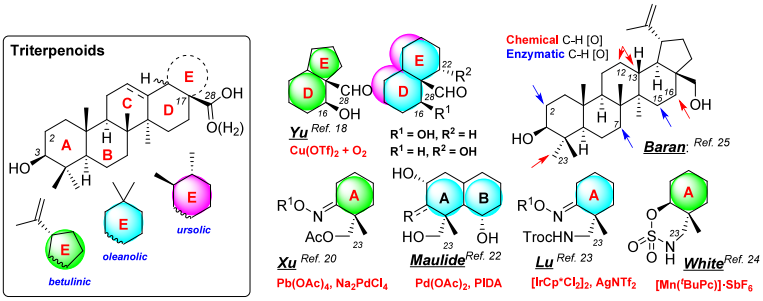


**Figure 1.** Previously reported C−H functionalized PCT.

diastereoselectivity.[24] Baran's group investigated different C−H oxidation methods on the betulin skeleton to improve the aqueous solubility of this natural product. The authors observed that nondirected or enzymatic oxidation of C−H bonds results in low selectivity and insufficient reaction yield.[25]

To the best of our knowledge, besides the aforementioned C−H hydroxylation and C−H amination examples, there are no reports on C−C bond forming C−H activation approaches within the pentacyclic terpenoid series; however, some successful examples of C($sp^3$)-H arylation of smaller natural terpene molecules were reported.[26] Furthermore, since the beginning of this century, plenty of different methods for C($sp^3$)-H arylation using different catalytic systems and directing groups suitable for the late-stage functionalization of complex molecules have been developed.[27] Hence, we report here an investigation of previously unexplored site-selective palladium-catalyzed C($sp^3$)-H (het)arylation of pentacyclic triterpenoids.

## RESULTS AND DISCUSSION

We started our investigation by preparing PCT derivatives bearing Daugulis directing groups[28] that are attached to the pentacyclic skeleton either by a native carboxylic amide **2a−d** or by a more flexible −$CH_2$−NH− linker **3a−d** (Figure 2). 8-

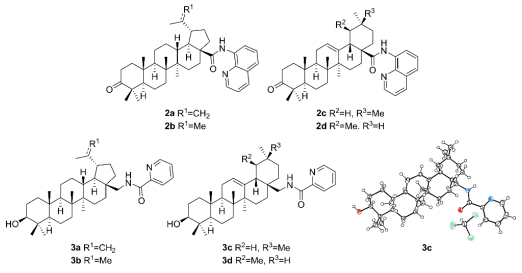


**Figure 2.** Triterpenic 8-aminoquinolinamides **2a−d** and picolinamides **3a−d**.

Aminoquinoline amides **2a−d** were prepared by the coupling of betulonic, ursonic, and oleanonic acids with an 8-aminoquinoline, with pretransformation of acids into acid chlorides.[29] On the other hand, picolinamide[30] directing auxiliary was introduced by an amine reaction with picolinic acid.

First, oxime **4a** was synthesized from commercially available betulin (**1a**) according to the literature procedure.[31] To explore and compare the possible reactivity of the isopropenyl moiety during the C−H activation, the saturated congener **4b** was also obtained (Scheme 1). Next, we proceeded with oxime **4a** and **4b** reduction using $NaBH_3CN/TiCl_4$ and amidation of the obtained primary amines by freshly generated picolinic chloride/$Et_3N$. Picolinic amides **3a** and **3b** were obtained over two steps with overall 81 and 60% yields, respectively. (Scheme 1).

Commercially available oleanolic and ursolic acids were converted into picolinamides **3c**[32] and **3d** in three steps.[33,34] In situ-generated activated esters were converted into amides **5a** and **5b**. Reduction of the latter with $LiAlH_4$ afforded primary amines that were converted into picolinamides using previously developed reaction conditions (Scheme 2).

With starting materials **2a** and **3a** in hand, we explored their ability to complex palladium and provide C−H deuteration products that would demonstrate the feasibility of the C−H activation event. We performed the C−H deuteration experiments in the presence of $Pd(OAc)_2$ and CsOAc using deuterated acetic acid as a solvent. Both of the tested directing groups provided C(16)/C(22) double-deuterated products (see Supporting Information Scheme S1 for C($sp^3$)-H deuteration of **2a,c,d** and Scheme 8 for deuteration of **3a,c** (vide infra)). Inspired by the feasibility of the C−H activation event, we started to test possible conditions for the C−H arylation reaction. Surprisingly, no efficient reaction conditions for successful C-arylation were found in the case of quinolinamides **2a,c,d.**

To our delight, conformationally more flexible picolinamide **3a** was found to be a suitable starting material for the envisaged C−H arylation reactions. The reactive cocktail containing picolinamide **3a** (1 equiv), 4-iodoanisole (4 equiv), $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (10 mol %)[35] and CsOAc (4 equiv) in toluene yielded a mixture of C(22)- and C(16)-regioisomers **6a** and **7a** in 92:8 ratio with 23% total yield (Table 1, entry 1). Changing the solvent to HFIP produced no product at all (entry 2). Then we switched to *t*AmOH and examined different bases, but CsOAc was found to be still the most efficient one (entry 6). It should be pointed out that the Ag(I) additive did not facilitate the reaction at a reasonable rate (entry 5). Gratifyingly, the use of $Pd(OAc)_2$ (5 mol %) in the presence of $CuBr_2$ (10 mol %) and CsOAc (4 equiv) in *t*AmOH gave C-arylated products **6a**/**7a** in 83% total isolated yield (entry 10). These appeared to be the best conditions, and any further variations of palladium source (entries 7,8) and


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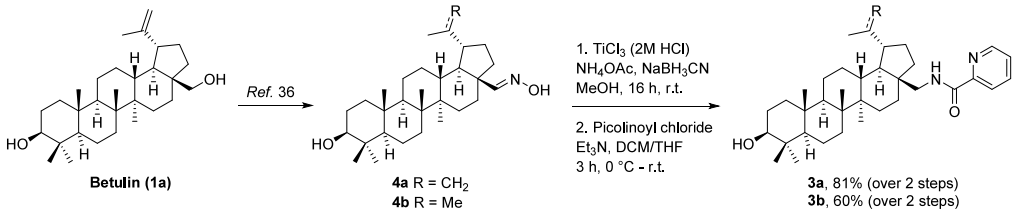
**Scheme 1. Synthesis of Picolinic Amides 3a,b**




**Scheme 2. Synthesis of Picolinamides 3c,d**

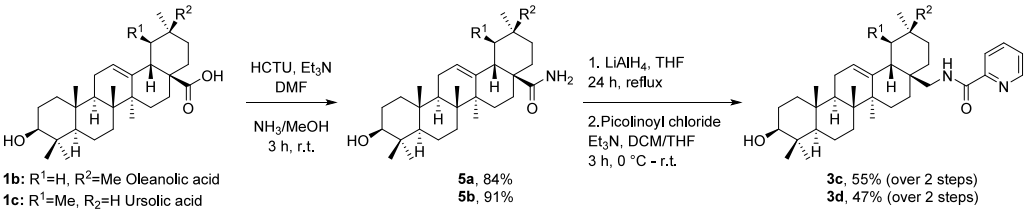
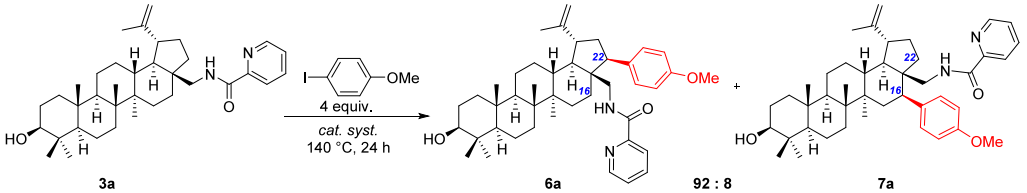



**Table 1. Optimization of C($sp^3$)-H Arylation Conditions for Reaction 3a → 6a + 7a**




| entry | catalyst (mol %) | | additive (mol %) | | base (4 equiv) | solvent | total isolated yield of 6a + 7a (92:8), % |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | 5 | $CuBr_2$ | 10 | CsOAc | Tol | 23 |
| 2 | $Pd(OAc)_2$ | 5 | $CuBr_2$ | 10 | CsOAc | HFIP | 0 |
| 3 | $Pd(OAc)_2$ | 5 | $CuBr_2$ | 10 | $K_2CO_3$ | *t*AmOH | 2 |
| 4 | $Pd(OAc)_2$ | 5 | $CuBr_2$ | 10 | $Cs_2CO_3$ | *t*AmOH | 19 |
| 5 | $Pd(OAc)_2$ | 5 | | | AgOAc | *t*AmOH | 17 |
| 6 | $Pd(OAc)_2$ | 5 | | | CsOAc | *t*AmOH | 70 |
| 7 | $Pd_2(dba)_3$ | 5 | $CuBr_2$ | 10 | CsOAc | *t*AmOH | 76 |
| 8 | $PdCl_2$ | 5 | $CuBr_2$ | 10 | CsOAc | *t*AmOH | 78 |
| 9 | $Pd(OAc)_2$ | 2.5 | $CuBr_2$ | 5 | CsOAc | *t*AmOH | 21 |
| 10 | **$Pd(OAc)_2$** | 5 | **$CuBr_2$** | 10 | **CsOAc** | ***t*AmOH** | **83** |
| 11 | $Pd(OAc)_2$ | 7.5 | $CuBr_2$ | 15 | CsOAc | *t*AmOH | 79 |
| 12 | $Pd(OAc)_2$ | 10 | $CuBr_2$ | 20 | CsOAc | *t*AmOH | 75 |
| 13 | $Pd(OAc)_2$ | 20 | $CuBr_2$ | 40 | CsOAc | *t*AmOH | 58 |
| 14 | $Pd(OAc)_2$ | 5 | $Cu(OAc)_2$ | 10 | CsOAc | *t*AmOH | 58 |
| 15 | $Pd(OAc)_2$ | 5 | $CuCl_2$ | 10 | CsOAc | *t*AmOH | 78 |

amount (entries 11−13), or Cu(II) source (entries 14,15) did not provide any improvement. We detected practically the same 92:8 ratio of regioisomers **6a**/**7a** by $^1$H NMR in all crude reaction mixtures. We have also tested the influence of 4-iodoanisole excess on reaction outcome: the use of 2 equiv diminished the total isolated yield of products **6a** + **7a** to a 73−78% range. On the other hand, the use of 3 equiv of 4-iodoanisole in some experiments gave the total isolated yield of products **6a** + **7a** as high as 90%, yet the results had some dispersion, and a yield range of 83−90% was observed. Hence, we considered the iodoarene use in 4-fold excess as optimal.

Having found suitable C($sp^3$)-H arylation conditions, we examined the scope of the aryl iodide components (Table 2). Reactions with aryl iodides possessing electron-rich aryl rings worked well, and C($sp^3$)-H arylation products **6a−d**/**7a−d** were obtained in the summary yield range 50−83% (entries 1−4, Table 2). Two molecular structures of compounds **6a**[36] and **6b**[37] were unambiguously proven by their single crystal X-ray analysis (Figure 3). Once we started to perform reactions at a larger scale, the formation of C(22)-azetidine byproduct **8** was observed. Arylation employing iodoarenes with electron-withdrawing substituents proceeded poorly and provided both arylated regioisomers within a 29−54% yield range. On


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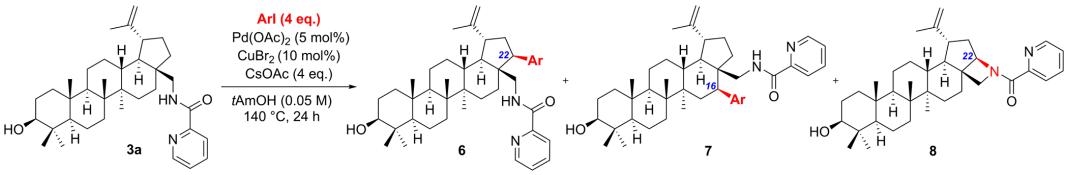
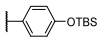
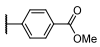
**Table 2. Scope and Isolated Yields of C($sp^3$)-H Arylation Products of Picolinamide 3a**




| Ar | Yield of **6a-i** (%) | Yield of **7a-i** (%) | Yield of **8** (%) |
|---|---|---|---|
|  | **6a**, 76 | **7a**, 7 | 10 |
|  | **6b**, 64 | **7b**, 9 | 26 |
|  | **6c**, 60 | **7c**, 5 | 19 |
|  | **6d**, 45 | **7d**, 6 | 10 |
|  | **6e**, 32 | **7e**, 6 | 36 |
|  | **6f**, 32 (31)[a] | **7f**, 6 (3)[a] | 56 (51)[a] |
|  | **6g**, 22 | **7g**, 7 | 40 |
|  | **6h**, 19 | **7h**, 12 | 64 |
|  | **6i**, 42 | **7i**, 12 | 44 |
|  | - | - | 61 |

[a]Reaction time 48 h.

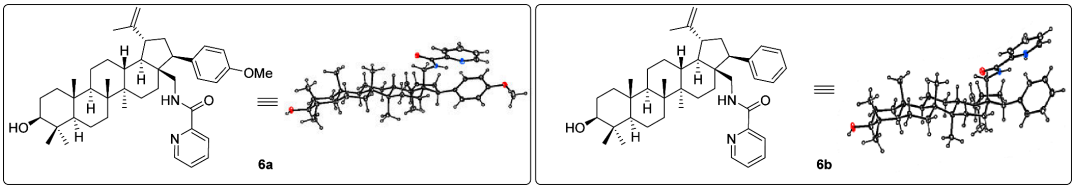



**Figure 3.** Single crystal X-ray diffraction analysis of **6a** and **6b**.

the other hand, iodobenzenes with substituents such as −COOMe, −C(O)Me, −CN, −Cl, $-NO_2$ (entries 6−10, Table 2) gave azetidine **8** as the major product in 40−64% yields. The highest azetidine yield was observed with I−$C_6H_4$−CN (64%), but I−$C_6H_4$−$NO_2$ provided it as a single reaction product in 61% yield, which facilitated its isolation and purification. An additional experiment with methyl 4-iodobenzoate and extended reaction time to 48 h was performed, but it did not improve the C($sp^3$)-H arylation outcome. Azetidines as C($sp^3$)-H arylation byproducts have been reported before, and a targeted azetidination protocol employing AgOAc/$C_6F_5I$ on simple model substrates has been previously reported by Wu and co-workers.[38] Additionally, it is known that azetidines can be formed in Pd-catalyzed and picolinamide-directed intramolecular C−H amination employing PhI($OAc)_2$ as oxidant and $Li_2CO_3$ as a base.[39,40] However, in our hands, such a control experiment, which would lead to azetidine **8** as the main product, did not result in any conversion of starting material **3a**. It should be mentioned that the picolinamide directing group is instrumental also for the azetidination step, as a control experiment with free amine **4a′** (3$\beta$-hydroxy-lup-20(29)en-28-amine) did not result in azetidine formation. Also, control experiments run in the absence of ArI did not provide the azetidine product, and only the unchanged starting material was recovered.

We have also explored C($sp^3$)-H (het)arylation reactions of **3a** with 4-iodo *N*,*N*-dimethyl aniline, 3-iodopyridine and 4-iodo-1-methyl-*1H*-pyrazole, but no conversion of starting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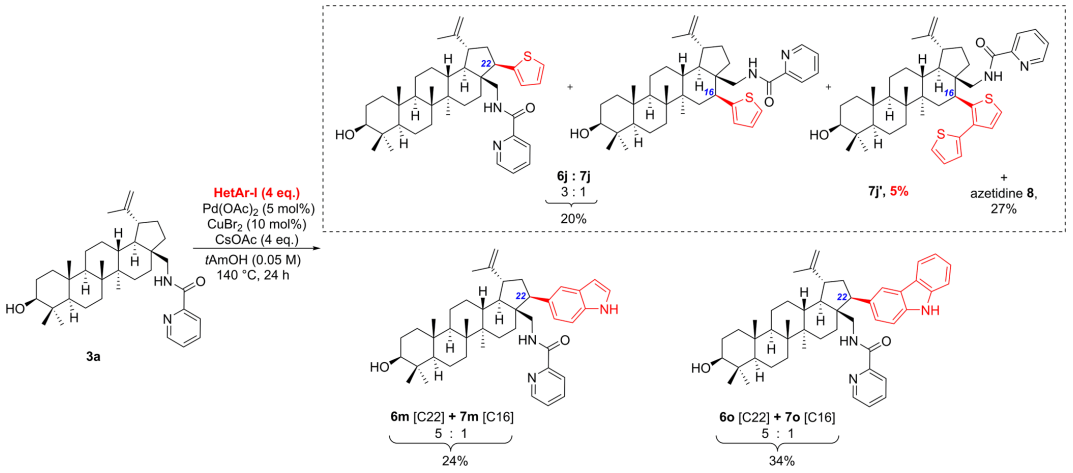
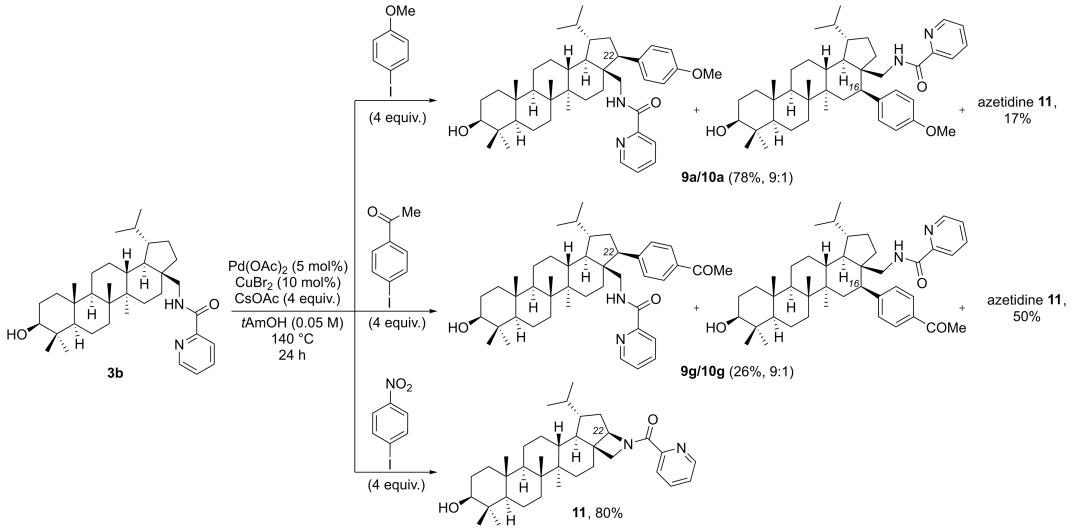
**Scheme 3. C($sp^3$)-H Hetarylation of Picolinamide 3a**




**Scheme 4. C($sp^3$)-H Arylation and Azetidination of Lupane-Derived Picolinamide 3b**




material was observed. Additionally, we have performed hetarylation with 5-iodo indole and 7-iodo carbazole (Scheme 3), and the expected products **6***m*/**7m** and **6***o*/**7o** were isolated in 24 and 34% yields, respectively, albeit without formation of azetidine. We also tested *N*-Cbz-protected 5-iodo indole and 7-iodo carbazole, but unexpectedly low conversion of a **3a** was observed that encumbered product isolation and characterization.

In all C($sp^3$)-H (het)arylation cases discussed above, we have not detected any formation of diarylated products. Longer reaction time, higher concentration of an (het)aryl iodide component, as well as higher catalyst loading were found to be ineffective. The only exception was the reaction between **3a** and 2-iodo thiophene, which resulted in a detectable amount of diarylated product **7j′** (5%) besides monoaddition products **6***j*/**7j** and azetidine **8**. However, the second C−H activation has taken place at the first installed thiophene moiety in product **7j** (Scheme 3).

In a parallel series of experiments reaction of saturated lupane-derived picolinamide **3b** with 4-iodoanisole leads to the formation of 9:1 regioisomers **9a**/**10a** in 78% total yield, along with 17% of azetidine **11** (Scheme 4). Next, a reaction between **3b** and 1-(4-iodophenyl)ethan-1-one gave 9:1 regioisomers **9g**/**10g** in 26% total yield along with 50% of azetidine **11**, but reaction with 1-iodo-4-nitrobenzene provided only azetidine **11** in very good 80% yield. Regardless of some differences in yields between the product series **6**/**7**/**8** and **9**/**10**/**11**, there are no notable differences in the reactivity between betulin-derived picolinic amide **3a** and saturated lupane-derived picolinamide **3b**.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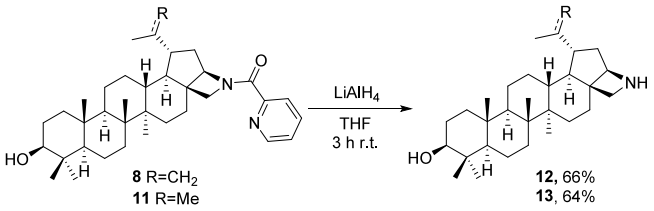
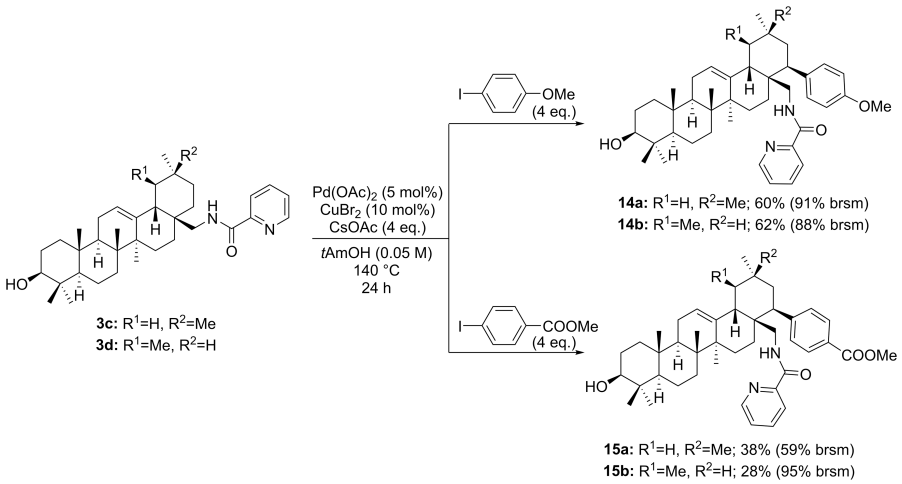
**Scheme 5. Synthesis of Unprotected Azetidines 12 and 13**

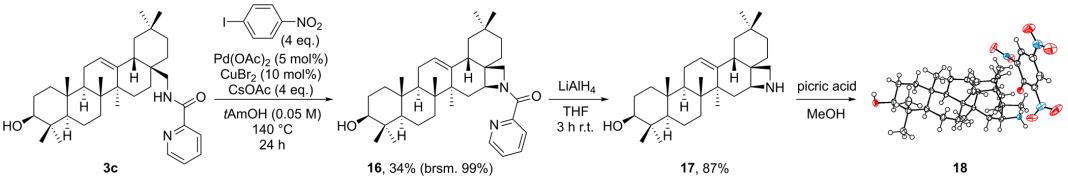



**Scheme 6. C($sp^3$)-H Arylation of Oleanolic and Ursolic Amides 3c,d**[a]




[a]brsm = based on recovered starting material.

**Scheme 7. Azetidine 17 Formation from Oleanolic Amide 3c**




Azetidines **8** and **11** were observed as 1:1 mixtures of rotamers in their NMR spectra. In order to simplify the NMR characterization and to provide NH azetidines for further synthetic applications, we tested the cleavage of the picolinamide moiety. First, subjecting both **8** and **11** to alkaline hydrolysis conditions afforded no product. Consequently, reductive cleavage conditions employing $LiAlH_4$ in THF at room temperature afforded desired NH-azetidines **12** and **13** (Scheme 5).

Encouraged by the successful arylation of betulin and lupane core, we also have examined the arylation of oleanolic and ursolic acid-derived picolinamides **3c,d** employing 4-methoxyphenyl iodide and 4-iodobenzoic acid methyl ester (Scheme 6). Arylation of ursane and oleane cores resulted in higher 19:1 site-selectivity at C(22). Full conversion of **3c** and **3d** was not reached, but in most cases, reactions were quite clean, and after subtraction of the recovered unreacted starting material, high yields of products can be formally calculated. It is worth mentioning that analogously, as in previous cases, electron-deficient 4-iodobenzoic acid methyl ester provides significantly lower yields of arylation products **15a,b** than the reaction with 4-methoxyphenyl iodide. Interestingly, reactions of oleane and ursane starting materials **3c,d** → **14a,b**/**15a,b** did not provide the azetidine byproduct.

On the other hand, slow yet clean reaction between oleanolic amide **3c** and 1-iodo-4-nitrobenzene provided only azetidine **16**, which was isolated in 34% yield along with 65% of unreacted starting material (Scheme 7). Surprisingly, C−N bond formation in this case occurred at C(16) of the oleanolic core. Product **16** exists as a mixture of two stable rotamers in a 2:1 ratio. Further reductive cleavage of the directing group with $LiAlH_4$ released corresponding azetidine **17**, which was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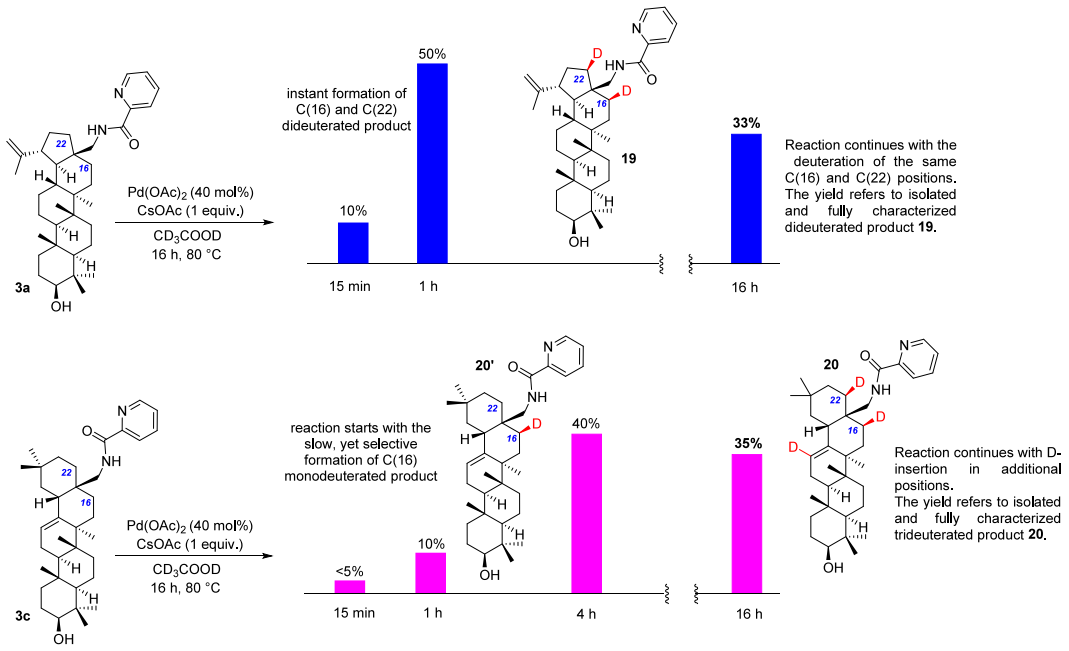
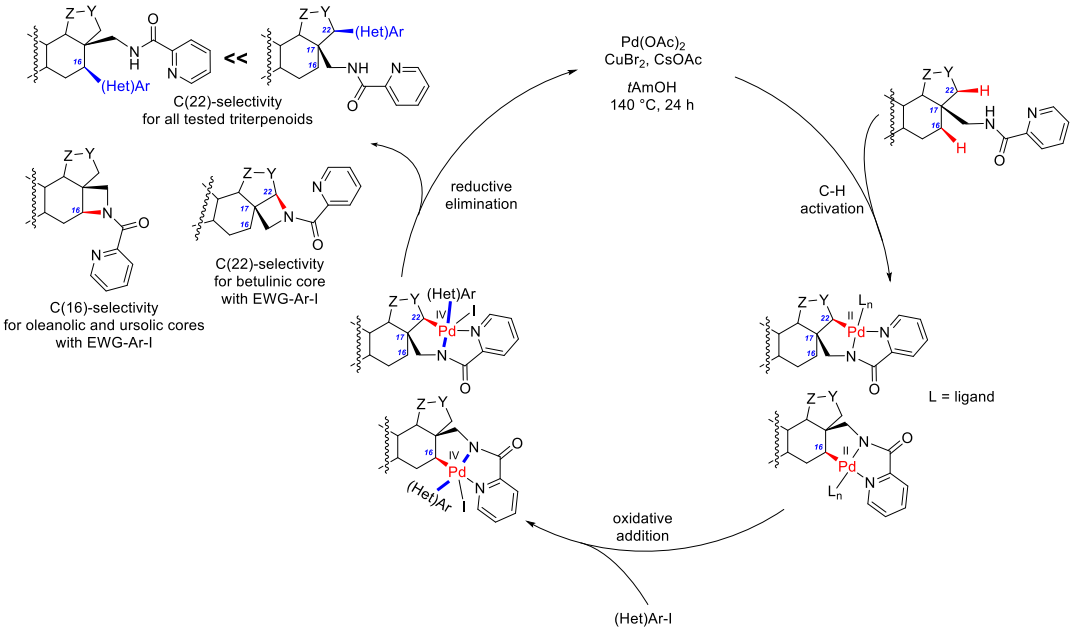
**Scheme 8. C−H Deuteration of Picolinamides 3a,c at Different Times**[a]




[a]D-insertion rate during reactions **3a** → **19** and **3c** → **20′** → **20** was established by integration of 2D HSQC NMR cross-peaks; depicted yields of final products **19** and **20** are the isolated yields.

**Scheme 9. Plausible Pd-Catalyzed C($sp^3$)-H Arylation and Azetidination Mechanism**



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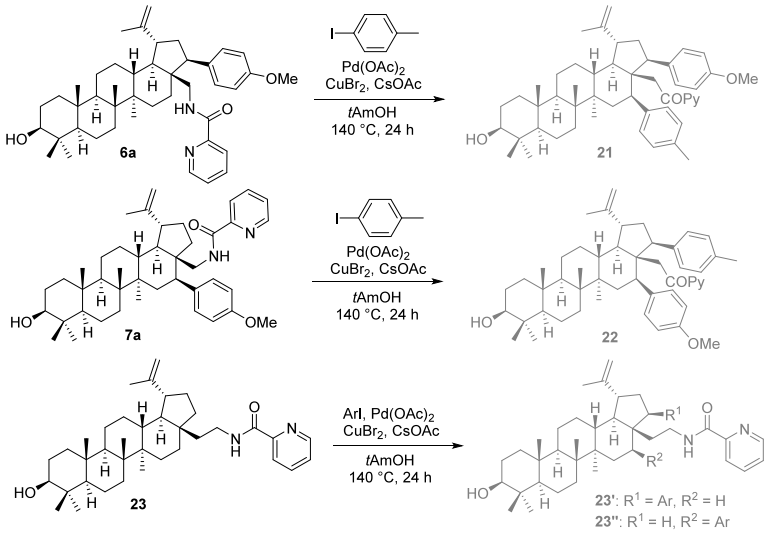
**Scheme 10. Arylation Attempts of Compounds 6a, 7a, and Extended Amide 23**




further transformed into crystalline azetidinium picrate **18**. The molecular structure of the latter was unambiguously established by its single-crystal X-ray diffraction analysis.[41]

In order to explain the differences in C−H amination regioselectivity between betulin derived picolinamide **3a** and oleanolic acid derived picolinic amide **3c**, additional C−H deuteration experiments were carried out. In the beginning of our study we discovered that C−H deuteration of betulin derived picolinamide **3a** proceeded at both reaction sites C(16) and C(22) in 16 h at 80 °. Similar type of product was observed in the case of oleanolic acid derived picolinamide **3c** after 16 h reaction, but for this substrate also vinylic proton at C(12) was substituted with deuterium, yielding trideuterated product **20** (Scheme 8).

For clarity, the acidic −OH and −NH groups in Scheme 8 are depicted in their nondeuterated form as they undergo fast proton exchange during the isolation process. It was observed that the C(16)/C(22) C−H dideuteration of betulin core occurs without site selectivity, albeit with a higher rate. Thus, within 15 min already 10% conversion of starting material **3a** into dideuterated product **19** was observed. After 1 h, the conversion has reached 50%, and after 16 h, product **19** was isolated in 33% yield. On the other hand, picolinamide **3c** initially underwent C(16)-selective deuteration with a lower rate, providing only 10% conversion into monodeuterated intermediate **20′** after 1 h. After an additional 3 h (total reaction time 4 h), there was ∼ 40% conversion of starting material **3c** into C(16)-monodeuterated intermediate **20′**. Finally, after 16 h at 80 °C, trideuterated product **20** was isolated in 35% yield in the oleane series. From this, we can conclude that C(16)-H deuteration and C(22)-H deuteration rates for the betulin core are very similar, but the oleane molecular skeleton exhibits a certain kinetic preference for C(16)-H deuteration. A similar C(16)-H selectivity of oleanolic acid-derived quinoline amide was reported by Yuyong and co-workers.[42]

Based on the generally accepted concept, most likely, reductive elimination is the rate-limiting step in the C($sp^3$)-H arylation process.[43] This assumption is also supported by the experiments with 8-aminoquinoline amide auxiliary that contains a less flexible CO-NH linker (compounds **2a,c,d**), which was able to ensure C($sp^3$)-H deuteration, but failed in the arylation/azetidination experiments. Summing up the obtained regioselectivity patterns with more reactive starting materials bearing a flexible $-CH_2-NH-$ linker (compounds **3a−d**), we can conclude that reductive elimination occurs more slowly with palladium(IV) complexes bearing aryl substituents with electron-withdrawing substituents. In such complexes, at some point, reductive elimination forming the C−N bond is faster than that forming the C−C bond.[44,45] In the betulinic series, reductive elimination from C(22)-[Pd]-NC(O) system outperforms reductive elimination C(22)-[Pd]-Ar-EWG if 4-$NO_2-C_6H_4I$ is used in the oxidative addition step (Scheme 9). This leads to the formation of azetidine. In the oleanolic series, the general rule for reductive elimination rates is the same: Ar-EDG > picolinamide > Ar-EWG. Only in this case, the C−H activation step is slower, C(16)-H-selective, and apparently kinetically comparable with the reductive elimination from the C(16)-[Pd]-NC(O) system. Therefore, starting material **3c** provides azetidine **16** at C (16) when treated with 4-$NO_2-C_6H_4I$. Additionally, azetidine formation at C(22) in the oleanolic core would result in an unfavorable 1,3-diaxial interaction with one of the C(20)-geminal methyl groups, but such a steric constraint is absent in the betulin molecular skeleton. Radical scavengers TEMPO and galvinoxyl, which were used in the control experiments, did not influence the yield and selectivity of reaction **3a → 6f + 7f + 8**, thus ruling out a single electron transfer mechanistic pathway for the C−Pd bond formation step (Scheme S2, Supporting Information).

Next, we explored the possibility of additional C−H arylation of previously obtained products **6a** and **7a** that, if successful, shall provide C(16),C(22)-bis-arylated products **21**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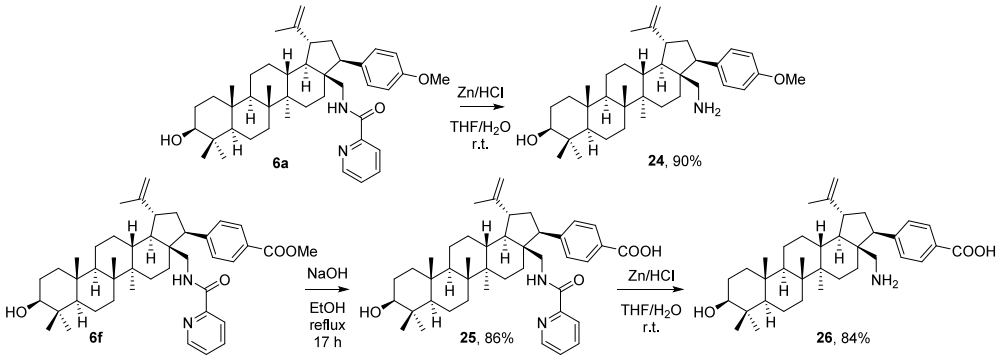
**Scheme 11. Synthesis of Amine 24 and Amino Acid 26**




and **22** (Scheme 10). Also, betulin amine homologue **23**, containing $-(CH_2)_2-$ linker between the terpene core and directing group, was explored as a starting material. In all these experiments, starting materials **6a**, **7a,** and **23** remained intact under our developed C−H arylation conditions.

Finally, the pyridyl amide was effectively removed from the arylated product **6a** in high yield by reductive cleavage with Zn/HCl to give the free amine **24**. The ester cleavage from compound **6f** and subsequent cleavage of the directing group gave novel betulin-derived amino acid **24** (Scheme 11).

## SUMMARY

We have developed a palladium-catalyzed C($sp^3$)-H arylation of different triterpenoid picolinamides with aryl iodides, which is the first C−C bond forming C−H activation protocol in the triterpenoid series. All three tested congeners possessing betulin, oleane, and ursane cores provided C(22)-arylation selectivity, and the aryl products were obtained in average to good yields. Oleane and ursane-derived picolinamides gave better C(22)/C16 selectivity up to 19:1, but betulin-derived picolinamides gave higher isolated yields − up to 83%. As expected, iodoarenes bearing electron-donating groups gave higher yields of C($sp^3$)-arylation products, but in all cases azetidine side product was observed. On the other hand, switching to iodoarenes bearing electron-withdrawing groups shifted reactivity toward C($sp^3$)- azetidination. The latter was the only detectable process when 4-$NO_2$−$C_6H_4$I was used. Interestingly, the C(22)/C16 selectivity of the C($sp^3$)-azetidination process was substrate-dependent. Thus, the betulin scaffold provided C(22)-azetidine, but the oleane scaffold gave C(16)-azetidine. The picolinamide directing group was successfully removed from the modified triterpenoids in the presence of Zn/HCl without any cationic rearrangements. Additionally, the obtained annulated betulin- and oleane-derived azetidines open broad possibilities for their further derivatization that may provide a novel approach to important terpenoid-based compounds in terms of medicinal chemistry.

## EXPERIMENTAL SECTION

**General Information.** Solvents for the reactions were dried over standard drying agents and freshly distilled prior to use. All purchased chemicals (Fluka, Aldrich) were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 $F_{254}$ and visualized by using a UV lamp. Column chromatography was performed on silica gel (60 Å, 40−63 $\mu$m, ROCC). Flash column chromatography was performed on a Büchi Sepacore system (Büchi-Labortechnik GmbH, Essen, Germany) with a Büchi Control Unit C-620, an UV detector Büchi UV photometer C-635, a Büchi fraction collector C-660, and two Pump Modules C-605. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 300 and 500 MHz, in $CDCl_3$, [$D_6$]DMSO, [$D_8$]THF, or [$D_4$]MeOD at 25 °C. Chemical shifts ($\delta$) values are reported in ppm. The residual solvent peaks are used as internal reference ($CDCl_3$) 7.26 ppm, [$D_6$]DMSO 2.50 ppm, [$D_8$]THF 3.58 ppm, [$D_4$]MeOD 3.31 ppm for $^1$H NMR, $CDCl_3$ 77.16 ppm, [$D_6$]DMSO 39.52 ppm, [$D_8$]THF 67.57 ppm, [$D_4$]MeOD 49.00 ppm for $^{13}$C NMR), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); *J* in hertz. High-resolution mass spectra (ESI) were performed on an Agilent 1290 Infinity series UPLC connected to an Agilent 6230 TOF mass spectrometer (calibration at *m*/*z* 121.050873 and *m*/*z* 922.009798).

*3β-Hydroxy-lup-20(29)en-28-amine (**4a′**).* Solution of oxime **4a** (5 g, 10.9 mmol, 1 equiv) and $NH_4OAc$ (3.11 g, 40.4 mmol, 3.7 equiv) in MeOH (120 mL) was cooled to −10 °C, and $NaBH_3CN$ (1.99 g, 31.7 mmol, 2.9 equiv) was added portion-wise. The resulting reaction mixture was stirred at ambient temperature for 10 min, and then $TiCl_3$ solution in 2 M HCl (20% w/v, 21.8 mL, 43.6 mmol, 4 equiv) was added dropwise. After 1 h, the reaction mixture was heated up to room temperature and left stirring until complete conversion of the starting material was observed (TLC control). The reaction mixture was cooled to 0 °C, and 1 M NaOH aqueous solution (125 mL) was added dropwise, maintaining the temperature at 0−10 °C. The obtained precipitate was filtered through a Celite pad (H = 70 mm, d = 50 mm) and washed with a hot THF/MeOH 1:1 mixture (1000 mL). The filtrate was partially evaporated, and the obtained precipitate was filtered and subsequently washed with $H_2O$ (20 mL) and MTBE (30 mL), then dried in an oven at 120 °C for 1 h to give a white amorphous solid (4.36 g, 90%), which was used without additional purification.

*3β-Hydroxy-lupan-28-amine (**4b′**).* Solution of oxime **4b** (5 g, 11.0 mmol, 1 equiv) and $NH_4OAc$ (3.13 g, 40.7 mmol, 3.7 equiv) in MeOH (120 mL) was cooled to −10 °C, and $NaBH_3CN$ (2.00 g, 31.9 mmol, 2.9 equiv) was added portion-wise. The resulting mixture was stirred at ambient temperature for 10 min, and then $TiCl_3$ solution in 2 M HCl (22.0 mL, 44 mmol, 4 equiv) was added dropwise. After 1 h reaction was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ACS Omega XXXX, XXX, XXX−XXX

heated up to room temperature and left stirring until complete conversion of the starting material (TLC control). Reaction mixture was cooled to 0 °C, and 1 M NaOH aqueous solution (125 mL) was added dropwise, maintaining the temperature at 0−10 °C. Obtained precipitate was filtered through a Celite pad (H = 70 mm, d = 50 mm) and washed with a hot THF/MeOH 1:1 mixture (1000 mL). Filtrate was partially evaporated and obtained precipitate was filtered and subsequently washed with $H_2O$ (20 mL) and MTBE (30 mL), then dried in oven at 120 °C for 1 h to give white amorphous solid (3.24 g, 67%), which was used directly for the next step without additional purification.

*3β-Hydroxy-olean-12(13)-ene-28-amine (**5a**′) or 3β-Hydroxy-urs-12(13)-ene-28-amine (**5b**′).* HCTU (1.08 g, 2.62 mmol) and $Et_3N$ (0.44 g, 4.36 mmol) were added to a solution of oleanolic acid **1a** or ursolic acid **1b** (1g, 2.18 mmol) in DMF (5 mL) at room temperature. The resulting reaction mixture was stirred for 1 h; then, a saturated solution of $NH_3$ in EtOH (1 mL) was added at room temperature, and the obtained mixture was stirred for 12 h. The resulting mixture was diluted with water (15 mL) and filtered. The precipitate was washed with water (15 mL) and dried at 70 °C for 48 h to obtained amide **5a** or **5b** as a white solid (837 mg, 84% for **5a** and 908 mg, 91% for **5b**), which was used directly for the next step without additional purification. $LiAlH_4$ (140 mg, 3.68 mmol) was added portionwise to a solution of crude **5a** or **5b** (0.42 g, 0.92 mmol) in THF (3 mL) at 0 °C. Then the reaction mixture was stirred for 96 h at reflux temperature, cooled to 0 °C, and slowly quenched sequentially with water (1 mL), and 15% aqueous NaOH (2 mL). The obtained suspension was filtered, and the filtrate was evaporated to dryness and purified by silica column chromatography (DCM-MeOH 99:1−10:1) to yield pure oleanolic amine (0.26 g, 65%) or ursolic amine (0.21 g, 52%) after two steps.

**General Procedure I for the Synthesis of Picolinic Amides.** To a solution of picolinic acid (124 mg, 1 mmol, 1 equiv) in a mixture of anhydrous DCM (2 mL) and THF (2 mL), one drop of DMF and oxalyl chloride (127 mg, 1 mmol, 1 equiv) were subsequently added dropwise at 0 °C. Then the resulting reaction mixture was warmed up to room temperature and stirred for 1 h. The solution was concentrated in vacuo to remove excess oxalyl chloride and then redissolved back in DCM (6 mL) Then it was cooled to 0 °C and solution of triterpenoid amine (1.05 mmol, 1.05 equiv) and triethylamine (505 mg, 5 mmol, 5 equiv) in DCM (10 mL) was added dropwise during 30 min at ambient temperature. The resulting reaction mixture was warmed to room temperature and stirred for 5 h. Then it was diluted with DCM (50 mL) and washed with water (2 × 30 mL) and brine (2 × 30 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica column chromatography (Hexanes-EtOAc 10:1−4:1) to yield picolinic amide as a white amorphous solid.

*3β-Hydroxy-28-picolinamido-lup-20(29)ene (**3a**).* According to GP I, compound **3a** was prepared from the corresponding amine (390 mg, 0.882 mmol, 1.05 equiv), picolinic acid (103 mg, 0.841 mmo, 1 equiv), oxalyl chloride (86 μL, 1.009 mmol, 1 equiv), $Et_3N$ (293 μL, 2.106 mmol, 5 equiv), $DCM_{anh.}$ (15 mL), $THF_{anh.}$ (30 mL). Yield 457 mg, 90%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}N_2O_2 + H]^+$ 547.4258; found 547.4273. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′), 8.21 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.03 (t, $^3J$ = 6.5 Hz, 1H, H−N), 7.84 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′), 7.41 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 4.72 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.60 (s, 1H, $H_b$-C (29)), 3.71 (dd, $^2J$ = 13.8 Hz, $^3J$ = 6.5 Hz, 1H, $H_a$-C (28)), 3.24 (dd, $^2J$ = 13.8 Hz, $^3J$ = 6.5 Hz, 1H, $H_b$-C (28)), 3.18 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.55 (td, $^3J$ = 11.2, 5.6 Hz, 1H, H−C (19)), 2.18 −2.07, m, 1H, $H_a$-C (21)), 1.90 (ddd, $^2J$ = 13.7 Hz, $^3J$ = 13.6 Hz, 4.4 Hz, 1H, $H_a$-C (15)), 1.83 (td, $^3J$ = 12.0, 3.4 Hz, 1H, H−C (13)), 1.80−1.76 (m, 1H, $H_a$-C (16)), 1.76−1.71 (m, 1H, $H_a$-C (22)), 1.70 (s, 3H, $H_3$−C (30)), 1.69−1.47 (m, 5H, $H_a$-C (16), $H_a$-C (12), $H_2$−C (2), $H_a$-C (1)), 1.47−1.36 (m, 6H, $H_b$-C (6), $H_a$-C (11), $H_b$-C (21), $H_2$−C (7), H−C (18)), 1.34−1.22 (m, 3H, $H_b$-C (11), $H_b$-C (16), H−C (9)), 1.14−1.03 (m, 6H, $H_3$−C (26), $H_b$-C (12), $H_b$-C (15), $H_b$-C (22)), 0.99 (s, 3H, $H_3$−C (27)), 0.97 (s, 3H, $H_3$−C (23)), 0.93−0.86 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (25)), 0.72−0.66 (m, 1H, H−C (5)). $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 164.71 (N−C = O), 150.43 (C20), 150.17 (C2′), 148.14 (C6′), 137.51 (C4′), 126.17 (C5′), 122.37 (C3′), 109.92 (C29), 79.13 (C3), 55.47 (C5), 50.56 (C9), 49.17 (C18), 47.57 (C19), 47.33 (C17), 42.88 (C14), 41.08 (C8), 39.01 (C4), 38.86 (C1), 37.48 (C13), 37.43 (C28), 37.31 (C10), 35.22 (C22), 34.30 (C7), 30.51 (C16), 29.94 (C21), 28.13 (C23), 27.56 (C2), 27.41 (C15), 25.37 (C12), 20.98 (C11), 19.46 (C30), 18.43 (C6), 16.24 (C25), 16.20 (C26), 15.51 (C24), 14.96 (C27).

*3β-Hydroxy-28-picolinamido-lupane (**3b**).* According to GP I, compound **3b** was prepared from the corresponding amine (400 mg, 0.901 mmol, 1.05 equiv), picolinic acid (106 mg, 0.858 mmo, 1 equiv), oxalyl chloride (88 μL, 1.029 mmol, 1 equiv), $Et_3N$ (300 μL, 2.145 mmol, 5 equiv), $DCM_{anh.}$ (15 mL), $THF_{anh.}$ (30 mL). Yield 405 mg, 86%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{56}N_2O_2 + H]^+$ 549.4415; found 549.4416. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′), 8.20 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.00 (dd, $^3J$ = 6.5, 6.0 Hz, 1H, H−N), 7.84 (t, $^3J$ = 7.8 Hz, 1H, H−C(4′), 7.41 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 3.74 (dd, $^2J$ = 13.8 Hz, $^3J$ = 6.5 Hz, 1H, $H_a$-C (28)), 3.25−3.11 (m, 2H, H−C (3), $H_b$-C (28)), 1.97−1.81 (m, 4H, $H_a$-C (15), H−C (20), H−C (13), H−C (19)), 1.80−1.46 (m, 10H, $H_2$−C (21), $H_a$-C (6), $H_a$-C (11), $H_2$−C (2), $H_a$-C (16), $H_a$-C (12), $H_a$-C (22), $H_a$-C (1)), 1.47−1.17 (m, 8H, $H_b$-C (6), $H_b$-C (11), $H_b$-C (12), $H_b$-C (16), $H_2$−C (7), $H_b$-C (18), $H_b$-C (9)), 1.13 (s, 3H, $H_3$−C (26)), 1.08−1.02 (m, 1H, $H_b$-C (15)), 0.97 (s, 6H, $H_3$−C (23), $H_3$−C (27)), 0.96−0.87 (m, 2H, $H_b$-C (22), $H_b$-C (1)), 0.92 (d, $^3J$ = 6.8 Hz, 3H, H−C (30)), 0.85 (s, 3H, $H_3$−C (25)), 0.78 (d, $^3J$ = 6.0 Hz, 3H, $H_3$−C (29)), 0.77 (s, 3H, $H_3$−C (24)), 0.72−0.66 (m, 1H, H−C (5)). $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 164.66 (C═O), 150.24 (C2′), 148.14 (C6′), 137.50 (C4′), 126.13 (C5′), 122.36 (C3′), 79.16 (C3), 55.43 (C5), 50.24 (C9), 48.50 (C18), 47.43 (C17), 44.43 (C19), 43.04 (C14), 41.12 (C8), 39.02 (C4), 38.86 (C1), 37.51 (C28), 37.28 (C10), 37.05 (C13), 35.36 (C22), 34.37 (C7), 30.61 (C16), 29.60 (C20), 28.14 (C23), 27.55 (C2), 27.30 (C15), 27.00 (C12), 23.10 (C30), 21.97 (C21), 20.98 (C11), 18.45 (C6), 16.20 (C25 + C26), 15.53 (C24), 15.14 (C29), 14.85 (C27).

*3β-28-Picolinamido-olean-12(13)-ene (**3c**).* According to GP I, compound **3c** was prepared from the corresponding amine (1.04 g, 2.354 mmol, 1.05 equiv), picolinic acid (276 mg, 2.242 mmo, 1 equiv), oxalyl chloride (230 μL, 2.690 mmol, 1 equiv), $Et_3N$ (780 μL, 5.605 mmol, 5 equiv), $DCM_{anh.}$ (15 mL), $THF_{anh.}$ (5 mL). Yield 1.083 g, 88%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}N_2O_2 + H]^+$ 547.4258; found 547.4254.


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$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′), 8.20 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.10 (dd, $^3J$ = 7.5, 5.6 Hz, 1H, H−N), 7.83 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′), 7.41 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 5.27 (d, $^3J$ = 3.7 Hz, 1H, H−C (12)), 3.74 (dd, $^2J$ = 13.7 Hz, $^3J$ = 7.5 Hz, 1H, $H_a$-C (28)), 3.22 (dd, $^3J$ = 10.9, 4.8 Hz, 1H, H−C (3)), 2.97 (dd, $^2J$ = 13.7 Hz, $^3J$ = 5.6 Hz, 1H, $H_b$-C (28)), 2.08 (dd, $^3J$ = 13.5, 4.5 Hz, 1H, H−C (18)), 2.00−1.83 (m, 4H, $H_2$−C (11), $H_a$-C (16), $H_a$-C (15)), 1.75 (dd, $^2J$ = 13.6 Hz, $^3J$ = 13.5 Hz, 1H, $H_a$-C (19)), 1.68−1.47 (m, 7H, $H_a$-C (6), $H_2$−C (2), $H_a$-C (7), $H_a$-C (22), $H_a$-C (1), H−C (9)), 1.47−1.22 (m, 4H, $H_b$-C (6), $H_b$-C (7), $H_b$-C (22), $H_a$-C (21)), 1.22−1.18 (m, 1H, $H_b$-C (21)), 1.18 (s, 3H, $H_3$−C (27)), 1.14−1.09 (m, 2H, $H_b$-C (16), $H_b$-C (19)), 1.09 (s, 3H, $H_3$−C (26)), 1.04 −1.00 (m, 1H, $H_b$-C (15)), 0.99 (s, 3H, $H_3$−C (23)), 0.99−0.96 (m, 1H, $H_a$-C (1)), (s, 3H, $H_3$−C (25)), 0.89 (s, 3H, $H_3$−C (30)), 0.88 (s, 3H, $H_3$−C (29)), 0.79 (s, 3H, $H_3$−C (24)), 0.77−0.72 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.39 (C = O), 150.29 (C2′), 148.13 (C6′), 143.97 (C13), 137.46 (C4′), 126.09 (C5′), 122.99 (C12), 122.39 (C3′), 79.17 (C3), 55.35 (C5), 47.80 (C9), 47.41 (C28), 46.68 (C19), 44.78 (C18), 41.93 (C14), 40.04 (C8), 38.93 (C4), 38.78 (C1), 37.09 (C10), 36.83 (C17), 34.24 (C21), 33.34, (C30), 32.60 (C7), 32.14 (C22), 31.08 (C20), 28.24 (C13), 27.39 (C2), 26.24 (C27), 25.99 (C15), 23.77 (C11), 23.70 (C29), 22.59 (C16), 18.47 (C6), 16.86 (C26), 15.73 (C24), 15.67 (C25).

*3β-28-Picolinamido-urs-12(13)-ene (**3d**).* According to GP I, compound **3d** was prepared from the corresponding amine (230 mg, 0.498 mmol, 1.05 equiv), picolinic acid (62 mg, 0.504 mmo, 1 equiv), oxalyl chloride (56 μL, 0.504 mmol, 1 equiv), $Et_3N$ (120 μL, 1.261 mmol, 5 equiv),$DCM_{anh.}$ (5 mL). Yield 208 mg, 80%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}N_2O_2 + H]^+$ 547.4258; found 547.4267. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.55 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 8.20 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.06 (dd, $^3J$ = 7.6, 5.4 Hz, 1H, H−N), 7.83 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.40(dd, $^3J$ = 7.8, 4.7 Hz, 1H, H−C(5′)), 5.23 (t, $^3J$ = 3.6 Hz, 1H, H−C (12)), 3.75 (dd, $^2J$ = 13.7 Hz, $^3J$ = 7.6 Hz, 1H, $H_a$-C (28)), 3.23 (dd, $^3J$ = 11.0, 4.9 Hz, 1H, H−C (3)), 2.91 (dd, $^2J$ = 13.7 Hz, $^3J$ = 5.4 Hz, 1H, $H_b$-C (28)), 2.06−1.92 (m, 4H, $H_2$−C (11), $H_a$-C (16), $H_a$-C (15)), 1.77−1.50 (m, 7H, $H_a$-C (6), $H_2$−C (2), $H_a$-C (7), $H_a$-C (22), $H_a$-C (1), H−C (9)), 1.50−1.34 (m, 6H, $H_b$-C (6), $H_a$-C (22), $H_b$-C (7), $H_b$-C (22), H−C (19), H−C (18)), 1.28−1.20 (m, 1H, $H_b$-C (21)), 1.19-1.14 (m, 1H, $H_b$-C (16)), 1.13 (s, 3H, $H_3$−C (26)), 1.12 (s, 3H, $H_3$−C (26)), 1.06−0.99 (m, 2H, $H_b$-C (15), $H_b$-C (1)), 1.00 (s, 3H, $H_3$−C (23)), 0.96 (s, 3H, $H_3$−C (25)), 0.95−0.91 (m, 4H, $H_3$−C (30), H−C (20)), 0.83 (d, $^3J$ = 5.6 Hz, 3H, $H_3$−C (29)), 0.80 (s, 3H, $H_3$−C (24)), 0.74 (d, $^3J$ = 11.5 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.37 (C═O), 150.35 (C2′), 148.13 (C6′), 138.44 (C13), 137.44 (C4′), 126.06 (C5′), 125.77 (C12), 122.39 (C3′), 79.20 (C3), 56.51 (C18), 55.36 (C5), 47.89 (C9), 47.67 (C28), 42.27 (C14), 40.26 (C8), 39.64 (C19), 39.52 (C20), 38.98 (C4), 38.93 (C1), 37.88 (C17), 37.04 (C10), 36.29 (C22), 32.89 (C7), 30.80 (C21), 28.27 (C23), 27.43 (C2), 26.47 (C15), 23.93 (C16), 23.64 (C11), 23.53 (C27), 21.43 (C30), 18.45 (C6), 17.52 (C29), 16.96 (C26), 15.84 (C25), 15.77 (C24).

*(17R)-17-(2-(Picolinamido)ethyl)-28-norlup-20(29)-en-3β-ol (**23**).* According to GP I, compound **23** was prepared from the corresponding amine (860 mg, 4.492 mmol, 1.05 equiv), picolinic acid (221 mg, 1.797 mmo, 1 equiv), oxalyl chloride (185 μL, 2.156 mmol, 1.2 equiv), $Et_3N$ (626 μL, 4.492 mmol, 2.5 equiv), $DCM_{anh.}$ (40 mL)), $THF_{anh.}$ (60 mL). Yield 849 mg, 84%. HRMS (ESI): $m/z$ calc. for $[C_{37}H_{56}N_2O_2 + H]^+$ 561.4415; found 561.4398. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$ = 4.7 Hz, 1H, H−C(6′)), 8.21 (d, $J$ = 7.7 Hz, 1H, H−C(3′)), 8.00 (t, $^3J$ = 5.7 Hz, 1H, H−N), 7.85 (td, $J$ = 7.7, 1.8 Hz, 1H, H−C(4′)), 7.42 (ddd, $^3J$ = 7.7, 4.7 Hz, $^4J$ = 1.8 Hz, 1H, H−C(5′)), 4.67 (d, $^4J$ = 2.4 Hz, 1H, $H_a$-C (29)), 4.57 (s, 1H, $H_b$-C (29)), 3.45 (dddd, $^2J$ = 12.8 Hz, $^3J$ = 11.6, 5.9, 5.7 Hz, 1H, $H_a$-C(28′)) 3.38 (dddd, $^2J$ = 12.8 Hz, $^3J$ = 11.1, 5.7, 5.3 Hz, 1H, $H_b$-C(28′)), 3.18 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3), 2.41 (td, $^3J$ = 11.1, 5.6 Hz, 1H, H−C (19)), 1.97 (dtd, $^2J$ = 14.0, $^3J$ = 10.6, 8.2 Hz, 1H, $H_a$-C (21)), 1.86 (ddd, $^2J$ = 12.5 Hz, $^3J$ = 12.4 Hz, 6.1 Hz, 1H, $H_a$-C (28)), 1.82−1.70 (m, 3H, $H_a$-C (16), $H_a$-C (22), H−C (13)), 1.68 (s, 3H, H−C (30)), 1.67−1.57 (m, 4H, $H_a$-C (12), $H_a$-C (2), $H_a$-C (15), $H_a$-C (1)), 1.57−1.35 (m, 8H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (2), $H_b$-C (21), $H_2$−C (7), H−C (18)), 1.35−1.17 (m, 4H, $H_b$-C (28), $H_b$-C (11), $H_b$-C (16), H−C (9)), 1.12−1.06 (m, 2H, $H_b$-C (22), $H_b$-C (12)), 1.06−1.02 (m, 4H, $H_3$−C (26), $H_b$-C (15)), 0.97 (s, 3H, $H_3$−C (27)), 0.96 (s, 3H, $H_3$−C (23)), 0.93−0.89 (m, 1H, $H_b$-C (1)), 0.82 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.68 (d, $^3J$ = 9.3 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.32 (N−C═O), 150.79 (C20), 150.27 (C2′), 148.14 (C6′), 137.52 (C4′), 126.20 (C5′), 122.32 (C3′), 109.71 (C29), 79.14 (C3), 55.46 (C5), 50.61 (C9), 50.15 (C18), 47.49 (C19), 45.29 (C17), 42.70 (C14), 41.03 (C8), 39.02 (C1), 38.85 (C4), 37.35 (C13), 37.32 (C10), 35.99 (C28′), 35.95 (C22), 34.35 (C7), 31.33 (C16), 30.15 (C21), 28.13 (C23), 27.68 (C2), 27.55 (C28), 27.48 (C15), 25.24 (C12), 21.08 (C11), 19.44 (C30), 18.45 (C6), 16.29 (C25), 16.25 (C26), 15.51 (C24), 15.06 (C27).

**General Procedure II for Arylation Reaction.** A solution of picolinic amide (0.20 mmol, 1 equiv), iodo (het)arene (0.80 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.02 mmol, 0.1 equiv), and CsOAc (154 mg, 0.80 mmol, 4 equiv) in *t*-AmOH (2 mL) was stirred in a pressure vessel under a nitrogen atmosphere for 24 h at 140 °C. The resulting reaction mixture was cooled to room temperature and filtered through a Celite pad (H = 50 mm, d = 15 mm), followed by washing with THF/EtOAc 1:1 (10 mL). The filtrate was concentrated under reduced pressure, and the crude mixture was purified by column chromatography on silica gel (Hexanes-EtOAc 10:1 → 1:1), yielding desired arylation products as a white amorphous solid.

*(22S)-22-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)en (**6a**) and (16R)-16-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7a**).* According to GP II, compounds **6a** and **7a** were prepared from picolinic amide **3a** (50 mg, 0.091 mmol, 1 equiv), 1-iodo-4-methoxybenzene (86 mg, 0.366 mmol, 4 equiv), $Pd(OAc)_2$ (1 mg, 0.004 mmol, 0.05 equiv), $CuBr_2$ (2 mg, 0.009 mmol, 0.1 equiv), and CsOAc (70 mg, 0.366 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 46 mg, 83%. HRMS (ESI): $m/z$ calc. for $[C_{43}H_{60}N_2O_3 + H]^+$ 653.4677; found 653.4676.

*(22S)-22-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6a**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 (dd, $^3J$ = 5.3 Hz, $^4J$ = 1.8 Hz, 1H, H−C(6′)), 8.00 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.70 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.28−7.24 (m, 3H, H−C(5′), H−C(3″), H−C(5″)), 6.92 (d, $^3J$ = 9.3 Hz, 1H, H−N), 6.87 (d, $^3J$ = 8.7 Hz, 2H, H−C(2″), H−C(6″)), 4.80 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.66 (s, 1H, $H_b$-C (29)), 4.14 (dd, $^2J$ = 14.2, $^3J$ = 9.3 Hz, 1H, $H_a$-C (28)), 3.78 (s, 3H, $CH_3$−O) 3.19 (dd, $^3J$ = 11.3, 4.8 Hz, 1H,


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ACS Omega XXXX, XXX, XXX−XXX

H−C (3)), 2.96 (dd, $^2J$ = 14.2, $^3J$ = 2.8 Hz, 1H, $H_b$-C (28)), 2.88 (dd, $^3J$ = 10.0, 8.3 Hz, 1H, H−C (22)), 2.64 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 11.5, 10.0 Hz, $H_a$-C (21)), 2.61 (ddd, $^3J$ = 11.5, 10.9, 4.2 Hz, 1H, H−C (19)), 2.02 (td, $^3J$ = 12.0, 3.5 Hz, 1H, H−C (13)), 1.89 (dd, $^3J$ = 12.0, 10.9 Hz, 1H, H−C (18)), 1.84 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.9, 3.5 Hz, 1H, $H_a$-C (16)), 1.76 (s, 3H, H−C (30)), 1.76−1.70 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (15), $H_a$-C (1)), 1.65−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_b$-C (7), $H_b$-C (21), H−C (9)), 1.17 (s, 3H, $H_3$−C (26)), 1.15−1.07 (m, 1H, $H_b$.C (12)), 1.03 (s, 3H, $H_3$−C (27)), 1.03−0.97 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.94−0.85 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.64 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.98 (C═O), 158.95 (C4″) 150.14 (C20), 149.97 (C2′), 147.61 (C6′), 136.96 (C4′), 132.01 (C1″), 128.62 (C2″ + C6″), 125.69 (C5′), 121.78 (C3′), 114.40 (C3″ + C5″), 110.38 (C29), 79.20 (C3), 55.53 (C5), 55.29 (O−$CH_3$) 53.98 (C22), 50.68 (C9), 50.46 (C18), 50.14 (C17), 46.23 (C19), 42.73 (C14), 41.02 (C8), 39.02 (C1), 38.90 (C4), 37.68 (C13), 37.34 (C10), 35.91 (C28), 34.22 (C7), 34.09 (C21), 30.21 (C16), 28.13 (C23), 27.59 (C2), 27.41 (C15), 25.21 (C12), 20.99 (C11), 19.30 (C30), 18.37 (C6), 16.21 (C25), 16.06 (C26), 15.50 (C24), 15.14 (C27).

*(16R)-16-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7a**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.21 (d, $^3J$ = 4.5 Hz, 1H, H−C(6′), 7.99 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′), 7.71 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.29 (dd, $^3J$ = 7.8, 4.5 Hz, 1H, H−C(5′)), 7.24 (d, $^3J$ = 8.7 Hz, 2H, H−C(3″), H−C(5″)), 7.03 (d, $^3J$ = 9.9 Hz, 1H, H−N), 6.86 (d, $^3J$ = 8.7 Hz, 2H, H−C(2″), H−C(6″)), 4.74 (d, $^3J$ = 2.4 Hz, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3.79 (s, 3H, O−$CH_3$), 3.70 (dd, $^2J$ = 14.3, $^3J$ = 9.9 Hz, 1H, $H_a$-C (28)), 3.46 (d, $^2J$ = 14.3 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 2.88 (dd, $^3J$ = 13.2, 3.5 Hz, 1H, H−C (16)), 2.69 (td, $^3J$ = 11.2, 4.2 Hz, 1H, H−C (19)), 2.41 (dd, $^2J$ = 13.4 Hz, $^3J$ = 13.2 Hz, 1H, $H_a$-C (15)), 2.01 (dddd, $^2J$ = 13.7 Hz, $^3J$ = 11.2, 10.4, 6.5 Hz, 1H, $H_a$-C (21)), 1.89 (dd, $^3J$ = 12.0, 11.2 Hz, 1H, H−C (18)), 1.80 (td, $^3J$ = 12.0, 3.5 Hz, 1H, H−C (13)), 1.75 (s, 3H, H−C (30)), 1.74−1.58 (m, 5H, $H_a$-C (12), $H_2$−C (2), $H_a$-C (22), $H_a$-C (1)), 1.58−1.23 (m, 10H, $H_2$−C (6), $H_2$−C (11), $H_b$-C (21), $H_b$-C (15), $H_2$−C (7), $H_b$-C (22), H−C (9)), 1.18 (s, 3H, $H_3$−C (26)), 1.13−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (23)), 0.96−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.73−0.69 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.11 (C═O), 158.72 (C4″), 150.47 (C20), 149.85 (C2′), 147.68 (C6′), 137.02 (C4′), 135.77 (C1″), 128.60 (C2″ + C6″), 125.77 (C5′), 121.80 (C3′), 114.19 (C3″ + C5″), 109.64 (C29), 79.15 (C3), 55.48 (C5), 55.34 ($CH_3$−O), 51.32 (C17), 51.13 (C18), 50.62 (C9), 47.73 (C16), 46.93 (C19), 43.38 (C14), 41.44 (C8), 39.04 (C1), 38.93 (C4), 37.37 (C10), 37.09 (C13), 36.38 (C28), 35.14 (C22), 34.50 (C7), 32.49 (C15), 30.11 (C21), 28.16 (C23), 27.57 (C2), 25.71 (C12), 21.08 (C11), 20.22 (C30), 18.45 (C6), 16.41 (C26), 16.37 (C25), 15.58 (C24), 15.54 (C27).

*(22S)-22-Phenyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene* (**6b**) *and (16R)-16-Phenyl-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7b**). According to GP II, compounds **6b** and **7b** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), iodobenzene (149 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 83 mg, 73%. HRMS (ESI): *m*/*z* calc. for $[C_{42}H_{58}N_2O_2 + H]^+$ 623.4571; found 623.4574.

*(22S)-22-Phenyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene* (**6b**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.17 (dd, $^3J$ = 4.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C (6)), 7.99 (d, $^3J$ = 7.8, Hz, 1H, H−C(3′)), 7.69 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.36−7.28 (m, 4H, H−C(2″), H−C(3″), H−C(5″), H−C(6″)), 7.27−7.23 (m, 2H, H−C(4″), H−C(5′)), 6.92 (d, $^3J$ = 9.3 Hz, 1H, H−N), 4.81 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.66 (s, 1H, $H_b$-C (29)), 4.15 (dd, $^2J$ = 14.2, $^3J$ = 9.3 Hz, 1H, $H_a$-C (28)), 3.19 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 3.02 (dd, $^2J$ = 14.2, $^3J$ = 2.7 Hz, 1H, $H_b$-C (28)), 2.93 (dd, $^3J$ = 10.3 9.3 Hz, 1H, H−C (22)), 2.70 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 11.1, 10.3 Hz, 1H, $H_a$-C (21)), 2.64 (ddd, $^3J$ = 11.3, 11.1, 4.6 Hz, 1H, H−C (19)), 2.03 (td, $^3J$ = 12.0, 3.6 Hz, 1H, H−C (13)), 1.91 (dd, $^3J$ = 12.0, 11.3 Hz, 1H, H−C (18)), 1.84 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 7.0, 3.6 Hz, 1H, $H_a$-C (16)), 1.77 (s, 3H, H−C (30)), 1.76−1.65 (m, 4H, $H_a$-C (12), $H_b$-C (21), $H_a$-C (1), $H_a$-C (15)), 1.65−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_2$−C (7), H−C (9)), 1.17 (s, 3H, $H_3$−C (26)), 1.14−1.07 (m, 1H, $H_b$.C (12)), 1.03 (s, 3H, $H_3$−C (27)), 1.02−0.96 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.96−0.89 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.01 (C═O), 150.06 (C20), 149.91 (C2′), 147.43 (C6′), 140.10 (C1″), 136.95 (C4′), 129.01 (C3″ + C5″), 127.92 (C2″ + C6″), 126.67 (C4″), 125.60 (C5′), 121.75 (C3′), 110.43 (C29), 79.19 (C3), 55.53 (C5), 54.83 (C22), 50.68 (C9), 50.66 (C18), 50.39 (C17), 46.23 (C19), 42.72 (C14), 41.02 (C8), 39.02 (C4), 38.90 (C1), 37.69 (C13), 37.34 (C10), 35.90 (C28), 34.09 (C7 + C21), 30.25 (C16), 28.13 (C23), 27.59 (C2), 27.40 (C15), 25.21 (C12), 21.00 (C11), 19.29 (C30), 18.37 (C6), 16.21 (C25), 16.07 (C26), 15.50 (C24), 15.15 (C27).

*(16R)-16-Phenyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene* (**7b**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.17 (dd, $^3J$ = 4.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C (6)), 7.98 (d, $^3J$ = 7.8, Hz, 1H, H−C(3′)), 7.71 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.35−7.24 (m, 6H, H−C(2″), H−C(3″), H−C(5″), H−C(6″), H−C(4″), H−C(5′)),7.06 (d, $^3J$ = 9.3 Hz, 1H, H−N), 4.75 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3,73 (dd, $^2J$ = 14.2 Hz, $^3J$ = 9.3 Hz, 1H, $H_a$-C (28)), 3.40 (d, $^2J$ = 14.2 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 2.92 (dd, $^3J$ = 13.0, 3.5 Hz, 1H, H−C (16)), 2.70 (td, $^3J$ = 10.9, 4.5 Hz, 1H, H−C (19)), 2.47 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 2.02 (dddd, $^2J$ = 12.8 Hz, $^3J$ = 12.5, 10.9, 7.5 Hz, 1H, $H_a$-C (21)), 1.91 (dd, $^3J$ = 11.9, 10.9 Hz, 1H, H−C (18)), 1.82 (td, $^3J$ = 11.9, 3.7 Hz, 1H, H−C (13)), 1.77 (s, 3H, H−C (30)), 1.76−1.65 (m, 3H, $H_a$-C (12), $H_b$-C (22), $H_a$-C (1)), 1.65−1.40 (m, 8H, $H_2$−C (6), $H_a$-C (11), $H_2$−C (2), $H_b$-C (22), $H_2$−C (7)), 1.40- 1.23 (m, 4H, $H_b$-C (11), $H_b$-C (21), $H_b$-C (15), H−C (9)), 1.19 (s, 3H, $H_3$−C (26)), 1.14−1.08 (m, 4H, $H_b$.C (12), $H_3$−C (27)), 0.98 (s, 3H,$H_3$−C (23)), 0.96−0.89 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.74−0.67 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.14 (C═O), 150.44 (C20), 149.82 (C2′), 147.54 (C6′), 143.76 (C1″), 137.01 (C4′), 128.83 (C3″ + C5″), 127.82 (C2″ + C6″), 126.51 (C4″), 125.69 (C5′), 121.76 (C3′), 109.66 (C29), 79.14 (C3), 55.48 (C5), 51.33 (C18), 51.30 (C17), 50.62 (C9), 48.73 (C16), 46.94 (C19), 43.38 (C14), 41.45 (C8), 39.03 (C4), 38.92 (C1), 37.37 (C10), 37.11 (C13), 36.38 (C28), 35.06 (C22), 34.49 (C7), 32.33 (C15), 30.13 (C21),


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28.15 (C23), 27.56 (C2), 25.71 (C12), 21.08 (C11), 20.24 (C30), 18.44 (C6), 16.41 (C25), 16.36 (C26), 15.57 (C24), 15.53 (C27).

*(22S)-22-Tolyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene (**6c**) and (16R)-16-Tolyl-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7c**).* According to GP II, compounds **6c** and **7c** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 1-iodo-4-methylbenzene (159 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 75 mg, 65%. HRMS (ESI): *m*/*z* calc. for $[C_{43}H_{60}N_2O_2 + H]^+$ 637.4728; found 637.4726.

*(22S)-22-Tolyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene (**6c**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 (dd, 1H, $^3J$ = 5.3 Hz, $^4J$ = 1.8 Hz, H−C(6′)), 8.01 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.70 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.28−7.24 (m, 1H, H−C(5′)), 7.23 (d, $^3J$ = 7.9 Hz, 2H, H−C(2″), H−C(6″)), 7.13 (d, $^3J$ = 7.9 Hz, 2H, H−C(3″), H−C(5″)), 6.90 (d, $^3J$ = 9.4 Hz, 1H, H−N), 4.80 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.66 (s, 1H, $H_b$-C (29)), 4.13 (dd, $^2J$ = 14.2, $^3J$ = 9.4 Hz, 1H, $H_a$-C (28)), 3.19 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 3.00 (dd, $^2J$ = 14.4, $^3J$ = 2.8 Hz, 1H, $H_b$-C (28)), 2.89 (dd, $^3J$ = 10.1, 9.1 Hz, 1H, H−C (22)), 2.73−2.58 (m, 2H, $H_a$-C (21), H−C (19)), 2.33 (s, 3H, $H_3$C-Ph), 2.02 (td, $^3J$ = 12.0, 3.6 Hz, 1H, H−C (13)), 1.89 (dd, $^3J$ = 12.0, 11.2 Hz, 1H, H−C (18)), 1.84 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.9, 3.5 Hz, 1H, $H_a$-C (16)), 1.76 (s, 3H, H−C (30)), 1.76−1.65 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (1), $H_a$-C (15)), 1.65−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_b$-C (7), $H_b$-C (21), H−C (9)), 1.16 (s, 3H, $H_3$−C (26)), 1.14−1.08 (m, 1H, $H_b$-C (12)), 1.03 (s, 3H, $H_3$−C (27)), 1.03−0.96 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.96−0.85 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.02 (C═O), 150.12 (C20), 150.05 (C2′), 147.52 (C6′), 136.94 (C4′ + C1″), 136.33 (C4″), 129.62 (C3″ + C5″), 127.71 (C2″+ C6″), 125.57 (C5′), 121.88 (3′), 110.36 (C29), 79.17 (C3), 55.52 (C5), 54.40 (C22), 50.67 (C9), 50.59 (C18), 50.18 (C17), 46.25 (C19), 42.70 (C14), 41.00 (C8), 39.00 (C1), 38.88 (C4), 37.67 (C13), 37.33 (C10), 35.95 (C28), 34.14 (C7), 34.09 (C21), 30.23 (C16), 28.11 (C23), 27.57 (C2), 27.40 (C15), 25.19 (C12), 21.22 ($CH_3$−Ph), 20.99 (C11), 19.29 (C30), 18.36 (C6), 16.20 (C25), 16.05 (C26), 15.49 (C24), 15.13 (C27).

*(16R)-16-Tolyl-3β-hydroxy-28-picolinamido-lup-20(29)-ene (**7c**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 (d, $^3J$ = 4.5 Hz, 1H, H−C(6′), 8.00 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′), 7.72 (td, $^3J$ = 7.8, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.29−7.26 (m, 1H, H−C(5′)), 7.21 (d, $^3J$ = 7.9 Hz, 2H, H−C(2″), H−C(6″)), 7.12 (d, $^3J$ = 7.9 Hz, 2H, H−C(3″), H−C(5″)), 7.04 (d, $^3J$ = 9.5 Hz, 1H, H−N), 4.74 (d, $^3J$ = 2.4 Hz, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3.72 (dd, $^2J$ = 14.4, $^3J$ = 9.5 Hz, 1H, $H_a$-C (28)), 3.38 (d, $^2J$ = 14.4 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 2.88 (dd, $^3J$ = 13.2, 3.2 Hz, 1H, H−C (16)), 2.69 (td, $^3J$ = 11.0, 4.4 Hz, 1H, H−C (19)), 2.44 (dd, $^2J$ = 13.4 Hz, $^3J$ = 13.2 Hz, 1H, $H_a$-C (15)), 2.06−1.96 (m, 1H, $H_a$-C (21)), 1.89 (dd, $^2J$ = 12.0 Hz, $^3J$ = 11.4 Hz, 1H, H−C (18)), 1.80 (td, $^3J$ = 12.0, 3.5 Hz, 1H, H−C (13)), 1.75 (s, 3H, H−C (30)), 1.74−1.67 (m, 3H, $H_a$-C (12), $H_a$-C (22), $H_a$-C (1)), 1.66−1.23 (m, 12H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (21), $H_b$-C (15), $H_2$−C (7), $H_b$-C (22), H−C (9)), 1.18 (s, 3H, $H_3$−C (26)), 1.13−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.97 (s, 3H, $H_3$−C (23)), 0.96−0.90 (m, 1H, $H_b$-C (1)), 0.87 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.73−0.69 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.16 (C═O), 150.48 (C20), 149.97 (C2′), 147.63 (C6′), 140.68 (C1″), 137.03 (C4′), 136.15 (C4″), 129.45 (C3″ + C5″), 127.63 (C2″+ C6″), 125.68 (C5′), 121.90 (3′), 109.64 (C29), 79.14 (C3), 55.48 (C5), 50.62 (C9), 50.22 (C18), 50.21 (C17), 48.28 (C16), 46.95 (C19), 43.37 (C14), 41.44 (C8), 39.04 (C1), 38.92 (C4), 37.37 (C13), 37.10 (C10), 36.42(C28), 35.08 (C22), 34.46 (C7), 32.39 (C15), 30.13 (C21), 28.16 (C23), 27.57 (C2), 25.71 (C12), 21.22 ($CH_3$−Ph), 21.08 (C11), 20.21 (C30), 18.45 (C6), 16.41 (C25), 16.36 (C26), 15.57 (C24), 15.54 (C27).

*(22S)-22-(4-Hydroxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6d**) and (**7d**).* According to GP II, compounds **6d** and **7d** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 4-iodophenol (161 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 58 mg, 50%. HRMS (ESI): *m*/*z* calc. for $[C_{42}H_{58}N_2O_3 + H]^+$ 639.4520; found 639.4504.

*(22S)-22-(4-Hydroxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6d**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.34 (dd, 1H, $^3J$ = 5.1 Hz, $^4J$ = 1.8 Hz, H−C(6′)), 8.00 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.70 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.29−7.23 (m, 1H, H−C(5′)), 7.20 (d, $^3J$ = 8.6 Hz, 2H, H−C(2″), H−C(6″)), 7.03 (d, $^3J$ = 9.0 Hz, 1H, H−N), 6.83 (d, $^3J$ = 8.6 Hz, 2H, H−C(3″), H−C(5″)), 4.79 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.66 (s, 1H, $H_b$-C (29)), 4.16 (dd, $^2J$ = 14.1, $^3J$ = 9.0 Hz, 1H, $H_a$-C (28)), 3.49 (s, 1H, OH) 3.19 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 2.94 (dd, $^2J$ = 14.1, $^3J$ = 2.4 Hz, 1H, $H_b$-C (28)), 2.87 (dd, $^3J$ = 10.1, 8.7 Hz, 1H, H−C (22)), 2.69−2.55 (m, 2H, $H_a$-C (21), H−C (19)), 1.99 (td, $^3J$ = 11.9, 4.2 Hz, 1H, H−C (13)), 1.88 (dd, $^3J$ = 11.9, 10.9 Hz, 1H, H−C (18)), 1.82 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.8, 3.5 Hz, 1H, $H_a$-C (16)), 1.76 (s, 3H, H−C (30)), 1.76−1.65 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (1), $H_a$-C (15)), 1.65−1.23 (m, 9H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_b$-C (7), $H_b$-C (21), H−C (9)), 1.15 (s, 3H, $H_3$−C (26)), 1.13−1.05 (m, 1H, $H_b$-C (12)), 1.02 (s, 3H, $H_3$−C (27)), 1.01−0.97 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.94−0.88 (m, 1H, $H_b$-C (1)), 0.83 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.65 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.19 (C═O), 155.25 (C4″), 150.08 (C20), 149.74 (C2′), 147.95 (C6′), 137.02 (C4′), 131.85 (C1″), 128.87 (C2″ + C6″), 125.75 (C5′), 121.75 (C3′), 115.94 (C3″ + C5″), 110.40 (C29), 79.26 (C3), 55.52 (C5), 53.97 (C22), 50.66 (C9), 50.42 (C18), 50.11 (C17), 46.20 (C19), 42.72 (C14), 40.99 (C8), 39.01 (C4), 38.88 (C1), 37.68 (C13), 37.33 (C10), 35.97 (C28), 34.21 (C7), 34.08 (C21), 30.20 (C16), 28.12 (C23), 27.55 (C2), 27.40 (C15), 25.20 (C12), 20.98 (C11), 19.31 (C30), 18.37 (C6), 16.21 (C25), 16.07 (C26), 15.50 (C24), 15.13 (C27).

*(22S)-22-(4-(tert-Butyldimethylsilyl)oxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6e**) and (16R)-16-(4-(tert-Butyldimethylsilyl)oxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7e**).* According to GP II, compounds **6e** and **7e** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), *tert*-butyl(4-iodophenoxy)dimethylsilane (244 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 45


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ACS Omega XXXX, XXX, XXX−XXX

mg, 33%. HRMS (ESI): $m/z$ calc. for $[C_{48}H_{72}N_2O_3Si + H]^+$ 753.5385; found 753.5368.

*(22S)-22-(4-(tert-Butyldimethylsilyl)oxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6e**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.32 (d, 1H, $^3J$ = 4.7 Hz, H−C(6′)), 8.00 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.69 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)),7.25 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 7.19 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 6.98 (d, $^3J$ = 9.8 Hz, 1H, H−N), 6.81 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 4.79 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.65 (s, 1H, $H_b$-C (29)), 4.14 (dd, $^2J$ = 14.1 Hz, $^3J$ = 9.8 Hz 1H, $H_a$-C (28)), 3.18 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.95 (d, $^2J$ = 14.1 Hz, 1H, $H_b$-C (28)), 2.86 (dd, $^3J$ = 9.6, 9.2 Hz, 1H, H−C (22), 2.66 −2.57 (m, 2H, $H_a$-C (21), H−C (19)), 2.01 (td, $^3J$ = 12.2, 3.4 Hz, 1H, H−C (13)), 1.91−1.80 (m, 2H, H−C (18), $H_a$-C (16)), 1.76 (s, 3H, $H_3$−C (30)), 1.75−1.64 (m, 4H, $H_a$-C (22), $H_a$-C (15), $H_b$-C (21), $H_a$-C (1)), 1.65−1.24 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16), $H_2$−C (7), H−C (9)), 1.17 (s, 3H, $H_3$−C (26)), 1.15−1.08 (m, 1H, $H_b$-C (15)), 1.02 (s, 3H, $H_3$−C (27)), 1.00 (s, 9H, $(CH_3)_3C$), 1.00−0.96 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H, $H_3$−C (23)), 0.95−0.90 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.68 (d, $^3J$ = 10.5 Hz, 1H, H−C (5)), 0.17 (s, 3H, $H_3$−C-Si), 0.16 (s, 3H, $H_3$−C-Si). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.07 (C═O), 154.96 (C4′), 150.16 (C20), 149.97 (C2′), 147.97 (C6′), 136.92 (C4′), 132.49 (C1″), 128.66 (C2″ + C6″), 125.56 (C5′), 121.69 (C3′), 120.49 (C3″ + C5″), 110.38 (C29), 79.20 (C3), 55.54 (C5), 54.08 (C22), 50.68 (C9), 50.48 (C18), 50.16 (C17), 46.24 (C19), 42.72 (C14), 41.01 (C8), 39.02 (C4), 38.90 (C1), 37.69 (C13), 37.35 (C10), 35.90 (C28), 34.28 (C21), 34.09 (C7), 30.23 (C16), 28.13 (C23), 27.59 (C2), 27.42 (C15), 25.81 (C12), 25.20 ($(CH_3)_3C$), 21.00 (C11), 19.26 (C30), 18.37 (C6), 18.25 ($C(CH_3)_3$), 16.21 (C25), 16.06 (C26), 15.50 (C24), 15.15 (C27), −4.32 ($(CH_3)_2Si$).

*(16R)-16-(4-(tert-Butyldimethylsilyl)oxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7e**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.32 (d, 1H, $^3J$ = 4.7 Hz, H−C(6′)), 7.99 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.71 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.26 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 7.18 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.09 (d, $^3J$ = 9.7 Hz, 1H, H−N), 6.79 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 4.74 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3.71 (dd, $^2J$ = 14.3 Hz, $^3J$ = 9.7 Hz, 1H, $H_a$-C (28)), 3.33 (d, $^2J$ = 14.3 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.86 (dd, $^3J$ = 13.0, 3.2 Hz, 1H, H−C (16)), 2.69 (td, $^3J$ = 11.0, 4.4 Hz, 1H, H−C (19)), 2.39 (dd, $^2J$ = 13.6 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 2.08−1.96 (m, 2H, $H_a$-C (21), $H_a$-C (2)), 1.88 (dd, $^3J$ = 11.9, 11.0 Hz, 1H, H−C (18)), 1.79 (td, $^3J$ = 11.9, 3.7 Hz, 1H, H−C (13)), 1.74 (s, 3H, H−C (30)), 1.76−1.20 (m, 15H, $H_2$−C (12), $H_2$−C (22), $H_a$-C (1), $H_b$-C (2), $H_2$−C (11), $H_2$−C (6), $H_2$−C (7), $H_b$-C (15), $H_b$-C (21), H−C (9)), 1.17 (s, 3H, $H_3$−C (26)), 1.09 (s, 3H, $H_3$−C (27)), 1.01 (s, 9H, $(H_3C)_3C$), 0.98 (s, 3H,$H_3$−C (23)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.74−0.69 (m, 1H, H−C (5)), 0.18 (s, 3H, $H_3$−C-Si), 0.17 (s, 3H, $H_3$−C-Si).$^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.20 (N−C═O), 154.71 (C4″), 150.50 (C20), 149.87 (C2′), 148.02 (C6′), 136.97 (C4′), 136.25 (C1″), 128.56 (C2″ + C6″), 125.65 (C5′), 121.71 (C3′), 120.25 (C3″ + C5″), 109.61 (C29), 79.15 (C3), 55.48 (C5), 51.31 (C18), 51.17 (C17), 50.62 (C9), 47.86 (C16), 46.94 (C19), 43.38 (C14), 41.44 (C8), 39.04 (C4), 38.93 (C1), 37.37 (C13), 37.09 (C10), 36.39 (C28), 35.13 (C22), 34.51 (C7), 32.51 (C15), 30.13 (C21), 28.16 (C23), 27.57 (C2), 25.82 ($(CH_3)_3$), 25.71 (C12), 21.09 (C11), 20.25 (C30), 18.44 (C6), 18.28 ($C(CH_3)_3C$), 16.40 (C25), 16.36 (C26), 15.54 (C24), 14.27 (C27), −4.28 ($(CH_3)Si$), −4.31 ($(CH_3)Si$).

*(22S)-22-(4-Methoxycarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6f**) *and (16R)-16-(4-Methoxycarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7f**). According to GP II, compounds **6f** and **7f** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), methyl 4-iodobenzoate (161 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 47 mg, 38%. HRMS (ESI): $m/z$ calc. for $[C_{44}H_{60}N_2O_4 + H]^+$ 681.4626; found 681.4606.

*(22S)-22-(4-Methoxycarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6f**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (dd, 1H, $^3J$ = 4.9 Hz, $^4J$ = 1.6 Hz, H−C(6′)), 7.96 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.95 (d, $^3J$ = 8.2 Hz, 2H, H−C(3″), H−C(5″)), 7.68 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.6 Hz, 1H, H−C(4′)), 7.40 (d, $^3J$ = 8.2 Hz, 2H, H−C(2″), H−C(6″)), 7.22 (dd, $^3J$ = 7.7, 4.9 Hz, 1H, H−C(5′)),), 6.87 (d, $^3J$ = 9.0 Hz, 1H, H−N), 4.81 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.68 (s, 1H, $H_b$-C (29)), 4.06 (dd, $^2J$ = 14.3, $^3J$ = 9.0 Hz, 1H, $H_a$-C (28)), 3.90 (s, 3H, O−$CH_3$) 3.20 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3)), 2.94 (dd, $^2J$ = 14.3, $^3J$ = 2.4 Hz, 1H, $H_b$-C (28)), 2.87 (dd, $^3J$ = 9.8, 9.6 Hz, 1H, H−C (22)), 2.73 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 11.2, 9.8 Hz, 1H $H_a$-C (21)), 2.68−2.53 (m, 2H, H−C (19), OH), 2.00 (td, $^3J$ = 11.7, 3.5 Hz, 1H, H−C (13)), 1.93 (dd, $^3J$ = 11.7, 11.0 Hz, 1H, H−C (18)), 1.86 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.7, 3.5 Hz, 1H, $H_a$-C (16)), 1.77 (s, 3H, H−C (30)), 1.76−1.65 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (1), $H_a$-C (15)), 1.65−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_b$-C (7), $H_b$-C (21), H−C (9)), 1.14 (s, 3H, $H_3$−C (26)), 1.13−1.05 (m, 1H, $H_b$-C (12)), 1.04 (s, 3H, $H_3$−C (27)), 1.01−0.97 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.94−0.88 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.73−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.26 (O−C═O), 164.12 (N−C═O), 149.66 (C20), 149.41 (C2′), 147.54 (C6′), 145.88 (C1″), 137.05 (C4′), 130.23 (C3″ + C5″), 128.61 (C4″), 127.81 (C2″ + C6″), 125.84 (C5′), 121.84 (C3′), 110.68 (C29), 79.26 (C3), 55.51 (C5), 54.81 (C22), 52.12 (O−$CH_3$), 50.87 (C17), 50.79 (C18), 50.64 (C9), 46.16 (C19), 42.68 (C14), 41.00 (C8), 39.00 (C4), 38.88 (C1), 37.69 (C13), 37.32 (C10), 36.00 (C28), 34.11 (C7), 33.85 (C21), 30.27 (C16), 28.11 (C23), 27.51 (C2), 27.37 (C15), 25.20 (C2), 20.97 (C11), 19.36 (C30), 18.36 (C6), 16.21 (C25), 16.03 (C26), 15.49 (C24), 15.15 (C27).

*(16R)-16-(4-Methoxycarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7f**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.07 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′), 7.96 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.94 (d, $^3J$ = 8.2 Hz, 2H, H−C(3″, H−C(5″)), 7.70 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.39 (d, $J$ = 8.2 Hz, 2H, H−C(2″), H−C(6″)), 7.24 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 6.99 (d, $^3J$ = 9.0 Hz, 1H, H−N), 4.75 (d, $^3J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 3.92 (s, 3H, O−$CH_3$), 3.64 (dd, $^2J$ = 14.5 Hz, $^3J$ = 9.0 Hz, 1H, $H_a$-C (28)), 3.45 (dd, $^2J$ = 14.5 Hz, $^3J$ = 3.2 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.3, 4.9 Hz, 1H, H−C (3)), 2.97 (dd, $^3J$ = 13.0, 3.4 Hz, 1H, H−C (16)), 2.68 (td, $^3J$ = 11.1, 4.5 Hz, 1H H−C (19)),


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ACS Omega XXXX, XXX, XXX−XXX

2.48 (dd, $^2J$ = 13.2 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 2.03 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 11.0, 7.6 Hz, 1H, $H_a$-C (21)), 1.92 (dd, $^3J$ = 12.0, 11.1 Hz, 1H, H−C (18)), 1.82 (td, $^3J$ = 12.0, 3.6 Hz, 1H, H−C (13)), 1.75 (s, 3H, $H_3$−C (30)), 1.75−1.58 (m, 5H, $H_a$-C (12), $H_2$−C (2), $H_a$-C (22), $H_a$-C (1)), 1.58−1.42 (m, 6H, $H_2$−C (6), $H_a$-C (21), $H_b$-C (22), $H_2$−C (7)), 1.42−1.23 (m, 4H, $H_b$-C (11), $H_b$-C (21), $H_b$-C (16), H−C (9)), 1.21 (s, 3H, $H_3$−C (26)), 1.14−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (27)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.75−0.68 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.32 (O−C═O), 164.20 (N−C═O), 150.17 (C20), 149.46 (C2′), 149.35 (C1″), 147.62 (C6′), 137.11 (C4′), 130.07 (C3″ + C5″), 128.44 (C4″), 127.77 (C2″ + C6″), 125.88 (C5′), 121.82 (C3′), 109.86 (C29), 79.18 (C3), 55.48 (C5), 52.15 (O−$CH_3$), 51.49 (C17), 51.38 (C18), 50.59 (C9), 48.81 (C16), 46.86 (C19), 43.39 (C14), 41.45 (C8), 39.03 (C4), 38.92 (C1), 37.37 (C10), 37.11 (C13), 36.35 (C28), 35.06 (C22), 34.51 (C7), 32.12 (C15), 30.04 (C21), 28.14 (C23), 27.53 (C2), 25.65 (C12), 21.04 (C11), 20.20 (C30), 18.43 (C6), 16.43 (C26), 16.36 (C25), 15.60 (C27), 15.54 (C24).

*(22S)-22-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6g**) *and (16R)-16-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7g**). According to GP II, compounds **6g** and **7g** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 1-(4-iodophenyl)ethan-1-one (180 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 35 mg, 29%. HRMS (ESI): $m/z$ calc. for $[C_{44}H_{60}N_2O_3 + H]^+$ 665.4677; found 665.4658.

*(22S)-22-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6g**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 7.96 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.86 (d, $^3J$ = 8.2 Hz, 2H, H−C(3″), H−C(5″)), 7.69 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.42 (d, $^3J$ = 8.2 Hz, 2H, H−C(2″), H−C(6″)), 7.23 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 6.90 (dd, $^3J$ = 8.5, 4.7 Hz, 1H, H−N), 4.82 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.68 (s, 1H, $H_b$-C (29)), 4.03 (dd, $^2J$ = 14.3 Hz, $^3J$ = 8.5 Hz, 1H, $H_a$-C (28)), 3.21 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3)), 3.12 (dd, $^2J$ = 14.3 Hz, $^3J$ = 4.7 Hz, 1H, $H_b$-C (28)), 2.97 (dd, $^3J$ = 9.9, 9.5 Hz, 1H, H−C (22)), 2.85−2.62 (m, 2H, $H_a$-C((21), H−C (19)), 2.50 (s, 3H, $H_3$C−C═O), 2.00 (td, $^3J$ = 11.8, 3.6 Hz, 1H, H−C (13)), 1.94 (dd, $^3J$ = 11.8, 10.9 Hz, 1H, H−C (18)), 1.88 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 13.1, 3.6 Hz, 1H, $H_a$-C (16)), 1.77 (s, 3H, H−C (30)), 1.77−1.65 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (1), $H_b$-C (21)), 1.65−1.44 (m, 6H, $H_a$-C (6), $H_a$-C (11), $H_a$-C (15), $H_2$−C (2), $H_b$-C (16)), 1.44−1.25 (m, 4H, $H_b$-C (7), $H_b$-C (6), $H_b$-C (11), H−C (9)), 1.13 (s, 3H, $H_3$−C (26)), 1.13−1.08 (m, 1H, $H_b$-C (12)), 1.07−1.02 (m, 4H, $H_3$−C (27), $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.95−0.88 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.73−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 197.99 (C═O), 164.13 (N−C═O), 149.60 (C20), 149.32 (C2′), 147.55 (C6′), 146.23 (C1″), 137.15 (C4′), 135.76 (C4″), 128.99 (C3″ + C5″), 128.02 (C2″ + C6″), 126.02 (C5′), 121.88 (C3′), 110.73 (C29), 79.30 (C3), 55.51 (C5), 54.83 (C22), 50.85 (C17), 50.84 (C18), 50.64 (C9), 46.16 (C19), 42.69 (C14), 41.00 (C8), 39.00 (C4), 38.88 (C1), 37.71 (C13), 37.33 (C10), 36.05 (C28), 34.13 (C7), 33.88 (C21), 30.27 (C16), 28.11 (C23), 27.50 (C2), 27.37 (C15), 26.66 ($CH_3$−C═O)), 25.20 (C2), 20.98 (C11), 19.38 (C30), 18.36 (C6), 16.21 (C25), 16.03 (C26), 15.49 (C24), 15.17 (C27).

*(16R)-16-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7g**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (dd, 1H, $^3J$ = 4.9 Hz, $^4J$ = 1.6 Hz, H−C(6′)), 7.97 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.86 (d, $^3J$ = 8.0 Hz, 2H, H−C(3″), H−C(5″)), 7.70 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.6 Hz, 1H, H−C(4′)), 7.41 (d, $^3J$ = 8.0 Hz, 2H, H−C(2″), H−C(6″)), 7.24 (dd, $^3J$ = 7.7, 4.9 Hz, 1H, H−C(5′))), 7.00 (dd, $^3J$ = 8.5, 3.6 Hz, 1H, H−N), 4.76 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 3.61 (dd, $^2J$ = 14.5 Hz, $^3J$ = 8.5 Hz, 1H, $H_a$-C (28)), 3.50 (dd, $^2J$ = 14.5 Hz, $^3J$ = 3.5 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 2.98 (dd, $^3J$ = 13.1, 3.5 Hz, 1H, H−C (16)), 2.68 (td, $^3J$ = 11.0, 4.4 Hz, 1H H−C (19)), 2.49 (dd, $^2J$ = 13.5 Hz, $^3J$ = 13.1 Hz, 1H, $H_a$-C (15)), 2.53 (s, 3H, $H_3$C−C═O), 2.09−1.97 (m, 1H, $H_a$-C (21)), 1.93 (dd, $^3J$ = 11.9, 11.0 Hz, 1H, H−C (18)), 1.82 (td, $^3J$ = 11.9, 3.6 Hz, 1H, H−C (13)), 1.76 (s, 3H, $H_3$−C (30)), 1.75−1.58 (m, 5H, $H_a$-C (12), $H_2$−C (2), $H_a$-C (22), $H_a$-C (1)), 1.58−1.42 (m, 6H, $H_2$−C (6), $H_a$-C (21), $H_b$-C (22), $H_2$−C (7)), 1.42−1.23 (m, 4H, $H_b$-C (11), $H_b$-C (21), $H_b$-C (16), H−C (9)), 1.21 (s, 3H, $H_3$−C (26)), 1.14−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (23)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.75−0.68 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 198.00 (O═C−$CH_3$), 164.12 (N−C═O), 150.13 (C20), 149.68 (C2′), 149.49 (C1″), 147.61 (C6′), 137.14 (C4′), 135.60 (C4″), 128.80 (C3″ + C5″), 127.97 (C2″ + C6″), 125.98 (C5′), 121.85 (C3′), 109.89 (C29), 79.16 (C3), 55.48 (C5), 51.47 (C17), 51.40 (C18), 50.60 (C9), 48.83 (C16), 46.86 (C19), 43.38 (C14), 41.45 (C8), 39.03 (C4), 38.92 (C1), 37.38 (C10), 37.10 (C13), 36.34 (C28), 35.06 (C22), 34.51 (C7), 32.17 (C15), 30.04 (C21), 28.14 (C23), 27.54 (C2), 26.70 ($CH_3$−C═O), 25.65 (C12), 21.04 (C11), 20.20 (C30), 18.43 (C6), 16.44 (C26), 16.36 (C25), 15.61 (C27), 15.54 (C24).

*(22S)-22-(4-Cyanophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6h**) *and (16R)-16-(4-Cyanophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**7h**). According to GP II, compounds **6h** and **7h** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 4-iodobenzonitrile (167 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 37 mg, 31%. HRMS (ESI): $m/z$ calc. for $[C_{43}H_{57}N_3O_2 + H]^+$ 648.4524; found 648,4512.

*(22S)-22-(4-Cyanophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**6h**). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.29 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 7.99 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.74 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.55 (d, $^3J$ = 7.8 Hz, 2H, H−C(3″), H−C(5″)), 7.42 (d, $^3J$ = 7.8 Hz, 2H, H−C(2″), H−C(6″)), 7.34 (dd, $^3J$ = 7.7, 4.8 Hz, 1H, H−C(5′)), 6.82−6.73 (dd, $^3J$ = 8.4, 3.8 Hz, 1H, H−N), 4.82 (s, 1H, $H_a$-C (29)), 4.69 (s, 1H, $H_b$-C (29)), 4.02 (dd, $^2J$ = 14.4 Hz, $^3J$ = 8.4 Hz, 1H, $H_a$-C (28)), 3.19 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3)), 3.10 (dd, $^2J$ = 14.4, $^3J$ = 3.8 Hz, 1H, $H_b$-C (28)), 2.95 (dd, $^3J$ = 10.1, 8.3 Hz, 1H, H−C (22)), 2.76−2.62 (m, 2H, H−C (19), $H_a$-C (21)), 1.99 (td, $^3J$ = 12.0, 3.5 Hz, 1H, H−C (13)), 1.93 (dd, $^3J$ = 12.0, 10.9 Hz, 1H, H−C (18)), 1.81−1.77 (m, 1H, $H_a$-C (15)), 1.77 (s, 3H, $H_3$−C (30)), 1.76−1.65 (m, 3H, $H_a$-C (12), $H_b$-C(C21), $H_a$-C (1)), 1.65−1.44 (m, 5H, $H_a$-C (6), $H_a$-C (11), $H_2$−C (2), $H_b$-C (16)), 1.44−1.35 (m, 4H, $H_b$-C (6), $H_2$−C (7)), 1.34−1.24 (m, 2H, $H_b$-C (11), H−C (9)), 1.14 (s, 3H, $H_3$−C (26)), 1.14−1.10 (m, 1H, $H_b$-C


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(12)), 1.10−1.04 (m, 1H, $H_b$-C (15)), 1.04 (s, 3H, $H_3$−C (27)), 0.96 (s, 3H, $H_3$−C (23)), 0.95−0.89 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.68 (d, $^3J$ = 9.9 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.86 (N−C═O), 149.44 (C20), 149.40 (C2′), 147.75 (C6′), 146.26 (C1″), 137.25 (C4′), 132.56 (C3″ + C5″), 128.58 (C2″ + C6″), 126.24 (C5′), 121.85 (C3′), 119.16 (C4″), 110.85 (C29), 110.31 (CN), 79.15 (C3), 55.52 (C5), 54.90 (C22), 51.05 (C9), 50.87 (C18), 50.63 (C17), 46.03 (C19), 42.67 (C14), 41.02 (C8), 39.02 (C4), 38.89 (C1), 37.67 (C13), 37.33 (10), 35.78 (C28), 34.13 (C7), 33.72 (C21), 30.25 (C16), 28.12 (C23), 27.56 (C2), 27.36 (C15), 25.21 (C12), 20.96 (C11), 19.41 (C30), 18.36 (C6), 16.22 (C26), 16.06 (C25), 15.49 (C24), 15.17 (C27).

*(16R)-16-(4-Cyanophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7h**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.30 (d, 1H, $^3J$ = 4.7 Hz, H−C(6′)), 7.99 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.75 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.53 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.41 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.34 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 6.90 (dd, $^3J$ = 8.2, 4.1 Hz, 1H, H−N), 4.75 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 3.57 (dd, $^2J$ = 14.6 Hz, $^3J$ = 8.2 Hz, 1H, $H_a$-C (28)), 3.50 (dd, $^2J$ = 14.6 Hz, $^3J$ = 4.1 Hz, 1H, $H_b$-C (28)), 3.19 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.96 (dd, $^3J$ = 13.1, 3.4 Hz, 1H, H−C (16)), 2.67 (td, $^3J$ = 11.0, 4.4 Hz, 1H, H−C (19)), 2.46 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.1 Hz, 1H, $H_a$-C (15)), 2.06 (dddd, $^2J$ = 13.2 Hz, $^3J$ = 11.5, 11.0, 6.3 Hz, 1H, $H_a$-C (21)), 1.91 (dd, $^3J$ = 11.9, 11.0 Hz, 1H, H−C (18)), 1.82 (td, $^3J$ = 11.9, 3.7 Hz, 1H, H−C (13)), 1.76 (s, 3H, H−C (30)), 1.76−1.59 (m, 5H, $H_a$-C (12), $H_a$-C (22), $H_a$-C (1), $H_2$−C (2)), 1.58−1.43 (m, 6H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (22), $H_2$−C (7)), 1.43- 1.23 (m, 4H, $H_b$-C (11), $H_b$-C (21), $H_b$-C (15), H−C (9)), 1.21 (s, 3H, $H_3$−C (26)), 1.16−1.09 (m, 4H, $H_b$-C (12), $H_3$−C (27)), 0.98 (s, 3H,$H_3$−C (23)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.74−0.69 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.97 (N−C═O), 149.96 (C20), 149.61 (C1″), 149.40 (C2′), 147.84 (C6′), 137.27 (C4′), 132.37 (C3″ + C5″), 128.54 (C2″ + C6″), 126.27 (C5′), 121.85 (C3′), 119.21 (C4″), 110.15 (C29), 109.98 (CN), 79.09 (C3), 55.48 (C5), 51.53 (C17), 51.39 (C18), 50.57 (C9), 48.87 (C16), 46.81 (C19), 43.38 (C14), 41.44 (C8), 39.03 (C4), 38.92 (C1), 37.37 (C10), 37.07 (C13), 36.12 (C28), 35.04 (C22), 34.52 (C7), 32.00 (C15), 29.98 (C21), 28.14 (C23), 27.54 (C2), 25.61 (C12), 21.02 (C11), 20.20 (C30), 18.41 (C6), 16.45 (C25), 16.36 (C26), 15.61 (C24), 15.53 (C27).

*(22S)-22-(4-Chlorophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6i**) and (16R)-16-(4-Chlorophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7i**).* According to GP II, compounds **6i** and **7i** were prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 1-chloro-4-iodobenzene (174 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 65 mg, 54%. HRMS (ESI): *m*/*z* calc. for $[C_{42}H_{57}ClN_2O_2 + H]^+$ 657.4181; found 657.4170.

*(22S)-22-(4-Chlorophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6i**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.32 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 7.97 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.69 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.31−7.16 (m, 5H, H−C(5′), H−C(2″), H−C(3″), H−C(5″), H−C(6″)), 6.89 (dd, $^3J$ = 9.5, 2.8 Hz, 1H, H−N), 4.78 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 4.10 (dd, $^2J$ = 14.2 Hz, $^3J$ = 9.5 Hz, 1H, $H_a$-C (28)), 3.16 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3)), 2.96 (dd, $^2J$ = 14.2 Hz, $^3J$ = 2.8 Hz, 1H, $H_b$-C (28)), 2.86 (dd, $^3J$ = 9.6, 9.1 Hz, 1H, H−C (22)), 2.68−2.54 (m, 2H, $H_a$-C((21), H−C (19)), 1.97 (td, $^3J$ = 11.9, 3.5 Hz, 1H, H−C (13)), 1.88 (dd, $^3J$ = 11.9, 10.9 Hz, 1H, H−C (18)), 1.80 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 13.1, 3.6 Hz, 1H, $H_a$-C (16)), 1.74 (s, 3H, H−C (30)), 1.74−1.62 (m, 4H, $H_a$-C (12), $H_a$-C (15), $H_a$-C (1), $H_b$-C (21)), 1.62−1.51 (m, 2H, $H_2$−C (2)), 1.51−1.31 (m, 6H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (16), $H_2$−C (7)), 1.31−1.22 (m, 2H, $H_b$-C (11), H−C (9)), 1.13 (s, 3H, $H_3$−C (26)), 1.12−1.05 (m, 1H, $H_b$.C (12)), 1.01−0.96 (m, 4H, $H_3$−C (27), $H_b$-C (15)), 0.93 (s, 3H,$H_3$−C (23)), 0.93−0.88 (m, 1H, $H_b$-C (1)), 0.81 (s, 3H, $H_3$−C (25)), 0.74 (s, 3H, $H_3$−C (24)), 0.70−0.63 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.06 (N−C═O), 149.77 (C20), 149.61 (C2′), 148.05 (C6′), 138.71 (C1″), 137.06 (C4′), 132.73 (C4″), 129.12 (C2″ + C6″), 129.09 (C3″ + C5″), 125.87 (C5′), 121.76 (C3′), 110.59 (C29), 79.20 (C3), 55.52 (C5), 54.17 (C22), 50.65 (C9), 50.61 (C18), 50.45 (C17), 46.12 (C19), 42.69 (C14), 41.01 (C8), 39.01 (C4), 38.89 (C1), 37.65 (C13), 37.33 (10), 35.84 (C28), 34.09 (C7), 34.03 (C21), 30.17 (C16), 28.12 (C23), 27.56 (C2), 27.37 (C15), 25.21 (C12), 20.97 (C11), 19.36 (C30), 18.36 (C6), 16.21 (C26), 16.04 (C25), 15.49 (C24), 15.14 (C27).

*(16R)-16-(4-Chlorophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7i**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.36 (m, d, $^3J$ = 4.5 Hz, 1H, H−C(6′)), 8.00 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′), 7.72 (td, $^3J$ = 7.8, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.31 (dd, $^3J$ = 7.8, 4.5 Hz, 1H, H−C(5′)), 7.29−7.21 (m, 4H, H−C(2″), H−C(3″), H−C(5″), H−C(6″)), 7.05 (d, *J* = 9.3 Hz, 1H, H−N), 4.75 (d, $^3J$ = 2.4 Hz, 1H, $H_a$-C (29)), 4.63 (s, 1H, $H_b$-C (29)), 3.67 (dd, $^2J$ = 14.3, $^3J$ = 9.3 Hz, 1H, $H_a$-C (28)), 3.38 (d, $^2J$ = 14.3 Hz, 1H, $H_b$-C (28)), 3.21 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 2.90 (dd, $^3J$ = 13.0, 3.5 Hz, 1H, H−C (16)), 2.68 (td, $^3J$ = 11.4, 4.4 Hz, 1H, H−C (19)), 2.41 (dd, $^2J$ = 13.4 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 2.05−1.96 (m, 1H, $H_a$-C (21)), 1.90 (dd, $^2J$ = 12.0 Hz, $^3J$ = 11.4 Hz, 1H, H−C (18)), 1.79 (td, $^3J$ = 12.0, 3.5 Hz, 1H, H−C (13)), 1.75 (s, 3H, H−C (30)), 1.74−1.67 (m, 5H, $H_a$-C (12), $H_a$-C (22), $H_a$-C (1), $H_2$−C (2)), 1.66−1.23 (m, 10H, $H_2$−C (6), $H_2$−C (11), $H_b$-C (21), $H_b$-C (15), $H_2$−C (7), $H_b$-C (22), H−C (9)), 1.18 (s, 3H, $H_3$−C (26)), 1.13−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (23)), 0.96−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.73−0.68 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.01 (N−C═O), 149.94 (C20), 149.16 (C2′), 147.88 (C6′), 141.99 (C1″), 136.90 (C4′), 132.29 (C4″), 128.81 (C2″ + C6″), 128.64 (C3″ + C5″), 125.75 (C5′), 121.53 (C3′), 109.55 (C29), 78.94 (C3), 55.52 (C5), 51.03 (C17), 50.97 (C18), 50.34 (C9), 47.78 (C16), 46.59 (C19), 43.13 (C14), 41.17 (C8), 38.87 (C4), 38.66 (C1), 37.11 (C13), 36.82 (C10), 36.08(C28), 34.79 (C22), 34.26 (C7), 32.01 (C15), 29.77 (C21), 27.89 (C23), 27.26 (C2), 25.40 (C12), 20.78 (C11), 19.97 (C30), 18.17 (C6), 16.15 (C26), 16.10 (C25), 15.34 (C24), 15.28 (C27).

*(22S)-22-(Thiophen-2-yl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6j**) and (16R)-16-(2-Thiophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7j**).* According to GP II, a mixture of compounds **6j**, **7j**, **7j′**, and **8** was prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 2-iodothiophene (80 μL, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1


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equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Total yield of isomers **6j** and **7j** (3:1) 23 mg, 20% along with **7j′** (5%) and **8** (27%). HRMS (ESI) of **6j**: *m*/*z* calc. for $[C_{40}H_{56}N_2O_2S + H]^+$ 629.4135; found 629.4114.

*(22S)-22-(2-Thiophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6j**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.30 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)),8.04 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.72 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.29 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 7.19 (d, $^3J$ = 9.7 Hz, 1H, H−N), 7.17 (d, $^3J$ = 4.9 Hz, 1H, H−C(5″)), 7.01 (dd, $^3J$ = 4.9, 3.6 Hz, 1H, H−C(4″)), 6.97 (d, $^3J$ = 3.6 Hz, 1H, H−C(3″)), 4.79 (s, 1H, $H_a$-C (29)), 4.66 (s, 1H, $H_b$-C (29)), 4.17 (dd, $^2J$ = 14.2 Hz, $^3J$ = 9.7 Hz, 1H, $H_a$-C (28)), 3.19 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 3.10 (dd, $^3J$ = 10.1, 9.3 Hz, 1H, H−C (22)), 3.00 (d, $^2J$ = 14.2 Hz, 1H, $H_b$-C (28)), 2.63 (ddd, $^3J$ = 11.1, 10.8, 4.6 Hz, 1H, H−C (19)), 2.58 (ddd, $^2J$ = 13.4 Hz, $^3J$ = 11.1, 10.1 Hz 1H, $H_a$-C (21)), 2.08−1.98 (m, 2H, H−C (13), $H_a$-C (16)), 1.92 (ddd, $^2J$ = 13.4 Hz, $^3J$ = 9.3, 4.6 Hz, 1H, $H_b$-C (21)), 1.85 (dd, $^3J$ = 11.6, 10.8 Hz, 1H, H−C (18)), 1.84−1.76 (m, 1H, $H_a$-C (15)), 1.75 (s, 3H, H−C (30)), 1.74−1.65 (m, 2H, $H_a$-C (12), $H_a$-C (1)), 1.64−1.53 (m, 2H, $H_2$−C (2)), 1.51−1.34 (m, 6H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (16), $H_2$−C (7)), 1.33−1.22 (m, 2H, $H_b$-C (11), H−C (9)), 1.18 (s, 3H, $H_3$−C (26)), 1.12−1.07 (m, 1H, $H_b$C (12)), 1.06−1.00 (m, 4H, $H_3$−C (27), $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.95−0.87 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.66 (m, 1H, H−C (5)).$^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.13 (N−C═O), 150.05 (C20), 149.67 (C2′), 147.64 (C6′), 144.36 (C2″), 137.04 (C4′), 127.35 (C4″), 125.70 (C5′), 123.90 (C3″), 123.76 (C5″), 121.90 (C3′), 110.68 (C29), 79.19 (C3), 55.53 (C5), 50.66 (C9), 50.32 (C18), 50.19 (C19), 50.03 (C17), 46.24 (C22), 42.75 (C14), 41.03 (C8), 39.02 (C4), 38.90 (C1), 37.73 (C13), 37.34 (C10), 36.86 (C21), 36.18 (C28), 34.11 (C7), 29.84 (C16), 28.13 (C23), 27.58 (C2), 27.45 (C15), 25.18 (C12), 20.97 (C11), 19.32 (C30), 18.38 (C6), 16.21 (C25), 16.08 (C26), 15.51 (C24), 15.07 (C27).

*(16R)-16-(2-Thiophenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7j**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.30 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)),8.02 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.74 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.33−7.27 (m, 2H, H−C(5′), H−N)), 7.16 (d, $^3J$ = 5.2 Hz, 1H, H−C(5″)), 6.98 (dd, $^3J$ = 5.2, 3.5 Hz, 1H, H−C(4″)), 6.94 (d, $^3J$ = 3.5 Hz, 1H, H−C(3″)), 4.75 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3.75 (dd, $^2J$ = 14.6 Hz, $^3J$ = 9.8 Hz, 1H, $H_a$-C (28)), 3.36 (dd, $^2J$ = 14.6 Hz, $^3J$ = 2.9 Hz, 1H, $H_b$-C (28)) 3.20 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 3.15 (dd, $^3J$ = 12.9, 3.7 Hz, 1H, H−C (16)), 2.72 (ddd, $^3J$ = 11.1, 10.7, 5.8 Hz, 1H, H−C (19)), 2.34 (dd, $^2J$ = 13.2 Hz, $^3J$ = 12.9 Hz, 1H, $H_a$-C (15)), 2.16−2.02 (m, 1H, $H_a$-C (21)), 1.99 (dd, $^2J$ = 10.8 Hz, $^3J$ = 7.8 Hz, 1H, H−C (22)), 1.88−1.78 (m, 2H, H−C (13), H−C (18)), 1.74 (s, 3H, $H_3$−C (30)), 1.72−1.60 (m, 4H, $H_a$-C (12), $H_2$−C (2), $H_a$-C (1)), 1.60−1.35 (m, 8H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (21), $H_2$−C (7), $H_b$-C (22), $H_b$-C (15)), 1.42−1.23 (m, 2H, $H_b$-C (11), H−C (9)), 1.16 (s, 3H, $H_3$−C (26)), 1.12−1.07 (m, 4H, $H_3$−C (27), $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (23)), 0.93−0.88 (m, 1H, $H_b$-C (1)), 0.87 (s, 3H, $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.76−0.68 (m, 1H, H−C (5)).$^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.32 (N−C═O), 150.19 (C20), 149.83 (C2′), 147.90 (C2″), 147.71 (C6′), 137.12 (C4′), 126.94 (C4″), 125.83 (C5′), 123.54 (C3″), 123.35 (C5″), 121.92 (C3′), 109.84 (C29), 79.16 (C3), 55.46 (C5), 51.30 (C17), 50.76 (C18), 50.53 (C9), 47.14 (C19), 44.85 (C16), 43.57 (C14), 41.34 (C8), 39.03 (C4), 38.90 (C1), 37.36 (C10), 36.91 (C13), 36.67 (C28), 35.02 (C22), 34.44 (C7), 34.38 (C15), 30.08 (C21), 28.15 (C23), 27.54 (C2), 25.52 (C12), 21.01 (C11), 20.06 (C30), 18.43 (C6), 16.37 (C26), 16.32 (C25), 15.66 (C27), 15.53 (C24).

*(16R)-16-([2,3′-Bisthiophen]-2′-yl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7j′**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.52 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)), 8.14 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.13 (t, $^3J$ = 5.6 Hz, 1H, H−N), 7.82 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.39 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 7.30 (d, $^3J$ = 5.1 Hz, 1H, C(5‴)), 7.16 (d, $^3J$ = 5.2 Hz, 1H, H−C(5″)), 7.06 (d, $^3J$ = 3.5 Hz, 1H, H−C(3‴)), 7.00 (dd, $^3J$ = 5.1, 3.5 Hz, 1H, H−C(4‴)), 6.91 (d, $^3J$ = 5.2 Hz, 1H, H−C(4″)), 4.73 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.59 (s, 1H, $H_b$-C (29)), 3.80 (dd, $^2J$ = 13.6 Hz, $^3J$ = 5.6 Hz, 1H, $H_a$-C (28)), 3.63 (dd, $^2J$ = 13.6 Hz, $^3J$ = 5.6 Hz, 1H, $H_b$-C (28)) 3.18 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 3.05−2.94 (m, 1H, H−C (16)), 2.17−1.93 (m, 2H, H−C (19), $H_a$-C (22)), 1.76 (dd, $^3J$ = 10.1, 7.8 Hz, 1H, H−C (18)), 1.68−1.56 (m, 5H, $H_a$-C (1), $H_a$-C (15), $H_2$−C (2), $H_a$-C (12)), 1.55 (s, 3H, $H_3$−C (30)), 1.53−1.47 (m, 2H, $H_b$-C (22), $H_a$-C (6)), 1.46−1.32 (m, 6H, $H_b$-C (6), $H_a$-C (11), $H_2$−C (21), $H_a$-C (7), H−C (13)), 1.31−1.22 (m, 2H, $H_b$-C (7), H−C (9)), 1.17 (dd, $^2J$ = 11.2 Hz, $^3J$ = 5.9 Hz, 1H, $H_b$-C (15)), 1.14−1.02 (m, 2H, $H_b$-C (11), $H_b$-C (12)), 0.97 (s, 3H, $H_3$−C (26), 0.94 (s, 3H, $H_3$−C (23)), 0.94−0.91 (m, 1H, $H_b$-C (1)), 0.83 (s, 3H, $H_3$−C (25)), 0.76 (s, 6H, $H_3$−C (27), $H_3$−C (24)), 0.72−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.45 (N−C═O), 149.91 (C2′), 149.39 (C20), 148.95 (C2″), 148.33 (C6′), 139.22 (C2‴), 137.39 (C4′), 133.92 (C4″), 130.63 (C3″), 127.71 (C3‴), 126.91 (C4‴), 126.17 (C5′), 125.78 (C5″), 122.28 (C3′), 121.23 (C5″), 110.70 (C29), 79.21 (C3), 56.11 (C5), 53.59 (C13), 53.57 (C19), 51.61 (C9), 49.08 (C28), 47.79 (C14), 45.16 (C17), 44.62 (C16), 40.63 (C8), 39.24 (C4) 39.13 (C1), 38.09 (C18), 37.38 (C10), 35.22 (C7), 35.02 (C15), 31.91 (C22), 28.09 (C23), 27.53 (C2), 27.26 (C12), 27.19 (C21), 22.15 (C11), 19.49 (C27), 18.87 (C30), 18.42 (C6), 16.49 (C25), 15.91 (C26), 15.40 (C24).

*(22S)-22-(1H-5-Indolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6m**) and (16R)-16-(1H-5-Indolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7m**).* According to GP II, a mixture of compounds **6m** and **7m** was prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 5-iodo-1H-indole (173 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Total yield of isomers **6m** and **7m** (5:1) 28 mg, 24%. HRMS (ESI): *m*/*z* calc. for $[C_{44}H_{59}N_3O_2 + H]^+$ 662.4680; found 662.4683.

*(22S)-22-(1H-5-Indolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6m**).* 1H NMR (500 MHz, CDCl3) $\delta$ 8.17 (bs, 1H, H−N(1″)), 7.89 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.65 (s, 1H, H−C(4″), 7.58 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.44 (dd, $^3J$ = 4.7 Hz, $^4J$ = 1.5 Hz, 1H, H−C(6′)), 7.33 (d, $^3J$ = 8.4 Hz, 1H, H−C(6″), 7.22 (t, $^3J$ = 2.8 Hz, 1H, H−C(2″), 7.18 (d, $^3J$ = 8.4 Hz, 1H, H−C(7″)), 7.07 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 6.92 (d, $^3J$ = 9.7 Hz, 1H, H−N−C═O), 6.54 (dd, $^3J$ = 2.8 Hz, $^4J$ = 2.6 Hz, 1H, H−C(3″)), 4.82 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.67 (s, 1H, $H_b$-C (29)), 4.18 (dd, $^2J$ = 14.0, $^3J$ = 9.7 Hz, 1H, $H_a$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)) 3.06 (dd, $^3J$ = 11.2, 10.1 Hz, 1H, H−C (22)),


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3.02 (d, $^2J$ = 14.0 Hz, 1H, $H_b$-C (28)) 2.80 (dt, $^2J$ = 14.0, $^3J$ = 11.2 Hz, 1H, $H_a$-C (21)), 2.66 (td, $^3J$ = 11.2, 5.0 Hz, 1H, H−C (19)), 2.20−1.85 (m, 3H, H−C (13), H−C (18), $H_a$-C (16)), 1.79 (s, 3H, $H_3$−C (30)), 1.78−1.66 (m, 4H, $H_a$-C (12), $H_b$-C (21), $H_a$-C (1), $H_a$-C (15)), 1.66−1.21 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16), H−C (9), $H_2$−C (7), 1.17 (s, 3H, $H_3$−C (26)), 1.16−1.06 (m, 1H, $H_b$-C (12)), 1.05 (s, 3H, $H_3$−C (27)), 1.02−0.98 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H, $H_3$−C (23)) 0.94−0.88 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.73−0.66 (m, 1H, H−C (5)). 13C NMR (126 MHz, CDCl3) $\delta$ 164.07 (C═O), 150.36 (C20), 149.72 (C2′), 147.30 (C6′), 136.73 (C4′), 135.57 (C7a″), 131.25 (C5″), 129.00 (C3a″), 125.31 (C5′), 124.28 (C2″), 122.55 (C7″), 121.54 (C3′), 119.21 (C4″), 111.42 (C6″), 110.24 (C29), 103.10 (C3″), 79.25 (C3), 55.54 (C5), 54.83 (C22), 50.69 (C9), 50.47 (C18), 50.29 (C17), 46.30 (C19), 42.78 (C14), 41.02 (C8), 39.02 (C4), 38.89 (C1), 37.70 (C13), 37.34 (C10), 36.10 (C28), 34.50 (C7), 34.08 (C21), 30.36 (C16), 28.13 (C23), 27.58 (C2), 27.45 (C15), 25.26 (C12), 21.00 (C11), 19.38 (C30), 18.37 (C6), 16.21 (C25), 16.05 (C26), 15.50 (C24), 15.16 (C27).

*(16R)-16-(1H-5-Indolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7m**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.13 (bs, 1H, H−N(1″)), 7.89 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.63 (s, 1H, H−C(4″)), 7.60 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.49 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 7.32 (d, $^3J$ = 8.4 Hz, 1H, H−C(6″)), 7.23 (t, $^3J$ = 2.8 Hz, 1H, H−C(2″)), 7.16 (d, $^3J$ = 8.4 Hz, 1H, H−C(7″)), 7.08 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 7.05 (d, $^3J$ = 10.1 Hz, 1H, H−N−C═O), 6.54 (dd, $^3J$ = 2.8 Hz, $^4J$ = 2.6 Hz, 1H, H−C(3″)), 4.75 (s, 1H, $H_a$-C (29)), 4.62 (s, 1H, $H_b$-C (29)), 3.76 (dd, $^2J$ = 14.2 Hz, $^3J$ = 10.1 Hz, 1H, $H_a$-C (28)), 3.39 (d, $^2J$ = 14.2 Hz, 1H, $H_b$-C (28)), 3.20 (dd, $^3J$ = 11.2, 4.9 Hz, 1H, H−C (3)), 3.04 (dd, $^3J$ = 13.2, 3.1 Hz, 1H, H−C (16)), 2.71 (dt, $^3J$ = 11.2, 5.6 Hz, 1H, H−C (19)), 2.56 (dd, $^2J$ = 13.4 Hz, $^3J$ = 13.2 Hz, 1H, $H_a$-C (15)), 2.12−1.98 (m, 1H, $H_a$-C (21)), 1.94 (dd, $^3J$ = 11.8, 11.2 Hz, 1H, H−C (18)), 1.83 (td,$^3$ $J$ = 11.8, 3.2 Hz, 1H, H−C (13)), 1.76 (s, 3H, H−C (30)), 1.76−1.41 (m, 12H, $H_2$−C (6), $H_a$-C (11), $H_a$-C (12), $H_2$−C (2), $H_b$-C (15), $H_2$−C (7), $H_2$−C (22), $H_a$-C (1)), 1.38−1.24 (m, 3H, $H_b$-C (11), $H_b$-C (21), H−C (9)), 1.22 (s, 3H, $H_3$−C (26)), 1.13 (s, 3H, $H_3$−C (27)), 1.13−1.09 (m, 1H, $H_a$-C (12)) 0.98 (s, 3H, $H_3$−C (23)), 0.97−0.89 (m, 1H, $H_b$-C (1)), 0.89 (s, 3H, $H_3$−C (25)), 0.79 (s, 3H, $H_3$−C (24)), 0.75−0.69 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.12 (C═O), 150.66 (C20), 149.80 (C2′), 147.37 (C6′), 136.77 (C4′), 135.33 (C7a″), 131.07 (C5″), 128.86, (C3a″) 125.35 (C5′), 124.24 (C2″), 122.96 (C7″), 121.54 (C3′), 118.76 (C4″), 111.09 (C6″), 109.52 (C29), 103.20 (C3″), 79.17 (C3), 55.49 (C5), 51.61 (C17), 51.22 (C18), 50.67 (C9), 48.52 (C16), 46.99 (C19), 43.49 (C14), 41.50 (C8), 39.04 (C4), 38.94 (C1), 37.39 (C10), 37.17 (C13), 36.53 (C28), 35.29 (C22), 34.51 (C7), 32.83 (C15), 30.20 (C21), 28.16 (C23), 27.58 (C2), 25.77 (C12), 21.13 (C11), 20.28 (C30), 18.47 (C6), 16.44 (C25), 16.39 (C26), 15.65 (C27), 15.55 (C24).

*(22S)-22-(9H-3-Carbazolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6o**) and (16R)-16-(9H-3-Carbazolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7o**).* According to GP II, a mixture of compounds **6o** and **7o** was prepared from picolinic amide **3a** (100 mg, 0.183 mmol, 1 equiv), 3-iodo-9H-carbazole (214 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Total yield of isomers **6o** and **7o** (5:1) 44 mg, 34%. HRMS (ESI): $m/z$ calc. for $[C_{48}H_{61}N_3O_2 + H]^+$ 712.4837; found 712.4835.

*(22S)-22-(9H-3-Carbazolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**6o**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.16 (s, 1H, H−N (9)), 8.06−8.03 (m, 2H, H−C(4″), H−C(5″)), 7.80 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.45−7.40 (m, 3H, H−C(8″), H−C(4′), H−C(7″)), 7.38 (dd, $^3J$ = 8.6, $^4J$ = 1.9 Hz, 1H, H−C(2″), 7.34 (d, $J$ = 8.6 Hz, 1H, H−C(1″)), 7.23−7.17 (m, 2H, H−C(6′), H−C(6″), 6.92−6.86 (m, 2H, H−N−C═O, H−C(5′), 4.84 (d, $^4J$ = 2.4 Hz, 1H, $H_a$-C (29)), 4.69 (s, 1H, $H_b$-C (29)), 4.12 (dd, $^2J$ = 14.1, $^3J$ = 9.4 Hz, 1H, $H_a$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 3.12 (dd, $^3J$ = 11.3, 8.6 Hz, 1H, H−C (22)), 3.10 (dd, $^2J$ = 14.1 Hz, $^3J$ = 2.7 Hz, 1H, $H_b$-C (28)), 2.85 (ddd, $^2J$ = 14.0, $^3J$ = 11.3, 11.1 Hz, 1H, $H_a$-C (21)), 2.68 (td, $^3J$ = 11.1, 5.1 Hz, 1H, H−C (19)), 2.07−1.91 (m, 3H, H−C (13), H−C (18), $H_a$-C (16)), 1.86 (ddd, $^2J$ = 14.0, $^3J$ = 8.6, 5.1 Hz, 1H, $H_b$-C (21)), 1.80 (s, 3H, H−C (30)), 1.78−1.66 (m, 3H, $H_a$-C (12), $H_a$-C (1), $H_a$-C (15)), 1.66−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16), H−C (9), $H_2$−C (7),), 1.15 (s, 3H, $H_3$−C (26)), 1.14−1.06 (m, 1H, $H_b$-C (12)), 1.07 (s, 3H, $H_3$−C (27)), 1.05−0.98 (m, 1H, $H_b$-C (15)), 0.97 (s, 3H, $H_3$−C (23)), 0.95−0.86 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.73−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.04 (C═O), 150.25 (C20), 149.60 (C2′), 147.12 (C6′), 139.96 (C9a″), 139.07 (C8a″), 136.48 (C4′), 130.97 (C3″), 126.00 (C2″), 125.87 (C7″), 125.21 (C5′), 124.30 (C4a″), 123.56 (C4b″), 121.39 (C3′), 120.62 (C5″), 119.46 (C6″), 118.87 (C4″), 110.95 (C1″), 110.54 (C8″), 110.33 (C29), 79.20 (C3), 55.53 (C5), 54.82 (C22), 50.68 (C9), 50.53 (C18), 50.22 (C17), 46.28 (C19), 42.76 (C14), 41.01 (C8), 39.01 (C4), 38.89 (C1), 37.70 (C13), 37.33 (C10), 36.10 (C28), 34.53 (C7), 34.09 (C21), 30.40 (C16), 28.13 (C23), 27.58 (C2), 27.45 (C15), 25.25 (C12), 21.00 (C11), 19.39 (C30), 18.37 (C6), 16.20 (C25), 16.07 (C26), 15.50 (C24), 15.17 (C27).

*(16R)-16-(9H-3-Carbazolyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**7o**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (d, $^3J$ = 7.8 Hz, 1H, H−C(5″), 8.01 (s, 1H, H−C(4″)), 7.81 (bs, 1H, H−C(3′)), 7.53−7.39 (m, 3H, H-(C4′), H−C(7″), H−C(8″), 7.39−7.31 (m, 2H, H−C(2″), H−C(1″)), 7.22−7.17 (m, 2H, H−C(6′), H−C(6″), 7.08 (bs, 1H, H−N), 6.94−6.88 (m, 1H, H−C(5′)), 4.77 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 3.70 (dd, $^2J$ = 14.3, $^3J$ = 9.2 Hz, 1H, $H_a$-C (28)), 3.53 (d, $^2J$ = 14.3 Hz, 1H, $H_b$-C (28)), 3.21 (dd, $^2J$ = 11.5, 4.9 Hz, 1H, H−C (3)), 3.12 (dd, $^3J$ = 13.3, 3.5 Hz, 1H, H−C (16)), 2.71 (td, $^3J$ = 11.0, 4.5 Hz, 1H, H−C (19)), 2.62 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.3 Hz, 1H, $H_a$-C (15)), 2.11−2.00 (m, 1H, $H_a$-C (21)), 1.97 (dd, $^3J$ = 11.7, 11.2 Hz, 1H, H−C (18)), 1.93−1.80 (m, 1H, H−C (13)), 1.78 (s, 3H, $H_3$−C (30)), 1.78−1.66 (m, 3H, $H_a$-C (12), $H_a$-C (22)), $H_a$-C (1)), 1.67−1.45 (m, 9H, $H_2$−C (6), $H_a$-C (11), $H_2$−C (2), $H_b$-C (15), $H_2$−C (7), $H_b$-C (22)), 1.42−1.28 (m, 3H, $H_b$-C (11), $H_b$-C (21), H−C (9)), 1.26 (s, $H_3$−C (26)), 1.16 (s, 3H, $H_3$−C (27)), 1.16−1.09 (m, 1H, $H_b$-C (12)), 0.98 (s, 3H, $H_3$−C (23)), 0.98−0.93 (m, 1H, $H_b$-C (1)), 0.90 (s, 3H, $H_3$−C (25)), 0.80 (s, 3H, $H_3$−C (24)), 0.77−0.70 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.10 (C═O), 150.38 (C20), 149.23 (C2′), 147.02 (C6′), 139.78 (C9a″), 138.65 (C8a″), 136.55 (C4′), 134.85 (C3″), 126.23 (C2″), 125.76 (C7″), 125.25 (C5′), 124.01 (C4a″), 123.51 (C4b″), 121.39 (C3′), 120.58 (C5″), 119.35 (C6″), 118.40 (C4″), 110.51


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ACS Omega XXXX, XXX, XXX−XXX

(C1″), 110.37 (C8″), 109.52 (C29), 79.08 (C3), 55.36 (C5), 51.42 (C17), 51.17 (C18), 50.54 (C9), 48.55 (C16), 46.88 (C19), 43.45 (C14), 41.37 (C8), 38.91 (C4), 38.80 (C1), 37.26 (C10), 37.06 (C13), 36.55 (C28), 35.09 (C22), 34.39 (C7), 32.73 (C15), 30.00 (C21), 28.02 (C23), 27.42 (C2), 25.61 (C12), 20.97 (C11), 20.11 (C30), 18.33 (C6), 16.37 (C25), 16.26 (C26), 15.58 (C24), 15.42 (C27).

*(22S)-22-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lupane (**9a**) and (16R)-16-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lupane (**10a**).* According to GP II, compounds **9a** and **10a** were prepared from picolinic amide **3b** (30 mg, 0.055 mmol, 1 equiv), 1-iodo-4-methoxybenzene (51 mg, 0.218 mmol, 4 equiv), $Pd(OAc)_2$ (1 mg, 0.003 mmol, 0.05 equiv), $CuBr_2$ (2 mg, 0.005 mmol, 0.1 equiv), and CsOAc (42 mg, 0.218 mmol, 4 equiv) in *t*-AmOH (1 mL). Yield 28 mg, 78%. HRMS (ESI): *m*/*z* calc. for $[C_{43}H_{62}N_2O_3 + H]^+$ 655.4833; found 655.4839.

*(22S)-22-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lupane (**9a**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.18 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)), 8.00 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.69 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.29−7.21 (m, 3H, H−C(5′), H−C(2″), H−C(6″)), 6.97 (d, $^3J$ = 9.2 Hz, 1H, H−N), 6.86 (d, $^3J$ = 8.3 Hz, 2H, H−C(3″), H−C(5″)), 4.12 (dd, $^2J$ = 14.2, $^3J$ = 9.2 Hz, 1H, $H_a$-C (28)), 3.77 (s, 3H, $CH_3$−O) 3.20 (dd, $^3J$ = 11.3, 4.9 Hz, 1H, H−C (3)), 2.96 (dd, $^2J$ = 14.2, $^3J$ = 2.8 Hz, 1H, $H_b$-C (28)), 2.66 (dd, $^3J$ = 12.0, 8.1 Hz, 1H, H−C (22)), 2.30 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 13.2, 11.2 Hz, 1H, $H_a$-C (21)), 2.09−1.45 (m, 14H, $H_2$−C (6), $H_a$-C (11), H−C (20), H−C (19), H−C (13), $H_b$-C (21), $H_2$−C (2), $H_a$-C (12), $H_a$-C (15), $H_a$-C (16), $H_a$-C (1), H−C (18)), 1.47−1.19 (m, 6H, $H_b$-C (11), $H_2$−C (7), $H_b$-C (16), H−C (9), $H_b$-C (12)), 1.18 (s, 3H, $H_3$−C (26)), 1.01 (s, 3H, $H_3$−C (27)), 1.01−0.97 (m, 1H, $H_b$-C (15)), 0.96 (s, 3H, $H_3$−C (23)), 0.93 (d, $^3J$ = 6.8 Hz, 3H, $H_3$−C (30)), 0.91−0.87 (m, 1H, $H_b$-C (1)), 0.85 (s, 3H, $H_3$−C (25)), 0.84 (d, $^3J$ = 6.7 Hz, 3H, $H_3$−C (29)), 0.76 (s, 3H, $H_3$−C (24)), 0.71−0.67 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.98 (C═O), 158.81 (C4″), 149.99 (C2′), 147.57 (C6′), 136.91 (C4′), 132.57 (C1″), 128.68 (C2″ + C6″), 125.63 (C5′), 121.76 (C3′), 114.31 (C3″ + C5″), 79.19 (C3), 55.48 (C5), 55.27 (O−$CH_3$), 53.67 (C22), 50.32 (C9), 50.24 (C17), 49.89 (C18), 42.90 (C14), 42.75 (C19), 41.04 (C8), 39.01 (C4), 38.88 (C1), 37.29 (C10), 37.27 (C13), 36.05 (C28), 34.15 (C7), 30.45 (C16), 29.63 (C20), 28.12 (C23), 27.54 (C2), 27.30 (C15), 27.00 (C12), 26.53 (C21), 23.14 (C30), 20.99 (C11), 18.37 (C6), 16.15 (C25), 16.04 (C26), 15.52 (C24), 15.09 (C29), 15.00 (C27).

*(16R)-16-(4-Methoxyphenyl)-3β-hydroxy-28-picolinamido-lupane (**10a**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 (dd, 1H, $^3J$ = 4.9 Hz, $^4J$ = 1.7 Hz, H−C(6′)), 7.99 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.71 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.27 (dd, $^3J$ = 7.7, 4.9 Hz, 1H, H−C(5′)), 7.23 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.04 (dd, $^3J$ = 9.7, 2.2 Hz, 1H, H−N), 6.85 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 3.79 (s, 3H, $CH_3$−O), 3.64 (dd, $^2J$ = 14.3 Hz, $^3J$ = 9.7 Hz, 1H, $H_a$-C (28)), 3.34 (dd, $^2J$ = 14.3 Hz, $^3J$ = 2.2 Hz, 1H, $H_b$-C (28)), 3.21 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.66 (dd, $^3J$ = 13.0, 3.5 Hz, 1H, H−C (16)), 2.40 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 1.98 (ddd, $^3J$ = 10.6 Hz, 3.6, 2.6 Hz, 1H, H−C (19)), 1.88 (septd, $^3J$ = 6.8, 2.6 Hz, 1H, H−C (20)), 1.81 (td, $^3J$ = 12.1, 3.7 Hz, 1H, H−C (13)), 1.76−1.70 (m, 1H, $H_a$-C (1)), 1.70−1.39 (m, 12H, $H_2$−C (6), $H_a$-C (11), $H_2$−C (21), $H_2$−C (2), $H_a$-C (12), $H_2$−C (7), $H_a$-C (22), H−C (18)), 1.35−1.21 (m, 4H, $H_b$-C (11), $H_b$-C (12), $H_b$-C (15), H−C (9)), 1.19 (s, 3H, $H_3$−C (26)), 1.17−1.12 m, 1H, $H_b$-C (22)), 1.08 (s, 3H, $H_3$−C (27)), 0.98 (s, 3H, $H_3$−C (23)), 0.97−0.89 (m, 1H, $H_b$-C (1)), 0.89 (s, 3H, $H_3$−C (25)), 0.86 (d, $^3J$ = 6.8 Hz, 3H, H−C (30)), 0.83 (d, $^3J$ = 6.8 Hz, 3H, $H_3$−C (29)), 0.78 (s, 3H, $H_3$−C (25)), 0.72 (d, $^3J$ = 10.3 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.10 (C═O), 158.67 (C4″), 149.87 (C2′), 147.68 (C6′), 137.02 (C4′), 135.84 (C1″), 128.63 (C2″ + C6″), 125.75 (C5′), 121.78 (C3′), 114.12 (C3″ + C5″), 79.18 (C3), 55.44 (C5), 55.33 (O−$CH_3$), 51.20 (C17), 50.72 (C18), 50.39 (C9), 47.69 (C16), 44.02 (C19), 43.47 (C14), 41.50 (C8), 39.04 (C4), 38.92 (C1), 37.34 (C10), 36.67 (C28), 36.65 (C13), 35.39 (C22), 34.58 (C7), 32.36 (C15), 29.70 (C20), 28.16 (C23), 27.54 (C2), 27.15 (C12), 23.10 (C30), 21.91 (C21), 21.11 (C11), 18.45 (C6), 16.43 (C26), 16.33 (C25), 15.55 (C24), 15.52 (C27), 15.30 (C29).

*(22S)-22-(4-Methylcarbonylphenyl)-3β-hydroxy-28−28-picolinamido-lupane (**9g**) and (16R)-16-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lupane (**10g**).* According to GP II, compounds **9g** and **10g** were prepared from picolinic amide **3b** (100 mg, 0.183 mmol, 1 equiv), 1-(4-iodophenyl)ethan-1-one (179 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 31 mg, 26%. HRMS (ESI): *m*/*z* calc. for $[C_{44}H_{62}N_2O_3 + H]^+$ 667.4833; found 667.4815.

*(22S)-22-(4-Methylcarbonylphenyl)-3β-hydroxy-28−28-picolinamido-lupane (**9g**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)), 7.96 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.84 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.67 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.41 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.20 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 6.87 (dd, $^3J$ = 8.4, 3.7 Hz, 1H, H−N), 4.01 (dd, $^2J$ = 14.3 Hz, $^3J$ = 8.4 Hz, 1H, $H_a$-C (28)), 3.20 (dd, $^3J$ = 11.4, 4.7 Hz, 1H, H−C (3)), 3.11 (dd, $^2J$ = 14.3 Hz, $^3J$ = 3.7 Hz, 1H, $H_b$-C (28)), 2.74 (dd, $^3J$ = 11.8, 8.0 Hz, 1H, H−C (20)), 2.50 (s, 3H, $H_3$−C═O), 2.40 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 11.8, 11.4 Hz, 1H, $H_a$-C (21)), 2.02 (td, $^3J$ = 12.1, 3.9 Hz, 1H, H−C (13)), 1.99−1.93 (m, 2H, H−C (20), H−C (19)), 1.88 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.8, 3.5 Hz, 1H, $H_a$-C (16)), 1.85−1.75 (m, 2H, $H_b$-C (21), $H_a$-C (15)), 1.75−1.57 (m, 5H, $H_a$-C (12), $H_2$−C (2), $H_a$-C (1), H−C (18)), 1.56−1.44 (m, 3H, $H_a$-C (6), $H_a$-C (11), $H_b$-C (16)), 1.46−1.30 (m, 5H, $H_b$-C (11), $H_b$-C (6), $H_2$−C (7), H−C (9)), 1.30−1.22 (m, 1H, $H_b$-C (12)), 1.15 (s, 3H, $H_3$−C (26)), 1.06−1.00 (m, 4H, $H_3$−C (27), $H_b$-C (15)), 0.96 (s, 3H, $H_3$−C (23)), 0.94 (d, $^3J$ = 6.7 Hz, 3H, H−C (30)), 0.94−0.89 (m, 1H, $H_b$-C (1)), 0.86 (d, $^3J$ = 6.9 Hz, 3H, $H_3$−C (29)), 0.85 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (24)), 0.69 (d, $^3J$ = 9.3 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 197.94(O═C−$CH_3$), 163.88 (O═C-$NH_2$), 149.66 (C2′), 147.46 (C6′), 146.89 (C1″), 136.99 (C4′), 135.58 (C4″), 128.87 (C3″ + C5″), 128.00 (C2″ + C6″), 125.80 (C5′), 121.77 (C3′), 79.15 (C3), 55.47 (C5), 54.59 (C22), 51.04 (C17), 50.29 (C9 + C18), 42.87 (C14), 42.78 (C19), 41.05 (C8), 39.01 (C4), 38.87 (C1), 37.29 (C10), 37.28 (C13), 36.06 (C28), 34.19 (C7), 30.54 (C6), 29.58 (C20), 28.13 (C23), 27.54 (C2), 27.28 (C15), 26.98 (C12), 26.66 ($CH_3$−C═O), 26.29 (C21), 23.10 (C30), 20.98 (C11), 18.37 (C6), 16.16 (C25), 16.05 (C26), 15.52 (C24), 15.09 (C29), 15.03 (C27).

*(16R)-16-(4-Methylcarbonylphenyl)-3β-hydroxy-28-picolinamido-lupane (**10g**).* $^1$H NMR (500 MHz, $CDCl_3$ $^1$H NMR


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ACS Omega XXXX, XXX, XXX−XXX

(500 MHz, $CDCl_3$) $\delta$ 8.02 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′)), 7.97 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.84 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.70 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.39 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.24 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 7.01 (bs, 1H, H−N), 3.57 (m, 2H, $H_2$−C (28)), 3.22 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.92 (dd, $^3J$ = 13.0, 3.6 Hz, 1H, H−C (16)), 2.52 (s, 3H, $H_3$C−C═O), 2.47 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.0 Hz, 1H, $H_a$-C (15)), 1.97 (ddd, $^3J$ = 10.5 Hz, 3.5, 2.6 Hz, 1H, H−C (19)), 1.88 (septd, $^3J$ = 6.8, 2.6 Hz, 1H, H−C (20)), 1.85 (td, $^3J$ = 12.1, 3.7 Hz, 1H, H−C (13)), 1.76−1.70 (m, 1H, $H_a$-C (1)), 1.70−1.43 (m, 12H, $H_2$−C (6), $H_a$-C (11), $H_2$−C (21), $H_2$−C (2), $H_a$-C (12), $H_2$−C (7), $H_a$-C (22), H−C (18)), 1.39−1.31 (m, 3H, $H_b$-C (11), $H_b$-C (15), H−C (9)), 1.28−1.23 (m, 2H, $H_b$-C (12), $H_b$-C (12)), 1.23 (s, 3H, $H_3$−C (26)), 1.09 (s, 3H, $H_3$−C (27)), 0.98 (s, 3H, $H_3$−C (23)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.90 (s, 3H, $H_3$−C (25)), 0.87 (d, $^3J$ = 6.8 Hz, 3H, H−C (30)), 0.84 (d, $^3J$ = 6.8 Hz, 3H, $H_3$−C (29)), 0.79 (s, 3H, $H_3$−C (25)), 0.72 (d, $^3J$ = 10.3 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 198.06 (O═C−$CH_3$), 164.15 (O═C-$NH_2$), 149.74 (C2′), 149.42 (C1″), 147.62 (C6′), 137.17 (C4′), 135.54 (C4″), 128.75 (C3″ + C5″), 128.01 (C2″ + C6″), 126.00 (C5′), 121.85 (C3′), 79.21 (C3), 55.44 (C5), 51.34 (C17), 51.01 (C18), 50.36 (C9), 48.81 (C16), 43.97 (C19), 43.47 (C14), 41.50 (C8), 39.03 (C4), 38.92 (C1), 37.34 (C10), 36.67 (C13), 36.64 (C28), 35.30 (C22), 34.59 (C7), 32.02 (C15), 29.68 (C20), 28.14 (C23), 27.50 (C2), 27.08 (C12), 26.69 ($CH_3$−C═O), 23.06 (C30), 21.89 (C21), 21.06 (C11), 18.43 (C6), 16.45 (C26), 16.33 (C25), 15.55 (C24), 15.53 (C27), 15.28 (C29).

*(22S)-22-(4-Methoxyphenyl)-3β-28-picolinamido-olean-12(13)-ene (**14a**).* According to GP II, compound **14a** was prepared from picolinic amide **3c** (100 mg, 0.183 mmol, 1 equiv), 1-iodo-4-methoxybenzene (171 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 72 mg, 60% (brsm 91%). HRMS (ESI): *m*/*z* calc. for $[C_{43}H_{60}N_2O_3 + H]^+$ 653.4677; found 653.4678. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.32 (d, 1H, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 8.08 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.75 (t, $^3J$ = 7.7 Hz, 1H, H−C(4′)), 7.69−7.63 (m, 1H, H−N), 7.32 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 7.16 (d,$^3J$ = 8.2 Hz, 2H, H−C(2″), H−C(6″)), 6.79 (d, $^3J$ = 8.2 Hz, 2H, H−C(3″), H−C(5″)), 5.31 (d, $^3J$ = 3.6 Hz, 1H, H−C (12)), 3.73 (s, 3H, O−$CH_3$), 3.62 (dd, $^2J$ = 14.2 Hz, $^3J$ = 7.6 Hz, 1H, $H_a$-C (28)), 3.21 (dd, $^3J$ = 11.0, 4.8 Hz, 1H, H−C (3)), 3.11 (dd, $^2J$ = 14.2 Hz, $^3J$ = 3.7 Hz, 1H, $H_b$-C (28)), 2.86 (dd, $^3J$ = 13.7, 3.2 Hz, 1H, H−C (22)), 2.26 (dd, $^3J$ = 13.8, 4.0 Hz, 1H, H−C (18)), 1.91−1.78 (m, 3H, $H_a$-C (19), $H_a$-C (11), $H_a$-C (16)), 1.88 (dd, $^3J$ = 5.4, 5.0 Hz, 1H, $H_b$-C (11)), 1.82 (dd, $^3J$ = 13.7 Hz, $^2J$ = 13.5 Hz, 1H, $H_a$-C (21)), 1.67−1.46 (m, 7H, $H_a$-C (6), $H_a$-C (15), $H_2$−C (2), $H_a$-C (7), $H_a$-C (1), H−C (9)), 1.44−1.33 (m, 2H, $H_b$-C (6), $H_b$-C (16)), 1.33−1.24 (m, 3H, $H_b$-C (7), $H_b$-C (21), $H_b$-C (19)), 1.23 (s, 3H, $H_3$−C (27)), 1.04 (s, 3H, $H_3$−C (26)), 1.03 (s, 3H, $H_3$−C (29)), 1.02−0.99 (m, 1H, $H_b$-C (15)), 0.99−0.96 (m, 4H, $H_3$−C (23), $H_b$-C (1)), 0.96 (s, 3H, $H_3$−C (30)), 0.93 (s, 3H, $H_3$−C (25)), 0.77 (s, 3H, $H_3$−C (24)), 0.75−0.70 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.82 (C═O), 158.49 (C4″), 150.27 (C2′), 147.81 (C6′), 143.85 (C13), 137.07 (C4′), 135.18 (C1″), 130.35 (C2″ + C6″), 125.74 (C5′), 123.44 (C12), 121.87 (C3′), 113.77 (C3″ + C5″), 79.20 (C3), 55.34 (C5), 55.25 (O−$CH_3$), 47.81 (C22), 47.78 (C9), 46.70 (C19), 46.08 (C28), 45.46 (C18), 42.80 (C21), 41.72 (C14), 40.44 (C17), 39.96 (C8), 38.92 (C4), 38.82 (C1), 37.06 (C10), 33.56 (C30), 32.56 (C7), 31.39 (C20), 28.23 (C23), 27.39 (C2), 26.39 (C27), 25.64 (C15), 24.30 (C29), 23.85 (C11), 18.70 (C16), 18.42 (C6), 16.83 (C26), 15.71 (C24), 15.65 (C25).

*(22S)-22-(4-Methoxyphenyl)-3β-28-picolinamido-urs-12(13)-ene (**14b**).* According to GP II, compound **14b** was prepared from picolinic amide **3d** (100 mg, 0.183 mmol, 1 equiv), 1-iodo-4-methoxybenzene (171 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 74 mg, 62% (brms. 88%). HRMS (ESI): *m*/*z* calc. for $[C_{43}H_{60}N_2O_3 + H]^+$ 653.4677; found 653.4669. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.36 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 8.09 (d, $^3J$ = 7.9 Hz, 1H, H−C(3′)), 7.76 (t, $^3J$ = 7.7, 1H, H−C(4′)), 7.68 (bs, 1H, H−N), 7.36−7.31 (m, 1H, H−C(5′)), 7.15 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 6.78 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 5.26 (t, $^3J$ = 3.6 Hz, 1H, H−C (12)), 3.72(s, 3H, $H_3$C−O), 3.54 (dd, $^2J$ = 14.2 Hz, $^3J$ = 7.2 Hz, 1H, $H_a$-C (28)), 3.22 (dd, $^3J$ = 11.2, 4.9 Hz, 1H, H−C (3)), 3.13 (dd, $^2J$ = 14.2 Hz, $^3J$ = 3.9 Hz, 1H, $H_b$-C (28)), 2.82 (dd, $^3J$ = 12.6, 3.3 Hz, 1H, H−C (22)), 2.09−1.91 (m, 3H, $H_2$−C (11), $H_a$-C (16)), 1.77 (dt, $^2J$ = 12.8 Hz, $^3J$ = 12.7 Hz, 1H, $H_a$-C (21)), 1.70−1.58 (m, 6H, $H_a$-C (15), $H_2$−C (2), $H_a$-C (1), H−C (19), H−C (18)), 1.58−1.34 (m, 6H, $H_2$−C (6), $H_b$-C (16), $H_a$-C (7), $H_b$-C (21), H−C (9)), 1.32- 1.25 (m, 1H, $H_b$-C (7)), 1.22−1.13 (m, 4H, H−C (20), $H_3$−C (27)), 1.05 (s, 3H, $H_3$−C (26)), 1.05−9.99 (m,2H, $H_b$-C (15), $H_b$-C (1)), 0.99 (d, $^3J$ = 6.9 Hz, 3H, $H_3$−C (30)), 0.98 (s, 3H, $H_3$−C (23)), 0.94 (s, 3H, $H_3$−C (25)), 0.90 (d, $^3J$ = 5.4 Hz, 3H, $H_3$−C (29)), 0.77 (s, 3H, $H_3$−C (24)), 0.72 (dd, $^3J$ = 11.4, 1.8 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 163.87 (C = O), 158.42 (C4″), 150.32 (C2′), 147.87 (C6′), 138.20 (C13), 137.11 (C4′), 135.29 (C1″), 130.23 (C2″ + C6″), 126.34 (C12), 125.76 (C5′), 121.89 (C3′), 113.69 (C3″ + C5″), 79.24 (C3), 57.10 (C18), 55.36 (C5), 55.23 (O−$CH_3$), 51.98 (C22), 47.92 (C9), 45.77 (C28), 42.19 (C14), 41.09 (C17), 40.14 (C8), 39.76 (C19), 39.70 (C20), 39.02 (C4), 38.92 (C1), 38.76 (C21), 37.03 (C10), 32.93 (C7), 28.26 (C23), 27.41 (C2), 26.06 (C15), 23.70 (C11), 23.48 (C27), 21.36 (C30), 20.32 (C16), 18.40 (C6), 17.94 (C29), 17.00 (C26), 15.85 (C25), 15.75 (C24).

*(22S)-22-(4-Methoxycarbonylphenyl)-3β-28-picolinamido-olean-12(13)-ene (**15a**).* According to GP II, compound **15a** was prepared from picolinic amide **3c** (100 mg, 0.183 mmol, 1 equiv), methyl 4-iodobenzoate (161 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 46 mg, 37% (brsm. 57%). HRMS (ESI): *m*/*z* calc. for $[C_{44}H_{60}N_2O_4 + H]^+$ 681.4626; found 681.4609. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.21 (d, 1H, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 8.06 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7. 87 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.74 (dt, $^3J$ = 7.7, 1.7 Hz, 1H, H−C(4′)), 7.55 (bs, 1H, H−N), 7.31 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.28 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)), 5.32 (d, $^3J$ = 3.7 Hz, 1H, H−C (12)), 3.88 (s, 3H, O−$CH_3$), 3.57 (dd, $^2J$ = 14.2 Hz, $^3J$ = 7.0 Hz, 1H, $H_a$-C (28)), 3.22 (dd, $^3J$ = 11.0, 4.7 Hz, 1H, H−C (3)), 3.18 (dd, $^2J$ = 14.2 Hz, $^3J$ = 4.5 Hz, 1H, $H_b$-C (28)), 2.97 (dd, $^3J$ = 13.8, 3.2 Hz, 1H, H−C (22)), 2.27 (dd, $^3J$ = 13.8, 3.7 Hz, 1H, H−C (18)), 2.05 (ddd, $^2J$ = 13.7 Hz, $^3J$ =


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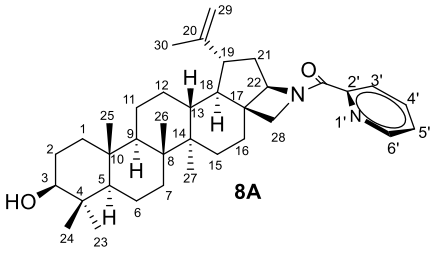
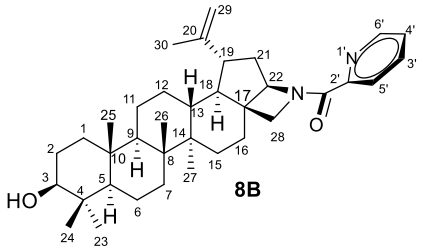
13.5, 4.6 Hz, 1H, $H_a$-C (16)), 2.04−1.91 (m, 2H, $H_a$-C (19), $H_a$-C (11)), 1.92−1.82 (m, 2H $H_b$-C (11), $H_a$-C (21)), 1.68−1.45 (m, 7H, $H_a$-C (6), $H_a$-C (15), $H_2$−C (2), $H_a$-C (7), $H_a$-C (1), H−C (9)), 1.44−1.34 (m, 2H, $H_b$-C (6), $H_b$-C (16)), 1.33−1.22 (m, 6H, $H_b$-C (7), $H_b$-C (21), $H_b$-C (19), $H_3$−C (27)), 1.06−1.00 (m, 7H, $H_3$−C (26), $H_3$−C (29), $H_b$-C (15)), 0.99−0.96 (m, 7H, $H_3$−C (23), $H_3$−C (30), $H_b$-C (1)), 0.93 (s, 3H, $H_3$−C (25)), 0.77 (s, 3H, $H_3$−C (24)), 0.75−0.70 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.25 (O−C═O), 163.87 (N−C═O), 150.00 (C2′), 148.86 (C1″), 147.74 (C6′), 143.56 (C13), 137.12 (C4′), 129.65 (C3″ + C5″), 129.50 (C2″ + C6″), 128.32 (C4″), 125.79 (C5′), 123.72 (C12), 121.90 (C3′), 79.19 (C3), 55.33 (C5), 52.06 (O−$CH_3$), 48.94 (C22), 47.78 (C9), 46.62 (C19), 46.03 (C28), 45.51 (C18), 42.39 (C21), 41.70 (C14), 40.71 (C17), 39.98 (C8), 38.92 (C4), 38.82 (C1), 37.06 (C10), 33.49 (C30), 32.55 (C7), 31.37 (C20), 28.23 (C23), 27.38 (C2), 26.38 (C27), 25.65 (C15), 24.23 (C29), 23.84 (C11), 18.82 (C16), 18.41 (C6), 16.81 (C26), 15.71 (C24), 15.66 (C25).

*(22S)-22-(4-Methoxycarbonylphenyl)-3β-28-picolinamido-urs-12(13)-ene (**15b**).* According to GP II, compound **15b** was prepared from picolinic amide **3d** (100 mg, 0.183 mmol, 1 equiv), methyl 4-iodobenzoate (191 mg, 0.731 mmol, 4 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv), $CuBr_2$ (4 mg, 0.018 mmol, 0.1 equiv), and CsOAc (140 mg, 0.731 mmol, 4 equiv) in *t*-AmOH (2 mL). Yield 35 mg, 28% (brsm. 95%). HRMS (ESI): *m*/*z* calc. for $[C_{44}H_{60}N_2O_4 + H]^+$ 681.4626; found 681.4608.$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′)), 8.06 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 7.86 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.76 (td, $^3J$ = 7.7, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.61 (dd, $^3J$ = 6.6, 4.9 Hz, 1H, H−N), 7.33−7.28 (m, 3H, H−C(5′), H−C(2″), H−C(6″)), 5.28 (t, $^3J$ = 3.6 Hz, 1H, H−C (12)), 3.87 (s, 3H, $H_3$C−O), 3.50 (dd, $^2J$ = 14.3 Hz, $^3J$ = 6.6 Hz, 1H, $H_a$-C (28)), 3.23 (dd, $^3J$ = 11.4, 4.9 Hz, 1H, H−C (3)), 3.20 (dd, $^2J$ = 14.3 Hz, $^3J$ = 4.9 Hz, 1H, $H_b$-C (28)), 2.82 (dd, $^3J$ = 13.2, 3.3 Hz, 1H, H−C (22)), 2.11 (ddd, $^2J$ = 13.6 Hz, $^3J$ = 13.6, 4.8 Hz, 1H, $H_a$-C (16)), 2.03−1.93 (m, 2H, $H_2$−C (11)), 1.81 (ddd, $^2J$ = 13.2 Hz, $^3J$ = 13.2, 12.8 Hz, 1H, $H_a$-C (21)), 1.71−1.58 (m, 6H, $H_a$-C (15), $H_2$−C (2), $H_a$-C (1), H−C (19), H−C (18)), 1.58−1.43 (m, 5H, $H_a$-C (6), $H_b$-C (16), $H_a$-C (7), $H_b$-C (21), H−C (9)), 1.40−1.34 (m, 1H, $H_b$-C (6)), 1.32- 1.25 (m, 1H, $H_b$-C (7)), 1.22- 1.13 (m, 4H, H−C (20), $H_3$−C (27)), 1.09−1.03 (m, 1H, $H_b$-C (15)), 1.02 (s, 3H, $H_3$−C (26)), 1.02−0.98 (m, 4H, $H_b$-C (1), $H_3$−C (30)), 0.98 (s, 3H, $H_3$−C (23)), 0.94 (s, 3H, $H_3$−C (25)), 0.91 (d, $^3J$ = 5.5 Hz, 3H, $H_3$−C (29)), 0.77 (s, 3H, $H_3$−C (24)), 0.73 (dd, $^3J$ = 11.8, 1.8 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.24 (O−C═O), 164.00 (N−C═O), 149.85 (C2′), 148.87 (C1″), 147.80 (C6′), 137.91 (C13), 137.23 (C4′), 129.59 (C3″ + C5″), 129.36 (C2″ + C6″), 128.29 (C4″), 126.66 (C12), 125.89 (C5′), 121.97 (C3′), 79.27 (C3), 57.17 (C18), 55.35 (C5), 53.16 (C22), 52.05 (O−$CH_3$), 47.88 (C9), 45.83 (C28), 42.16 (C14), 41.29 (C17), 40.15 (C8), 39.68 (C19), 39.59 (C20), 39.00 (C4), 38.91 (C1), 38.29 (C21), 37.02 (C10), 32.90 (C7), 28.25 (C23), 27.38 (C2), 26.05 (C15), 23.68 (C11), 23.49 (C27), 21.29 (C30), 20.37 (C16), 18.38 (C6), 17.89 (C29), 16.92 (C26), 15.83 (C25), 15.74 (C24).

Betulin core-derived picolinic azetidines **8** and **11** were isolated as a stable 1:1 mixture of rotamers and characterized together. Oleanane core-derived azetidine was isolated as a stable 2:1 mixture of rotamers, and characterization of both rotamers was found to be possible due to different integral intensities.

*N-Picolinoyl Azetidine 8 Mixture of Rotamers.*




HRMS (ESI): *m*/*z* calc. for $[C_{36}H_{52}N_2O_2 + H]^+$ 545.4102; found 545.4123. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.63 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′A), 8.54 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′B), 8.10 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′A)), 8.08 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′B)), 7.81 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′A)), 7.78 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′B)), 7.35 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′A)), 7.33 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′B)), 4.95 (d, $^3J$ = 5.8 Hz, 1H, H−C(22B)), 4.84 (s, 1H, $H_a$-C(29A)), 4.81 (s, 1H, $H_a$-C(29B)), 4.70 (s, 1H, $H_b$-C(29A)), 4.67 (s, 1H, $H_b$-C(29B)), 4.60 (d, $^2J$ = 11.0 Hz, 1H, $H_a$-C(28A)), 4.45 (d, $^3J$ = 5.8 Hz, 1H, H−C(22A)), 4.16 (d, $^2J$ = 11.0 Hz, 1H, $H_b$-C(28A)), 4.09 (d, $^2J$ = 11.0 Hz, 1H, $H_a$-C(28B)), 3.75 (d, $^2J$ = 11.0 Hz, 1H, $H_b$-C(28B)), 3.22−3.16 (m, 2H, H−C(3A), H−C(3B)), 2.73−2.75 (m, 1H, H−C(19A)), 2.71−2.67 (m, 1H, H−C(19B)), 2.18 (dd, $^2J$ = 13.8 Hz, $^3J$ = 5.8 Hz, 1H, $H_a$-C(21A)), 1.98−1.85 (m, 3H, $H_a$-C(21B), $H_a$-C(16A), $H_a$-C (16)), 1.84−1.77 (m, 2H, $H_a$-C(12A), $H_a$-C(12B)), 1.77−1.47 (m, 22H, $H_b$-C(16A), $H_b$-C(16B), $H_3$−C(30A), $H_3$−C(30B), $H_b$-C(21A), $H_b$-C(21B), $H_a$-C(6A), $H_a$-C(6B), $H_2$−C(2A), $H_2$−C(2B), H−C(13A), H−C(13B), $H_a$-C(1A), $H_a$-C(1B), H−C(18A), H−C(18B)), 1.47−1.35 (m, 10H, $H_b$-C(6A), $H_b$-C(6B), $H_a$-C(11A), $H_a$-C(11B), $H_a$-C(15A), $H_a$-C(15B), $H_2$−C(7A), $H_2$−C(7B)), 1.29−1.17 (m, 8H, $H_b$-C(11A), $H_b$-C(11B), $H_b$-C(12A), $H_b$-C(12B), $H_b$-C(15A), $H_b$-C(15B), H−C(9A), H−C(9B)), 0.99 (s, 3H, $H_3$−C(27B)), 0.99 (s, 3H, $H_3$−C(27A)), 0.97 (s, 9H, $H_3$−C(23A), $H_3$−C(23B), $H_3$−C(26A)), 0.94 (s, 3H, $H_3$−C(26B)), 0.94−0.88 (m, 2H, $H_b$-C(1A), $H_b$-C(1B)), 0.83 (s, 6H, $H_3$−C(25A), $H_3$−C(25B)), 0.76 (s, 6H, $H_3$−C(24A), $H_3$−C(24B)), 0.71−0.64 (m, 2H, H−C(5A), H−C(5B). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.93 (N−C═O A), 163.97 (N−C═O B), 152.77 (C2′A), 152.19 (C2′B), 148.18 (C6′B), 148.14 (C6′A), 147.43 (C20A + C20B), 136.87 (C4′B), 136.84 (C4′A), 125.26 (C5′A), 125.20 (C5′B), 124.09 (C3′B), 124.04 (C3′A), 111.67 (C29A + C29B), 79.12 (C3), 79.08 (C3), 71.97 (C22A), 66.98 (C22B), 60.69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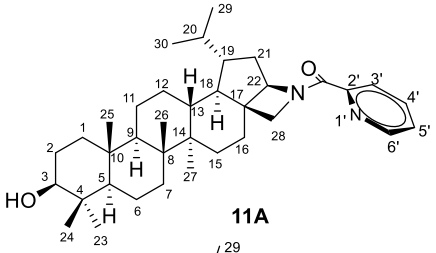
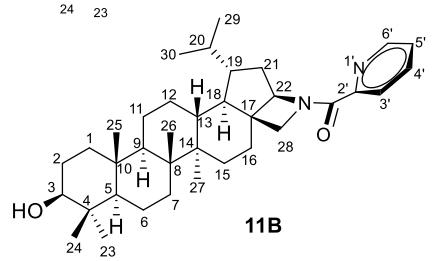
ACS Omega XXXX, XXX, XXX−XXX

(C28A), 55.45 (C5), 55.41 (C5), 54.66 (C28B), 50.59 (C9A + C9B), 49.10 (C17A), 48.57 (C17B), 48.21 (C19A), 48.15 (C19B), 47.20 (C18), 46.98 (C18), 42.32 (C14), 42.25 (C14), 41.35 (C21B), 41.07 (C8), 41.03 (C8), 39.02 (C13B), 39.00 (C1A + C1B), 38.89 (C4A + C4B), 38.88 (C21A), 38.81 (C13A), 37.31 (C10A + C10B), 34.51 (C7), 34.44 (C7), 31.00 (C16A + C16B), 28.31 (C15A + C15B), 28.12 (C23A + C23B), 27.53 (C2), 27.51 (C2), 25.42 (C12), 24.98 (C12), 21.01 (C11), 20.98 (C11), 18.42 (C6), 18.41 (C6), 16.33 (C26A), 16.30 (C25A + C25B), 16.04 (C26B), 15.52 (C24), 15.50 (C24), 14.51 (C27), 14.48 (C27).

*N-Picolinoyl Azetidine 11 Mixture of Rotamers.*



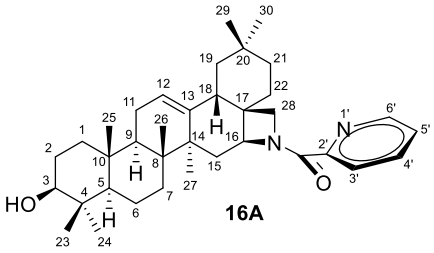
**11A**



**11B**

HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}N_2O_2 + H]^+$ 547.4258; found 547.4254. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.60 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′A)), 8.56 (d, $^3J$ = 4.7 Hz, 1H, H−C(6′B)), 8.10 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′A)), 8.08 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′B)), 7.80 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′A)), 7.77 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′B)) 7.35 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′A)), 7.33 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′B)), 4.86 (d, $^3J$ = 5.8 Hz, 1H, H−C(22B)), 4.54 (d, $^2J$ = 10.8 Hz, 1H, $H_a$-C(28A)), 4.36 (d, $^3J$ = 5.8 Hz, 1H, H−C(22A)), 4.12 (d, $^2J$ = 10.8 Hz, 1H, $H_b$-C(28A)), 4.02 (d, $^2J$ = 10.8 Hz, 1H, $H_a$-C(28B)), 3.70 (d, $^2J$ = 10.8 Hz, 1H, $H_b$-C(28B)), 3.22−3.16 (m, 2H, H−C(3A), H−C(3B)), 2.23−2.12 (m, 3H, H−C(20A), H−C(20B), H−C(18B)), 2.12−2.04 (m, 2H, H−C(18A, $H_a$-C(21A)), 1.94−1.82 (m, 5H, $H_a$-C(12A), $H_a$-C(12B), $H_b$-C(21A), H−C(16A, H−C(16B)), 1.80−1.74 (m, 1H, $H_a$-C(21B), 1.74−1.44 (m, 19H, $H_b$-C(16A), $H_b$-C(16B), $H_b$-C(21B), $H_a$-C(6A), $H_a$-C(6B), $H_a$-C(11A), $H_a$-C(11B), $H_2$−C(2A), $H_2$−C(2B), $H_a$-C(15A), $H_a$-C(15B), $H_b$-C(12A), $H_b$-C(12B), H−C(13A), H−C(13B), $H_a$-C(1A), $H_a$-C(1B)), 1.44−1.24 (m, 12H, $H_b$-C(6A), $H_b$-C(6B), $H_b$-C (11), $H_b$-C (11), $H_2$−C(7A), $H_2$−C(7B), H−C(19A), H−C(19B), H−C(9A), H−C(9B)), 1.23−1.15 (m, 2H, $H_b$-C(15A), $H_b$-C(15B)), 0.99−0.95 (m, 15H, $H_3$−C(23A), $H_3$−C(23B), $H_3$C(26A), $H_3$−C(27A), $H_3$−C(27B)), 0.94 (s, 3H, $H_3$−C(26B)), 0.94 −0.89 (m, 2H, $H_b$-C(1A), $H_b$-C(1B)), 0.89 (d, $^3J$ = 6.5 Hz, 3H, $H_3$−C(30B)), 0.84 (s, 6H, $H_3$−C(25A), $H_3$−C(25B)), 0.80 (d, $^3J$ = 6.5 Hz, 6H, $H_3$−C(30A), $H_3$−C(29B), 0.78−0.75 (m, 9H, $H_3$−C(29A), $H_3$−C(24A), $H_3$−C(24B)), 0.72−0.66 (m, 2H, H−C(5A), H−C(5B)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.98 (N−C = O A), 163.97(N−C = O B), 152.90 (C2′A), 152.36 (C2′B), 148.24 (C6′B), 148.11 (C6′B), 136.83 (C4′B), 136.80 (C4′A), 125.19, (C5′A), 125.11 (C5′B), 124.03 (C3′B), 123.96 (C3′A), 79.13 (C3), 79.08 (C3), 71.48 (C22A), 66.48 (C22B), 60.65 (C28A), 55.38 (C5), 55.34 (C5), 54.64 (C28B), 50.12 (C9A + C9B), 49.42 (C17A), 48.93 (C17B), 45.94 (C19), 45.76 (C19), 45.60 (C18A), 45.45 (C18B), 42.60 (C14), 42.52 (C14), 41.07 (C8), 41.04 (C8), 39.00 (C13), 38.99 (C4A + C4B), 38.86 (C1), 38.85 (C1), 38.80 (C13), 37.25 (C10A + C10B), 34.60 (C7), 34.53 (C7), 32.98 (C21B), 31.14 (C16), 31.11 (C16), 30.59 (C21A), 28.13 (C23A + C23B), 28.09 (C15), 28.00 (C20A + C20B), 27.92 (C15), 27.52 (C2), 27.51 (C2), 26.04 (C12), 26.01 (C12), 23.13 (C30A), 23.05 (C30B), 20.91(C11), 20.88 (C11), 18.44 (C6), 18.42 (C6), 16.31 (C26A), 16.25 (C25), 16.22 (C25), 16.04 (C26B), 15.54 (C24), 15.52 (C24), 15.35 (C29A), 15.28 (C29B), 14.35 (C27), 14.32 (C27).

*N-Picolinoyl Azetidine 16 Mixture of Rotamers: Rotamer A.*



**16A**

HRMS (ESI): $m/z$ calc. for $[C_{36}H_{52}N_2O_2 + H]^+$ 545.4102; found 545.4075. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.57 (d, $J$ = 5.4 Hz, 1H, H−C(6′)), 8.09 (d, $^3J$ = 7.9 Hz, 1H, H−C(3′)), 7.79 (td, $^3J$ = 7.9 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.37−7.30 (m, 1H, H−C(5′)), 5.50 (bs, 1H, H−C (12)), 4.46 (d, $^2J$ = 10.3 Hz, 1H, $H_a$-C (28)), 4.41 (t, $^3J$ = 7.4 Hz, 1H, H−C (16)), 4.22 (d, $^2J$ = 10.3 Hz, 1H, $H_b$-C (28)), 3.21 (dd, $^3J$ = 10.0, 4.5 Hz, 1H, H−C (3)), 2.55 (bs, 1H, H−C (18)), 2.06 (d, $J$ = 7.6 Hz, 2H, $H_2$−C (15)), 2.05 −1.97 (m, 1H, $H_a$-C (11)), 1.97−1.78 (m, 3H, $H_a$-C (19), $H_b$-C (11), $H_a$-C (22)), 1.77−1.53 (m, 6H, $H_a$-C (6), $H_2$−C (2), $H_b$-C (22), $H_a$-C (1), H−C (9)), 1.53−1.22 (m, 5H, $H_b$-C (6), $H_2$−C (7), $H_2$−C (21)), 1.21−1.14 (m, 1H, $H_b$-C (19)), 1.13 (s, 3H, $H_3$−C (27)), 1.05−1.00 (m, 1H, $H_b$-C (1)), 0.99 (s, 3H, $H_3$−C (25)), 0.91 (s, 3H, $H_3$−C (29)), 0.90 (s, 3H, $H_3$−C (30)), 0.89 (s, 3H, $H_3$−C (25)), 0.81−0.77 (m, 4H, $H_3$−C (26), H−C (5)), 0.77 (s, 3H, $H_3$−C (24)).$^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 165.40 (C═O), 152.46 (C2′), 148.10 (C6′), 140.95 (C13), 136.88 (C4′), 125.20 (C5′), 123.97 (C3′), 120.51 (C12), 79.15 (C3), 66.45 (C28), 64.60 (C16), 55.48 (C5), 47.33 (C9), 42.78 (C18), 42.39 (C14), 39.33 (C8), 38.93 (C4), 38.47 (C1), 37.46 (C10), 37.12 (C17), 36.35 (C21+ C19), 33.10 (C7), 31.48 (C30), 31.35 (C22), 30.65 (C20), 30.23 (C15), 28.78 (C29), 28.16 (C23), 27.32 (C2), 24.42 (C27) 23.50 (C11), 18.60 (C6), 16.35 (C26), 15.67 (C25), 15.59 (C24).



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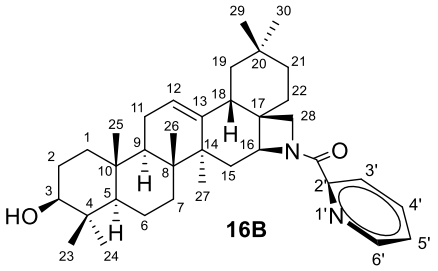
ACS Omega XXXX, XXX, XXX−XXX

*N-Picolinoyl Azetidine 16 Mixture of Rotamers: Rotamer B.*




HRMS (ESI): $m/z$ calc. for $[C_{36}H_{52}N_2O_2 + H]^+$ 545.4102; found 545.4075. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.57 (d, $J$ = 5.4 Hz, 1H, H−C(6′)), 8.05 (d, $^3J$ = 7.9 Hz, 1H, H−C(3′)), 7.79 (td, $^3J$ = 7.9 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.37−7.30 (m, 1H, H−C(5′)), 5.48 (bs, 1H, H−C (12)), 4.84 (t, $^3J$ = 7.4 Hz, 1H, H−C (16)), 3.86 (ABq, $\Delta\delta$ AB = 0.05 Hz, $^2J$ = 10.2 Hz, 2H, $H_2$−C (28)),3.21 (dd, $^3J$ = 10.0, 4.5 Hz, 1H, H−C (3)), 2.43 (bs, 1H, H−C (18)), 2.05 −1.97 (m, 1H, $H_a$-C (11)), 1.97−1.78 (m, 5H, $H_2$−C (15)), $H_a$-C (19), $H_b$-C (11), $H_a$-C (22)), 1.77−1.53 (m, 6H, $H_a$-C (6), $H_2$−C (2), $H_b$-C (22), $H_a$-C (1), H−C (9)), 1.53−1.22 (m, 5H, $H_b$-C (6), $H_2$−C (7), $H_2$−C (21)), 1.21−1.14 (m, 1H, $H_b$-C (19)), 1.09 (s, 3H, $H_3$−C (26)), 1.05−1.00 (m, 1H, $H_b$-C (1)), 0.96 (s, 3H, $H_3$−C (25)), 0.91 (s, 3H, $H_3$−C (29)), 0.90 (s, 3H, $H_3$−C (30)), 0.86 (s, 3H, $H_3$−C (25)), 0.81−0.77 (m, 1H, H−C (5)), 0.76 (s, 3H, $H_3$−C (24)), 0.71 (s, 3H, $H_3$C-26)). $^{13}$C NMR (126 MHz, CDCl3) $\delta$ 166.01 (C═O) 152.46 (C2′), 148.17 (C6′), 140.80 (C13), 136.88 (C4′), 125.30 (C5′), 124.11 (C3′), 120.61 (C12), 79.10 (C3), 68.95 (C16), 60.07 (C28), 55.61 (C5), 47.36 (C9), 43.28 (C18), 42.39 (C14), 39.19 (C8), 38.89 (C4), 38.47 (C1), 37.43 (C10), 36.73 (C17), 36.45 (C19), 36.25 (C21), 33.00 (C7), 31.81 (C15), 31.57 (C22), 31.48 (C30), 30.65 (C20), 28.78 (C29), 28.14 (C23), 27.33 (C2), 24.65 (C27), 23.44 (C11), 18.55 (C6), 16.51 (C26), 15.65 (C25), 15.58 (C24).

**General Procedure III for Directing Group Cleavage.** To a suspension of arylated picolinic amide (0.15 mmol, 1 equiv) in THF/$H_2O$ 1:1 (5 mL), aqueous 12 M HCl (0.24 mL) was added dropwise, and the reaction mixture was stirred for 10 min at room temperature. Then zinc dust (146 mg, 2.25 mmol, 15 equiv) was added portion wise and the resulting reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was filtered through Celite pad (H = 50 mm, d = 15 mm) and filtrate was washed with 2 M NaOH aqueous solution (25 mL) and the mixture was extracted with DCM (3 × 25 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica column chromatography (DCM-MeOH 100:1−20:1) to yield an amine as a white amorphous solid.

*(22S)-22-(4-Methoxyphenyl)-3β-hydroxy-lup-20(29)en-28-amine (**24**).* According to GP III, compound **24** was prepared from **6a** (100 mg, 0.153 mmol, 1 equiv), zinc dust (150 mg, 2.297 mmol, 15 equiv), and 12 M HCl (0.33 mL). Yield 78 mg, 90%. HRMS (ESI): $m/z$ calc. for $[C_{37}H_{57}NO_2 + H]^+$ 548.4462; found 548.4467. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.24−7.20 (m, 2H, H−C(2′), H−C(6′)), 6.88−6.79 (m, 2H, H−C(3′) + H−C(5′)), 4.75 (d, $^4J$ = 2.5 Hz, 1H, $H_a$-C (29)), 4.61 (s, 1H, $H_b$-C (29)), 3.78 (s, 3H, $H_3$C−O), 3.17 (dd, $^3J$ = 11.3, 4.9 Hz, 1H), 2.77−2.63 (m, 3H, $H_2$−C (28), H−C (22)), 2.57−2.43 (m, 2H, H−C (19), $H_a$-C (21)), 1.95 (dt, $^2J$ = 13.0, $^3J$ = 3.3 Hz, 1H, $H_a$-C (16)), 1.81 (td, $^3J$ = 12.0, 4.0 Hz, 1H, H−C (13)), 1.79 (dd, $^3J$ = 12.0, 10.9 Hz, 1H, H−C (18)), 1.72 (s, 3H, $H_3$−C (30)), 1.71−1.62 (m, 2H, $H_a$-C (12), $H_a$-C (1)), 1.62−1.48 (m, 3H, $H_2$−C (2), $H_a$-C (6)), 1.47−1.33 (m, 6H, $H_b$-C (6), $H_a$-C (11), $H_a$-C (15), $H_2$−C (7), $H_b$-C (21)), 1.33−1.17 (m, 3H, $H_b$-C (11), $H_b$-C (16), H−C (9)), 1.12−1.06 (m, 2H, $H_b$-C (12), $H_b$-C (15)), 1.03 (s, 3H, $H_3$−C (27)), 0.99 (s, 3H, $H_3$−C (26)), 0.96 (s, 3H, $H_3$−C (23)), 0.90−0.86 (m, 1H, $H_b$-C (1)), 0.82 (s, 3H, $H_3$−C (25)), 0.75 (s, 3H, $H_3$−C (24)), 0.72−0.65 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, CDCl3) $\delta$ 158.43 (C4′), 150.34 (C20), 132.63 (C1′), 128.58 (C2′ + C6′), 114.10 (C3′ + C5′), 110.17 (C29), 78.99 (C3), 55.49 (C5), 55.35 ($CH_3$−O), 54.04 (C22), 50.67 (C9), 50.57 (C18), 50.17 (C17), 46.16 (C19), 42.57 (C14), 40.97 (C8), 38.99 (C4), 38.87 (C1), 38.51 (C28), 37.56 (C13), 37.30 (C10), 34.70 (C21), 34.32 (C7), 29.14 (C16), 28.12 (C23), 27.54 (C2), 27.51 (C15), 25.12 (C12), 21.05 (C11), 19.12 (C30), 18.42 (C6), 16.26 (C25), 16.13 (C26), 15.49 (C24), 15.18 (C27)

*(22S)-22-(4-Carboxyphenyl)-3β-hydroxy-lup-20(29)en-28-amine (**26**).* According to GP III, compound **26** was prepared from **25** (60 mg, 0.097 mmol, 1 equiv), zinc dust (94 mg, 1.455 mmol, 15 equiv), and 12 M HCl (0.24 mL). Yield 42 mg, 84%. HRMS (ESI): $m/z$ calc. for $[C_{37}H_{55}NO_3 + H]^+$ 562.4255; found 562.4236. $^1$H NMR (500 MHz, DMSO) $\delta$ 7.86 (d, $^3J$ = 8.0 Hz, 2H, H−C(3″), H−C(5″)), 7.43 (d, $^3J$ = 8.0 Hz, 2H, H−C(3″), H−C(5″)), 4.73 (s, 1H, $H_a$-C (29)), 4.60 (s, 1H, $H_b$-C (29)), 4.28 (s, 1H, OH), 3.03 (d, $^2J$ = 14.0 Hz, 1H, $H_a$-C (28)), 3.00−2.93 (m, 2H, H−C (3), H−C (22)), 2.59 (d, $^2J$ = 14.0 Hz, 1H, $H_b$-C (28)), 2.55−2.50 (m, 1H, H−C (19)), 2.31−2.22 (m, 1H, $H_a$-C (21)), 1.91−1.79 (m, 2H, H−C (18), $H_a$-C (16)), 1.71 (s, 3H, H−C (30)), 1.67−1.52 (m, 5H, $H_a$-C (12), $H_2$−C (15), H−C (13), $H_a$-C (1)), 1.50−1.34 (m, 7H, $H_2$−C (6), $H_a$-C (11), $H_2$−C (2), $H_2$−C (7)), 1.33−1.18 (m, 3H, $H_b$-C (11), $H_b$-C (16), H−C (9)), 1.13−1.06 (m, 4H, $H_3$−C (26), $H_b$-C (21)), 1.04 (s, 3H, $H_3$−C (27)), 1.02−0.97 (m, 1H, $H_b$-C (12)), 0.87 (s, 3H, $H_3$−C (23)), 0.84−0.81 (m, 1H, $H_b$-C (1)), 0.80 (s, 3H, $H_3$−C (25)), 0.68−0.62 (m, 4H, $H_3$−C (24), H−C (5)). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 167.58 (COOH), 149.96 (C20), 148.20 (C4″), 129.34 (C3″ + C5″), 127.85 (C2″ + C6″), 116.19 (C1″), 109.79 (C29), 76.77 (C3), 54.83 (C5), 50.71 (C18), 50.34 (C17), 49.72 (C9), 48.12 (C22), 46.39 (C19), 42.74 (C14), 40.78 (C8), 38.53 (C4), 38.27 (C1), 37.73 (C28), 36.71 (C10), 36.06 (C13), 33.74 (C7), 32.85 (C15), 32.06 (C21), 29.15 (C16), 28.12 (C23), 27.16 (C2), 24.95 (C12), 20.33 (C11), 19.31 (C30), 17.92 (C6), 16.00 (C25), 15.82 (C26), 15.80 (C24), 14.98 (C27).

*(22S)-22-(4-Carboxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)en (**25′**) and (16R)-16-(4-Carboxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)en (**25′**).* To a solution of compound **7f** (80 mg, 0.117 mmol, 1 equiv) in EtOH (4 mL), NaOH (20 mg, 0.500 mmol, 4.3 equiv) was added. Reaction was stirred for 16 h at 80 °C, the reaction was quenched by addition of ion-exchange resin (Dowex 50WX8, 50−100 mesh, H−form) until pH 7, filtered, and evaporated in vacuum. The residue was purified by column chromatography on silica with Hex/EtOAc + (30%→50% EtOAc). Yield (67 mg, 86%, 9:1). HRMS (ESI): $m/z$ calc. for $[C_{43}H_{58}N_2O_4 + H]^+$ 667.4469; found 667.4454.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*(22S)-22-(4-Carboxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**25**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.13 (dd, 1H, $^3J$ = 4.5 Hz, $^4J$ = 1.5 Hz, H−C(6′)), 8.02 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.98 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.68 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.5 Hz, 1H, H−C(4′)), 7.45 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.22 (dd, $^3J$ = 7.7, 4.5 Hz, 1H, H−C(5′)),), 6.90 (dd, $^3J$ = 8.8, 3.4 Hz, 1H, H−N), 4.82 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.69 (s, 1H, $H_b$-C (29)), 4.07 (dd, $^2J$ = 14.3, $^3J$ = 8.8 Hz, 1H, $H_a$-C (28)), 3.21 (dd, $^3J$ = 11.4, 4.8 Hz, 1H, H−C (3)), 3.10 (dd, $^2J$ = 14.3, $^3J$ = 3.4 Hz, 1H, $H_b$-C (28)), 3.00 (dd, $^3J$ = 9.9, 9.6 Hz, 1H, H−C (22)), 2.75 (ddd, $^2J$ = 13.7 Hz, $^3J$ = 11.2, 9.9 Hz, 1H $H_a$-C (21)), 2.67 (ddd, $^3J$ = 11.2, 10.6, 5.1 Hz, 1H, H−C (19)), 2.02 (td, $^3J$ = 11.9, 3.5 Hz, 1H, H−C (13)), 1.95 (dd, $^3J$ = 11.9, 11.0 Hz, 1H, H−C (18)), 1.89 (ddd, $^2J$ = 13.1 Hz, $^3J$ = 6.7, 3.5 Hz, 1H, $H_a$-C (16)), 1.77 (s, 3H, H−C (30)), 1.77−1.65 (m, 4H, $H_a$-C (12), $H_a$-C (7), $H_a$-C (1), $H_a$-C (15)), 1.65−1.23 (m, 10H, $H_2$−C (2), $H_2$−C (6), $H_2$−C (11), $H_b$-C (16) $H_b$-C (7), $H_b$-C (21), H−C (9)), 1.14 (s, 3H, $H_3$−C (26), H−C (9)), 1.13−1.08 (m, 1H, $H_b$-C (12)), 1.07−1.02 (m, 4H, $H_3$−C (27), $H_b$-C (15)), 0.96 (s, 3H,$H_3$−C (23)), 0.95−0.88 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, $H_3$−C (24)), 0.73−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 170.52 (COOH), 164.11 (N−C═O), 149.61 (C20), 149.45 (C2′), 147.58 (C6′), 146.99 (C1″), 137.12 (C4′), 130.85 (C3″ + C5″), 128.00 (C4″), 127.50 (C2″ + C6″), 125.95 (C5′), 121.87 (C3′), 110.74 (C29), 79.27 (C3), 55.52 (C5), 54.92 (C22), 51.00 (C17), 50.86 (C18), 50.65 (C9), 46.16 (C19), 42.70 (C14), 41.02 (C8), 39.01 (C4), 38.89 (C1), 37.70 (C13), 37.34 (C10), 36.00 (C28), 34.13 (C7), 33.89 (C21), 30.31 (C16), 28.12 (C23), 27.53 (C2), 27.39 (C15), 25.22 (C2), 20.98 (C11), 19.39 (C30), 18.37 (C6), 16.22 (C25), 16.05 (C26), 15.50 (C24), 15.17 (C27).

*(16R)-16-(4-Carboxyphenyl)-3β-hydroxy-28-picolinamido-lup-20(29)ene (**25′**).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.15 (d, 1H, $^3J$ = 4.7 Hz, H−C(6′)), 8.02 (d, $^3J$ = 8.1 Hz, 2H, H−C(3″), H−C(5″)), 7.98 (d, $^3J$ = 7.7 Hz, 1H, H−C(3′)), 7.70 (td, $^3J$ = 7.7 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.43 (d, $^3J$ = 8.1 Hz, 2H, H−C(2″), H−C(6″)), 7.23 (dd, $^3J$ = 7.7, 4.7 Hz, 1H, H−C(5′)),), 7.01 (dd, $^3J$ = 9.1, 3.4 Hz, 1H, H−N), 4.76 (d, $^4J$ = 2.2 Hz, 1H, $H_a$-C (29)), 4.64 (s, 1H, $H_b$-C (29)), 3.71−3.61 (m, 1H, $H_a$-C (28)), 3.48 (dd, $^2J$ = 14.6 Hz, $^3J$ = 3.4 Hz, 1H, $H_b$-C (28)), 3.21 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 3.00 (dd, $^3J$ = 13.1, 3.4 Hz, 1H, H−C (16)), 2.69 (td, $^3J$ = 11.0, 4.4 Hz, 1H, H−C (19)), 2.50 (dd, $^2J$ = 13.3 Hz, $^3J$ = 13.1 Hz, 1H, $H_a$-C (15)), 2.11−1.99 (m, 1H, $H_a$-C (21)), 1.93 (dd, $^3J$ = 11.9, 11.0 Hz, 1H, H−C (18)), 1.83 (td, $^3J$ = 11.9, 3.7 Hz, 1H, H−C (13)), 1.76 (s, 3H, H−C (30)), 1.76−1.59 (m, 5H, $H_a$-C (12), $H_a$-C (22), $H_a$-C (1), $H_2$−C (2)), 1.58−1.43 (m, 6H, $H_2$−C (6), $H_a$-C (11), $H_b$-C (22), $H_2$−C (7)), 1.43- 1.23 (m, 4H, $H_b$-C (11), $H_b$-C (21), $H_b$-C (15), H−C (9)), 1.21 (s, 3H, $H_3$−C (26)), 1.16−1.09 (m, 4H, $H_b$-C (12), $H_3$−C (27)), 0.98 (s, 3H,$H_3$−C (23)), 0.97−0.90 (m, 1H, $H_b$-C (1)), 0.88 (s, 3H, $H_3$−C (25)), 0.79 (s, 3H, $H_3$−C (24)), 0.74−0.69 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 170.42 (O−C═O), 164.14 (N−C═O), 150.39 (C20), 150.16 (C1″), 149.54 (C2′), 147.67 (C6′), 137.12 (C4′), 130.67 (C3″ + C5″), 127.95 (C2″ + C6″), 127.39 (C4″), 125.95 (C5′), 121.82 (C3′), 109.88 (C29), 79.14 (C3), 55.49 (C5), 51.55 (C17), 51.43 (C18), 50.62 (C9), 48.94 (C16), 46.87 (C19), 43.40 (C14), 41.46 (C8), 39.04 (C4), 38.93 (C1), 37.38 (C10), 37.11 (C13), 36.31 (C28), 35.07 (C22), 34.53 (C7), 32.16 (C15), 30.06 (C21), 28.15 (C23), 27.55 (C2), 25.65 (C12), 21.05 (C11), 20.21 (C30), 18.43 (C6), 16.45 (C25), 16.37 (C26), 15.62 (C24), 15.54 (C27).

**General Procedure IV for Synthesis of Unprotected Azetidines.** To a solution of N-acyl azetidine **8**, **11**, or **16** (0.12 mmol, 1 equiv) in anhydrous THF (1.5 mL), $LiAlH_4$ (13 mg, 0.36 mmol, 3 equiv) was added in one portion at 0 °C. The resulting reaction mixture was stirred under a nitrogen atmosphere at 0 °C for 1 h. The reaction mixture was warmed up to room temperature, and after 3 h, it was cooled back to 0 °C and slowly quenched sequentially with MeOH (0.5 mL) and water (0.5 mL). The reaction mixture was diluted with DCM (15 mL) and washed with 10% NaOH aqueous solution (10 mL). The organic phase was then washed with water (1 × 10 mL), brine (1 × 10 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo, and the crude mixture was purified by silica column chromatography (DCM-MeOH 100:1→25:1) to yield an unprotected amine as a white amorphous solid.

*Azetidine 12.* HRMS (ESI): $m/z$ calc. for $[C_{30}H_{49}NO + H]^+$ 440.3887; found 440.3876. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.87 (s, 1H, $H_a$-C (29)), 4.69 (s, 1H, $H_b$-C (29)), 3.65 (d, $^3J$ = 5.2 Hz, 1H, H−C (22)), 3.61 (d, $^2J$ = 9.3 Hz, 1H, $H_a$-C (28)), 3.17 (dd, $^3J$ = 11.2, 4.8 Hz, 1H, H−C (3)), 3.14 (d, $^2J$ = 9.3 Hz, 1H, $H_b$-C (28)), 2.90 (ddd, $^3J$ = 10.3, 8.9, 8.5 Hz, 1H, H−C (19)), 2.01 (ddd, $^2J$ = 12.5 Hz, 3.7, 3.4 Hz, 1H, $H_a$-C (16)), 1.83−1.75 (m, 1H, $H_a$-C (12)), 1.69 (s, 3H, $H_3$−C (30)), 1.68−1.48 (m, 7H, $H_a$-C (6), $H_2$−C (2), $H_a$-C (21), $H_b$-C (16), H−C (13), $H_a$-C (1)), 1.47−1.18 (m, 9H, $H_b$-C (6), $H_2$−C (11), $H_b$-C (21), $H_a$-C (15), $H_2$−C (7), H−C (18), H−C (9)), 1.17 −1.09 (m, 2H, $H_b$-C (12), $H_b$-C (15)), 0.95 (s, 3H, $H_3$−C (23)), 0.94 (s, 3H, $H_3$−C (26)), 0.90−0.86 (m, 4H, $H_3$−C (27), $H_b$-C (1)), 0.81 (s, 3H, $H_3$−C (25)), 0.74 (s, 3H, $H_3$−C (24)), 0.66 (d, $^3J$ = 9.8 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 148.22 (C20), 111.23 (C29), 79.02 (C3), 64.37 (C22), 55.43 (C5), 52.45 (C28), 52.20 (C17), 50.59 (C9), 49.15 (C19), 47.79 (C18), 42.08 (C14), 41.01 (C8), 39.00 (C4), 38.89 (C1), 38.17 (C13), 37.30 (C10), 34.47 (C7), 31.61 (C16), 28.14 (C23), 27.99 (C15), 27.55 (C2), 27.05 (C21), 25.12 (C12), 21.01 (C11), 18.88 (C30),18.42 (C6), 16.30 (C25), 16.07 (C26), 15.52 (C24), 14.38 (C27).

*Azetidine 13.* HRMS (ESI): $m/z$ calc. for $[C_{30}H_{51}NO + H]^+$ 442.4043; found 442.4033. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.60 −3.54 (m, 2H, H−C (22), $H_a$-C (28)), 3.19 (dd, $^3J$ = 11.6, 4.8 Hz, 1H, H−C (3)), 3.12 (d, $^2J$ = 8.9 Hz, 1H, $H_b$-C (28)), 2.34−2.25 (m, 1H, H−C (19)), 2.24−2.16 (m, 1H, H−C (20)), 2.04−1.97 (m, 1H, $H_a$-C (16)), 1.89−1.83 (m, 1H, $H_a$-C (12)), 1.72−1.43 (m, 9H, $H_a$-C (1), $H_a$-C (6), $H_a$-C (11), $H_2$−C (2), $H_b$-C (16), $H_2$−C (21), H−C (13)), 1.43−1.19 (m, 8H, $H_b$-C (6), $H_b$-C (11), $H_b$-C (12), $H_a$-C (15), $H_2$−C (7), H−C (18), H−C (9)), 1.14−1.08 (m, 1H, $H_b$-C (15)), 0.97 (s, 3H, H−C (23)), 0.95−0.90 (m, 7H, $H_3$−C (30), $H_3$−C (27), $H_b$-C (1)), 0.89 (s, 3H, $H_3$−C (26)), 0.82 (s, 3H, $H_3$−C (25)), 0.78 (d, $^3J$ = 6.8 Hz, 3H, $H_3$−C (29)), 0.76 (s, 3H, $H_3$−C (24)), 0.68 (d, $J$ = 10.3 Hz, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 79.03 (C3), 63.70 (C22), 55.36 (C5), 52.47 (C17), 52.43 (C28), 50.12 (C9), 46.60 (C18), 46.40 (C19), 42.35 (C14), 41.00 (C8), 38.99 (C4), 38.85 (C1), 38.07 (C13), 37.23 (C10), 35.19 (C21), 34.55 (C7), 31.78 (C16), 28.25 (C23), 28.13 (C20), 27.79 (C15), 27.52 (C2), 26.12 (C12), 23.23 (C30), 20.91 (C11), 18.43 (C6), 16.21 (C25), 16.06 (C26), 15.54 (C24), 15.28 (C29), 14.22 (C27).


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*Azetidine 17 HRMS (ESI).* $m/z$ calc. for $[C_{30}H_{49}NO + H]^+$ 440.3887; found 440.3868. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.47 (t, $^3J$ = 3.5 Hz, 1H, H−C (12)), 3.81 (t, $^3J$ = 8.3 Hz, 1H, H−C (16)), 3.46 (d, $^2J$ = 8.4 Hz, 1H, $H_a$-C (28)), 3.37 (d, $^2J$ = 8.4 Hz, 1H, $H_b$-C (28)), 3.22 (dd, $^3J$ = 10.9, 4.6 Hz, 1H, H−C (3)), 2.65 (bs, 1H, H−C (18)), 2.08−1.99 (m, 1H, $H_a$-C (11)), 1.92−1.74 (m, 4H, $H_a$-C (19), $H_b$-C (11), $H_a$-C (15), $H_a$-C (22)), 1.69−1.54 (m, 7H, $H_a$-C (6), $H_2$−C (2), $H_b$-C (15), $H_b$-C (22), $H_a$-C (1), H−C (9)), 1.48−1.35 (m, 3H, $H_b$-C (6), $H_2$−C (7)), 1.26−1.16 (m, 2H, $H_b$-C (19), $H_a$-C (21)), 1.14−1.05 (m, 1H, $H_b$-C (21)), 1.04−1.00 (m, 1H, $H_b$-C (1)), 1.00 (s, 3H, $H_3$−C (27)), 0.99 (s, 3H, $H_3$−C (23)), 0.91 (s, 3H, $H_3$−C (25)), 0.88 (s, 3H, $H_3$−C (29)), 0.87 (s, 3H, $H_3$−C (30)), 0.84 (s, 3H, $H_3$−C (26)), 0.79 (s, 3H, $H_3$−C (24)), 0.78−0.74 (m, 1H, H−C (5)).$^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 141.05 (C13), 119.63 (C12), 79.17 (C3), 61.15 (C16), 58.34 (C28), 55.60 (C5), 47.16 (C9), 42.67 (C18), 42.06 (C14), 39.57 (C8), 39.19 (C17), 38.93 (C4), 38.38 (C1), 37.48 (C10), 36.09 (C22), 34.65 (C19), 33.59 (C30), 33.43 (C15), 33.24 (C7), 31.91 (C21), 30.65 (C20), 28.18 (C23), 28.09 (C29), 27.33 (C2), 23.52 (C11), 23.21 (C27), 18.74 (C6), 16.58 (C26), 15.62 (C25 + C24).

**Synthesis of Azetidinium Picrate 18.** Picric acid (1.6 mg, 0.0068 mmol, 1 equiv) was added in one portion to a solution of azetidine **17** (3.0 mg, 0.0068 mmol, 1 equiv) in MeOH (0.5 mL). After 5 min, the solvent was evaporated to dryness under reduced pressure to yield pure product as a yellow amorphous solid (4.6 mg, 100%). Obtained solid was slowly recrystallized from MeOH to obtain the crystalline form of azetidinium picrate **18**.

*Azetidinium Picrate **18**.* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.09 (s, 1H, H−N), 8.97 (s, 2H, H−$C_{Ar}$), 8.23 (s, 1H, H−N), 5.55 (t, $^3J$ = 3.5 Hz, 1H, H−C (12)), 4.49−4.42 (m, 1H, H−C (16)), 3.98−3.87 (m, 2H, $H_2$−C (28)), 3.20 (dd, $^3J$ = 10.9, 4.6 Hz, 1H, H−C (3)), 2.66 (bs, 1H, H−C (18)), 2.10−1.97 (m, 3H, $H_a$-C (11), $H_a$-C (19), $H_a$-C (15)), 1.91−1.82 (m, 2H, $H_a$-C (21), $H_b$-C (11)), 1.79−1.71 (m, 2H, $H_b$-C (15), $H_b$-C (21)), 1.66−1.54 (m, 5H, $H_a$-C (6), $H_2$−C (2), $H_a$-C (1), H−C (9)), 1.40−1.17 (m, 5H, $H_b$-C (6), $H_2$−C (7), $H_b$-C (19), $H_a$-C (22)), 1.06−1.01 (m, 1H, $H_b$-C (22)), 0.99 (s, 6H, $H_3$−C (23), $H_3$−C (27)), 0.99−0.94 (m, 1H, $H_b$-C (1)), 0.90 (s, 3H, $H_3$−C (30)), 0.87 (s, 6H, $H_3$−C (29), $H_3$−C (25)), 0.78 (s, 3H, $H_3$−C (24)), 0.75−0.70 (m, 1H, H−C (5)), 0.62 (s, 3H, $H_3$−C (26)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 160.16 (C1′), 140.87 (C2′ + C6′), 137.63 (C13), 131.17 (C4′), 126.85 (C3′ + C5′), 121.91 (C12), 79.05 (C3), 64.89 (C16), 57.52 (C28), 55.50 (C5), 46.81 (C9), 42.38 (C14), 41.05 (C18), 39.16 (C8), 38.91 (C17), 38.83 (C4), 38.29 (C1), 37.42 (C10), 35.82 (C22), 33.92 (C19), 33.44 (C30), 33.09 (C7), 30.57 (C21), 30.43 (C20), 28.50 (C15), 28.16 (C23), 27.67 (C29), 27.21 (C2), 23.43 (C11), 22.79 (C27), 18.56 (C6), 16.30 (C26), 15.59 (C24 + C25).

**General Procedure V for C−H Deuteration Experiments.** A solution of picolinic amide (20 mg, 0.0366 mmol, 1 equiv), CsOAc (7 mg, 0.0366 mmol, 1 equiv) and $Pd(OAc)_2$ (3 mg, 0.0146 mmol, 0.4 equiv) in $CD_3COOD$ (1 mL) was stirred at 80 °C for 16h. Reaction mixture was concentrated in vacuo, and the obtained residue was purified by silica column chromatography (Hexanes-EtOAc 10:1 → 5:1) to yield the desired deuterated product as a white amorphous solid.

*(16S,22R)-2,2,16,22-Tetradeutero-3-oxo-17-quinolin-8-ylcarbamoyl-28-norlup-20(29)ene (**2a′**).* Yield 15 mg, 74%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}D_2N_2O_2 + H]^+$ 585.4353; found 585.4357. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.16 (s, 1H, H−N), 8.81 (dd, $^3J$ = 4.2 Hz, $^4J$ = 1.7 Hz, 1H, H−C(2′)), 8.77 (d, $^3J$ = 7.6 Hz, 1H, H−C(7′)), 8.16 (dd, $^3J$ = 8.2 Hz, $^4J$ = 1.8 Hz, 1H, H−C(4′)), 7.53 (dd, $^3J$ = 7.9, 7.6 Hz, 1H, H−C(6′)), 7.50−7.42 (m, 2H, H−C(5′), H−C(3′)), 4.80 (s, 1H, $H_a$-C (29)), 4.63 (s, 1H, $H_b$-C (29)), 3.27 (td, $^3J$ = 11.2, 4.6 Hz, 1H, H−C (19)), 2.73 (td, $^3J$ = 12.4, 3.5 Hz, 1H, H−C (13)), 2.05 (dt, $^2J$ = 13.9 Hz, $^3J$ = 11.2 Hz, 1H, $H_a$-C (21)), 1.89 (d, $^2J$ = 13.4 Hz, 1H, $H_a$-C (1)), 1.87−1.78 (m, 1H, $H_a$-C (12)), 1.75−1.68 (m, 5H, $H_3$−C (30), H−C (16), H−C (18)), 1.66−1.55 (m, 2H, $H_a$-C (15), H−C (22)), 1.54−1.21 (m, 11H, $H_2$−C (6), $H_2$−C (11), $H_b$-C (15), $H_b$-C (21), $H_2$−C (7), $H_b$-C (1), H−C (9), H−C (5)), 1.07−1.04 (m, 1H, $H_b$-C (12)), 1.04 (s, 3H, $H_3$−C (23)), 1.03 (s, 3H, $H_3$−C (27)), 0.99 (s, 3H, $H_3$−C (24)), 0.95 (s, 3H, $H_3$−C (26)), 0.90 (s, 3H, $H_3$−C (25)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 218.43 (C3), 175.24 (O═C-NH), 151.00 (C20), 148.29 (C2′), 138.78 (C8a′), 136.46 (C4′), 135.13 (C8′), 128.10 (C4a′), 127.60 (C6′), 121.67 (C3′), 121.02 (C5′), 116.15 (C7′), 109.65 (C29), 57.34 (C17), 55.19 (C5), 50.19 (C18 + C9), 47.46 (C4), 46.72 (C19), 42.77 (C14), 40.83 (C8), 39.66 (C1), 38.25 (t, $^1J$ = 19.3 Hz, C (22)), 37.84 (C13), 37.04 (C10), 33.86 (quint, $^1J$ = 18.2 Hz, (C2)), 33.78 (C7), 33.67 (t, $^1J$ = 17.9 Hz, (C16)), 30.91 (C21), 29.70 (C15), 26.65 (C23), 25.83 (C12), 21.63 (C11), 21.08 (C24), 19.74 (C30), 19.66 (C6), 16.10 (C27), 14.73 (C26 + C25).

*(16S)-2,2,16-Trideutero-3-oxo-17-quinolin-8-ylcarbamoyl-28-norolean-12(13)ene (**2c′**).* Yield 10 mg, 50%. HRMS (ESI): $m/z$ calc. for $[C_{39}H_{49}D_3N_2O_2 + H]^+$ 584.4290; found 584.4283. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.38 (s, 1H, H−N), 8.85 (d, $^3J$ = 7.4 Hz, 1H, H−C(7′)), 8.80 (dd, $^3J$ = 4.2 Hz, $^4J$ = 1.7 Hz, 1H, H−C(2′)), 8.15 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′)), 7.56−7.41 (m, 3H, H−C(6′), H−C(5′), H−C(3′)), 5.73 (t, $^3J$ = 3.7 Hz, 1H, H−C (12)), 3.00 (dd, $^3J$ = 13.1, 4.4 Hz, 1H, H−C (18)), 2.20−2.11 (m, 1H, H−C (16)), 2.01−1.93 (m, 2H, $H_2$−C (11)), 1.89−1.79 (m, 3H, $H_a$-C (21), $H_a$-C (1), $H_a$-C (19)), 1.78−1.69 (m, 1H, $H_a$-C (15)), 1.65 (t, $^3J$ = 8.8 Hz, 1H, H−C (9)), 1.49−1.23 (m, 10H, $H_2$−C (6), $H_2$−C (7), $H_2$−C (22), $H_b$-C (21), $H_b$-C (1), $H_b$-C (19), H−C (5)), 1.22 (s, 3H, $H_3$−C (27)), 1.14 (dd, $^2J$ = 12.5 Hz, $^3J$ = 7.9 Hz, 1H, $H_b$-C (15)), 1.04 (s, 3H, $H_3$−C (23), 0.98 (s, 3H, $H_3$−C (29)), 0.96 (s, 3H, $H_3$−C (30)), 0.95 (s, 3H, $H_3$−C (24)), 0.85 (s, 3H, $H_3$−C (26)), 0.54 (s, 3H, $H_3$−C (25)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 217.98 (C3), 177.10 (C28), 147.97 (C2′), 143.38 (C8a′), 139.16 (C13), 136.37 (C4′), 135.07 (C8′), 128.12 (C4a′), 127.70 (C6′), 124.01 (C12), 121.58 (C3′), 121.27 (C5′), 116.51 (C7′), 55.43 (C5), 48.27 (C17), 47.56 (C4), 47.04 (C9), 46.90 (C19), 42.41 (C18), 42.12 (C14), 39.57 (C8), 39.21 (C1), 36.75 (C10), 34.45 (C22), 33.70 (quint, $^1J$ = 18.0 Hz, (C2)), 33.24 (C21), 33.10 (C30), 32.10 (C7), 30.95 (C20), 27.72 (C15), 26.49 (C23), 26.01 (C27), 23.83 (C29), 23.75 (C11), 23.65 (t, $^1J$ = 17.1 Hz, (C16)), 21.47 (C24), 19.60 (C6), 16.36 (C26), 15.17 (C25).

*(16S)-2,2,16-Trideutero-3-oxo-17-quinolin-8-ylcarbamoyl-28-norurs-12 (13),21(22)diene (**2d′**).* Yield 4 mg, 20%. HRMS (ESI): $m/z$ calc. for $[C_{39}H_{47}D_3N_2O_2 + H]^+$ 582.4133; found 582.4135. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.40 (d, $^3J$ = 5.3 Hz, 1H, H−C(2′)), 8.90 (d, $^3J$ = 7.9 Hz, 1H, H−C(7′)), 8.34 (d, $^3J$ = 8.2 Hz, 1H, H−C(4′)), 7.54−7.48 (m, 2H, H−C(3′), H−C(6′)), 7.39 (d, $^3J$ = 7.9 Hz, 1H, H−C(5′)), 6.36 (dd, $^3J$ = 8.0, 2.2 Hz, 1H, H−C (21)), 5.92 (dd, $^3J$ = 8.0 Hz, $^4J$ = 1.9 Hz, 1H, H−C (22)), 5.36 (t, $^3J$ = 4.0 Hz, 1H, H−C


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ACS Omega XXXX, XXX, XXX−XXX

(12)), 2.87 (dd, $^2J$ = 13.7 Hz, $^3J$ = 10.5 Hz, 1H, $H_a$-C (15)), 2.40 (dddd, $^3J$ = 8.3, 7.1, 2.2 Hz, $^4J$ = 1.9 Hz, 1H, H−C (20)), 2.28 (d, $^3J$ = 11.4 Hz, 1H, H−C (18)), 2.09−2.02 (m, 1H, $H_a$-C (11)), 1.96−1.88 (m, 2H, $H_b$-C (11), $H_a$-C (1)), 1.77 (dd, $^3J$ = 10.5, 4.3 Hz, 1H, H−C (16)), 1.57−1.41 (m, 7H, $H_2$−C (6), $H_2$−C (7), $H_b$-C (1), H−C (19), H−C (9)), 1.38−1.34 (m, 1H, H−C (5)), 1.34 (d, $^3J$ = 7.1 Hz, 3H, $H_3$−C (30)), 1.16 (s, 3H, $H_3$−C (26)),1.11 −1.08 (m, 1H, $H_b$-C (15), 1.11 (s, 3H, $H_3$−C (23)), 1.10 (s, 3H, $H_3$−C (27)), 1.09 (s, 3H, $H_3$−C (25)), 1.07 (s, 3H, $H_3$−C (24)), 0.90 (d, $^3J$ = 6.5 Hz, 3H, $H_3$−C (29)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 219.33 (C3), 187.68 (C28), 148.41 (C2′), 148.08, (C8a′), 147.23 (C8), 140.01 (C4′), 136.98 (C13), 130.48 (C4a′), 129.95 (C6′), 127.22 (C12), 123.23 (C7′), 121.03 (C3′), 120.25 (C5′), 115.25 (C21), 104.92 (C22), 56.45 (C18), 55.60 (C5), 50.69 (C17), 47.55 (C4), 47.17 (C9), 42.26 (C14), 40.47 (C20), 40.15 (C8), 39.82 (C19), 39.56 (C1), 36.87 (C10), 33.63 (quint, $^1J$ = 18.0 Hz, (C2)), 33.16 (C7), 30.37 (t, $^1J$ = 15.6 Hz, (C16)), 26.85 (C23), 25.61 (C15), 23.94 (C11), 23.80 (C27), 21.60 (C24), 19.94 (C30), 19.78 (C6), 17.62 (C26), 17.05 (C25), 15.87 (C29).

*(16S,22R)-16,22-Dideutero-3β-hydroxy-28-picolinamido-lup-20(29)ene* (**19**). Yield 6 mg, 30%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{54}D_2N_2O_2 + H]^+$ 549.4384; found 549.4364. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′), 8.21 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.03 (t, $^3J$ = 6.5 Hz, 1H, H−N), 7.84 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′), 7.41 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 4.72 (d, $^4J$ = 2.3 Hz, 1H, $H_a$-C (29)), 4.60 (s, 1H, $H_b$-C (29)), 3.71 (dd, $^2J$ = 13.8 Hz, $^3J$ = 6.5 Hz, 1H, $H_a$-C (28)), 3.24 (dd, $^2J$ = 13.8 Hz, $^3J$ = 6.5 Hz, 1H, $H_b$-C (28)), 3.18 (dd, $^3J$ = 11.3, 4.8 Hz, 1H, H−C (3)), 2.55 (td, $^3J$ = 11.2, 5.6 Hz, 1H, H−C (19)), 2.12 (dt, $^2J$ = 13.0 Hz, 11.3 Hz, 1H, $H_a$-C (21)), 1.90 (dd, $^2J$ = 13.7 Hz, $^3J$ = 13.5 Hz, 1H, $H_a$-C (15)), 1.83 (td, $^3J$ = 12.0, 3.4 Hz, 1H, H−C (13)), 1.70 (s, 3H, $H_3$−C (30)), 1.69−1.47 (m, 5H, $H_a$-C (16), $H_a$-C (12), $H_2$−C (2), $H_a$-C (1)), 1.47−1.36 (m, 6H, $H_b$-C (6), $H_a$-C (11), $H_b$-C (21), $H_2$−C (7), H−C (18)), 1.34−1.22 (m, 3H, $H_b$-C (11), H−C (16), H−C (9)), 1.14−1.03 (m, 6H, $H_3$−C (26), $H_b$-C (12), $H_b$-C (15), H−C (22)), 0.99 (s, 3H, $H_3$−C (27)), 0.97 (s, 3H, $H_3$−C (23)), 0.93−0.86 (m, 1H, $H_b$-C (1)), 0.84 (s, 3H, $H_3$−C (25)), 0.76 (s, 3H, $H_3$−C (25)), 0.72−0.66 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.71 (N−C═O), 150.43 (C20), 150.17 (C2′), 148.14 (C6′), 137.51 (C4′), 126.17 (C5′), 122.37 (C3′), 109.92 (C29), 79.13 (C3), 55.47 (C5), 50.56 (C9), 49.17 (C18), 47.57 (C19), 47.18 (C17), 42.88 (C14), 41.08 (C8), 39.01 (C4), 38.86 (C1), 37.48 (C13), 37.43 (C28), 37.31 (C10), 35.91 (t, $^1J$ = 14.3 Hz, C22), 34.30 (C7), 30.20 (t, $^1J$ = 18.4 Hz, C16), 29.88 (C21), 28.13 (C23), 27.56 (C2), 27.32 (C15), 25.37 (C12), 20.98 (C11), 19.46 (C30), 18.43 (C6), 16.24 (C25), 16.20 (C26), 15.51 (C24), 14.96 (C27).

*(16S,22R)-12,16,22-Trideutero-3β-28-picolinamido-olean-12(13)-ene* (**20**). Yield 7 mg, 35%. HRMS (ESI): $m/z$ calc. for $[C_{36}H_{53}D_3N_2O_2 + H]^+$ 550.4446; found 550.4422. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (d, $^3J$ = 4.8 Hz, 1H, H−C(6′), 8.20 (d, $^3J$ = 7.8 Hz, 1H, H−C(3′)), 8.10 (dd, $^3J$ = 7.5, 5.6 Hz, 1H, H−N), 7.83 (td, $^3J$ = 7.8 Hz, $^4J$ = 1.7 Hz, 1H, H−C(4′), 7.41 (dd, $^3J$ = 7.8, 4.8 Hz, 1H, H−C(5′)), 3.74 (dd, $^2J$ = 13.7 Hz, $^3J$ = 7.5 Hz, 1H, $H_a$-C (28)), 3.22 (dd, $^3J$ = 10.9, 4.8 Hz, 1H, H−C (3)), 2.97 (dd, $^2J$ = 13.7 Hz, $^3J$ = 5.6 Hz, 1H, $H_b$-C (28)), 2.08 (dd, $^3J$ = 13.5, 4.5 Hz, 1H, H−C (18)), 2.00−1.83 (m, 4H, $H_2$−C (11), H−C (16), $H_a$-C (15)), 1.75 (dd, $^2J$ = 13.6 Hz, $^3J$ = 13.5 Hz, 1H, $H_a$-C (19)), 1.68−1.47 (m, 7H, $H_a$-C (6), $H_2$−C (2), $H_a$-C (7), H−C (22), $H_a$-C (1), H−C (9)), 1.46−1.36 (m, 2H, $H_b$-C (6), $H_b$-C (7)), 1.32−1.25 (m, 1H, $H_a$-C (21)), 1.22−1.18 (m, 1H, $H_b$-C (21)), 1.18 (s, 3H, $H_3$−C (27)), 1.14−1.09 (m, 1H, $H_b$-C (19)), 1.09 (s, 3H, $H_3$−C (26)), 1.04 −1.00 (m, 1H, $H_b$-C (15)), 0.99 (s, 3H, $H_3$−C (23)), 0.99−0.96 (m, 1H, $H_a$-C (1)), (s, 3H, $H_3$−C (25)), 0.89 (s, 3H, $H_3$−C (30)), 0.88 (s, 3H, $H_3$−C (29)), 0.79 (s, 3H, $H_3$−C (24)), 0.77−0.72 (m, 1H, H−C (5)). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.39 (C = O), 150.29 (C2′), 148.13 (C6′), 143.97 (C13), 137.46 (C4′), 126.09 (C5′), 122.81 (t, $^1J$ = 23.3 Hz, C12), 122.39 (C3′), 79.17 (C3), 55.35 (C5), 47.80 (C9), 47.41 (C28), 46.70 (C19), 44.67 (C18), 41.88 (C14), 40.04 (C8), 38.93 (C4), 38.78 (C1), 37.09 (C10), 36.83 (C17), 34.15 (C21), 33.34, (C30), 32.60 (C7), 31.69 (t, $^1J$ = 16.6 Hz, C22), 31.08 (C20), 28.24 (C13), 27.39 (C2), 26.24 (C27), 25.99 (C15), 23.77 (C11), 23.70 (C29), 22.14 (t, $^1J$ = 18.0 Hz, C16), 18.47 (C6), 16.86 (C26), 15.73 (C24), 15.67 (C25).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.5c01632.

Single crystal X-ray analysis data for compounds **3c** (CIF)

Single crystal X-ray analysis data for compounds **6a** (CIF)

Single crystal X-ray analysis data for compounds **6b** (CIF)

Single crystal X-ray analysis data for compounds **18** (CIF)

NMR spectral data for all compounds, description of deuteration experiments on compounds **2a, 2c, 2d** and description of radical trap experiments (PDF)

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### Notes

The authors declare no competing financial interest.

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Pielikums VI

Appendix VI

Kroškins, V., Lugiņina, J., Lācis, R., Mishnev, A., Turks, M.

# Site-selective C-H amination of lupane type triterpenoids

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# Site-Selective C—H Amination of Lupane-Type Triterpenoids

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A synthetic protocol for rhodium-catalyzed, site-selective C—H amination of the betulin scaffold has been developed. Under catalytic conditions, betulin-derived 28-*O*-sulfamate ester undergoes intramolecular C—H amination to afford 1,2,3-oxathiazinane-2,2-dione-fused lupane triterpenoids with a C16/C22 selectivity ratio 9:1. Introduction of a C16-substituent enables a second sequential C—H amination, which occurs with C22 selectivity. Betulin-derived oxathiazinanes can be cleaved and the ring-opened products provide straightforward access to 16-amino- and 16-azido-betulin, 16-amino-betulinic, and 16-amino-betulonic acids. Betulin analogs with selectively introduced amine and azide functionalities are versatile building blocks for further medicinal chemistry applications in semisynthetic triterpenoid series.

## 1. Introduction

Naturally occurring pentacyclic triterpenoids are significant secondary metabolites that possess wide range of biological activities.[1] Betulin is the lupane type pentacyclic triterpenoid, which is one of most abundant compound of this family, primarily common in birch bark.[2] Betulin and its derivatives show remarkable antitumor,[3,4] antidiabetic,[5–7] anti-inflammatory,[8–10] and antiviral properties.[11,12] The ability to derivatize readily available terpenoid feedstock using various synthetic approaches has led to development of novel semisynthetic triterpenoids. That, in turn, has influenced their medicinal chemistry applications during the past few decades.[13–15] The acquired knowledge has shown that medicinal applications of the majority of these complex molecules very often have been hindered by their poor water solubility.[16–18] Several research groups have contributed the efforts to overcome the low bioavailability of lipophilic triterpenoids by chemical modifications, creating different pentacyclic triterpenoid derivatives and prodrugs.[19] Successful examples of decoration of the lipophilic terpenoid skeleton with ionogenic groups have been reported, providing triterpenoid molecules with significantly enhanced water solubility.[20–22] The latter examples make the use of already existing functionalities at C3, C28, or C29.

Introduction of additional polar heteroatoms at the terpenoid core is another option to enhance aqueous solubility. However, the aliphatic structure of the terpenoid core makes it challenging. Several examples on introducing of polar HO-groups by C—H hydroxylation approach have been published.[23–28] Additionally, pentacyclic triterpenoids can undergo enzymatic C—H hydroxylation, catalyzed by cytochrome P-450.[29]

Enhanced aqueous solubility can also be reached by introduction of amino groups that shall be achievable by C—H amination. Amino groups offer both salt formation possibility and polar center for hydrogen bond formation, and therefore, are important structural elements in medicinal chemistry design.[30–32] Various protocols have been reported for selective transition-metal-catalyzed and photocatalytic C($sp^3$)—H bond amination during last few decades.[33–37] Several examples of C—N bond formation via intermolecular C($sp^3$)—H amination in terpene, steroid, and alkaloid molecules have been reported.[38–41] However, these approaches have not been reported on pentacyclic triterpenoids. To the best of our knowledge, there is only one example of lupane type triterpenoid intramolecular C—H amination by White's group, which involves manganese-catalyzed conversion of betulin 3-*O*-sulfamate ester into 1,2,3-oxathiazinane-2,2-dione by formation of C—N bond at C23.[42] In this context, more intriguing is the use of C28—OH group of betulin to tether the nitrene precursor in the proximity of C16 and C22 positions (**Figure 1**). Selective C—H amination of the latter will be an important synthetic tool in the advancement of medicinal chemistry of betulin and betulinic acid. Hence, we report here rhodium-catalyzed C16-selective C—H amination procedure with betulin 28-*O*-sulfamate ester and further transformation of the formed 1,2,3-oxathiazinane-2,2-dione intermediate, which provides a broad spectrum of betulin derivatives, containing previously unknown nitrogen substituent at C16.

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## 2. Results and Discussion

Starting materials bearing tethered nitrene precursor were prepared in a straightforward fashion from naturally occurring betulin (**1**). Its 3,28-di-*O*-acetylation followed by selective cleavage of primary acetate provided C28-alcohol **2**,[43] which was transformed into 28-*O*-sulfamate ester **3** using chlorosulfonyl isocyanate in the presence of formic acid.[44] Additionally, we have prepared 28-*O*-carbamoyl ester **4** to check the influence of the tether to the C—H amination step. With the starting materials

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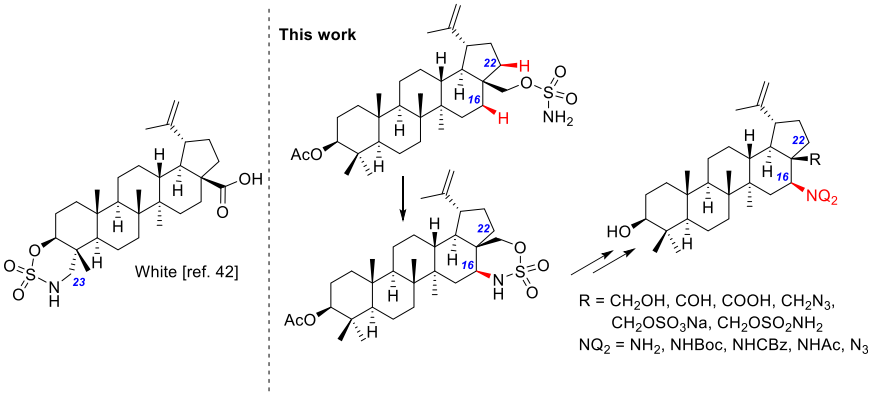
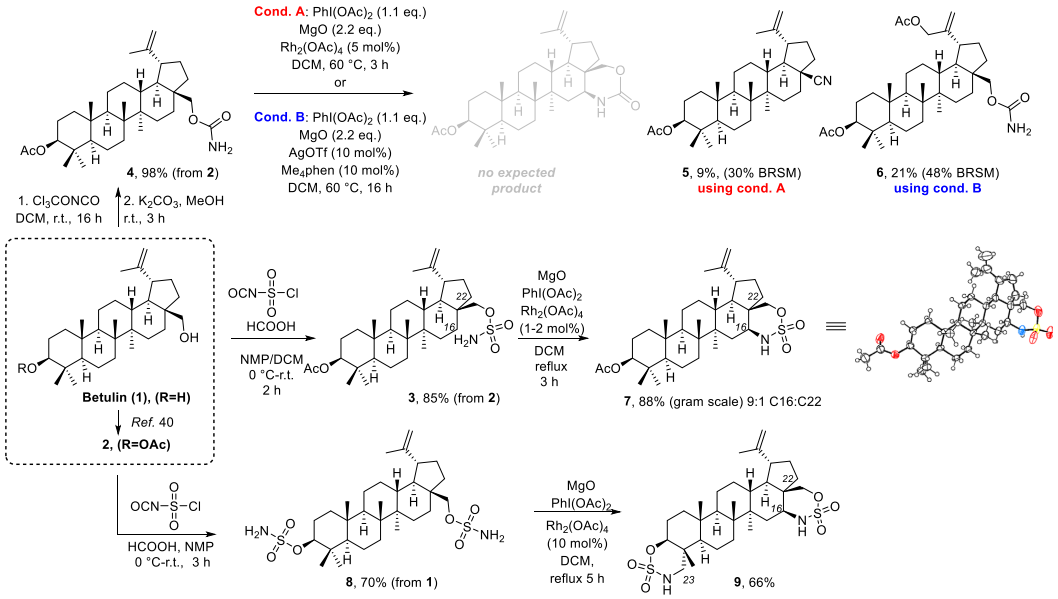



**Figure 1.** Previously known C—H amination in betulinic acid series and proposed C16—H amination with following derivatization. Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, and Ac = acetyl.

in hand, we proceeded to explore the C—H amination. We have found that carbamoyl ester **4** does not provide the expected amination products under Rh- and Ag-catalytic conditions. Instead, upon increased temperature (60 °C in pressure tube) and longer reaction time, formation of degradation products of the linker and C28 nitrile **5** was detected. Formation of the latter, can be explained by C—H amination reaction at C28, forming unstable 4 membered ring, which rapidly underwent decarboxylative oxidation by diacetoxy iodobenzene (PIDA) to yield the nitrile (**Scheme 1**).[45] Changing rhodium catalyst to different silver[46] sources (e.g., AgOTf, $AgPF_6$, or $AgSbF_6$) in the presence of previously used base and $PhI(OAc)_2$ or PhIO, resulted with no conversion of starting material or slow formation of degradation products. Addition of $Me_4$phen ligand promoted acetoxylation and C30 allyl acetate **6** was isolated as a main reaction product.

To our delight, sulfamate ester **3** gave full conversion of starting material after 3 h and two regioisomers in 9:1 ratio were obtained using the following reaction conditions: 2.2 equiv. MgO, 1.1 equiv. $PhI(OAc)_2$, and 1–2 mol% $Rh_2(OAc)_4$ (see Table S1, Supporting Information).[47] The structure of major isomer **7** was

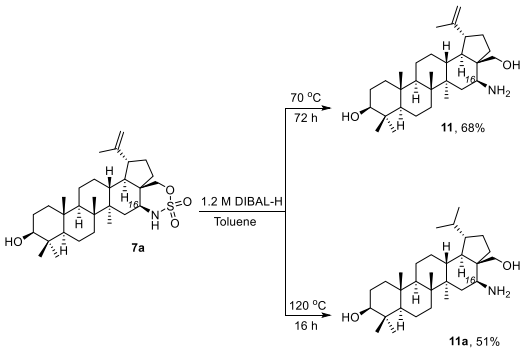



**Scheme 1.** C—H amination of betulin core and Oak Ridge Thermal-Ellipsoid Plot Program (ORTEP) representation of molecular structure **7**. NMP = *N*-methylpyrrolidone, DCM = dichloromethane, MeOH = methanol, AgOTf = silver trifluoromethanesulfonate, $Me_4$phen = 3,4,7,8-tetramethyl-1,10-phenanthroline, and BRSM = based on recovered starting material.

unambiguously determined by X-ray diffraction analysis.[48] The minor C22 isomer was isolated and characterized in its *N*-Cbz form (see Experimental Section). In a similar fashion, betulin 3,28-di-*O*-sulfamate ester **8** was prepared with 70% yield. The latter smoothly underwent double C—H amination using previous conditions to yield C23 and C16 aminated product **9** as the major isomer, albeit with a higher catalyst loading (Scheme 1). Regio- and diastereoselectivity of C—H activation most probably is determined by substrate control. The intermediate metallonitrene likely tends to insert into the equatorially aligned C—H bond of the D-ring of starting material **3**. This provides product **7** containing the newly formed cycle in low energy chair-like conformation.[49] The intrinsic properties of lupane core do not permit chair-like conformation of the newly formed cycle, if it is attached to the E-ring.

Next, we examined utility of the obtained 1,2,3-oxathiazinane-2,2-dione **7** in nucleophilic ring opening reactions to cleave the ring and liberate C16—$NH_2$ moiety. Several attempts for this transformation employing vigorous reaction conditions and different nucleophiles (e.g., $N_3^-$, $AcO^-$, $PhS^-$, morpholine, and water) did not provide any conversion of the starting material due to low electrophilicity of the oxathiazinane ring. Only basic hydrolysis using 0.5 M NaOH ethanolic solution led to nucleophilic attack at sulfur atom, yielding exclusively 1,3-aminosulfate **10**. Interestingly, subsequent acidification of sulfate salt **10** induced rapid ring closure back to oxathiazinane ring, giving to C3-hydroxy-oxathiazinane derivative **7a** (**Scheme 2**). Sulfate **10** undergoes selective precipitation from ethanolic solution, which results in improvement of the initial C16:C22 9:1 regioisomer ratio in compound **7** to 30:1 for compound **7a**. In-depth NMR structural elucidation of compounds from the filtrate after compound **10** precipitation has revealed that the minor C22-isomer of **7** did not undergo ring opening in the presence of 0.5 M NaOH ethanolic solution. Several strongly acidic and strongly basic hydrolytic conditions have been tried to cleave sulfate moiety from the intermediate **10**, but none of them has affected O—S bond.

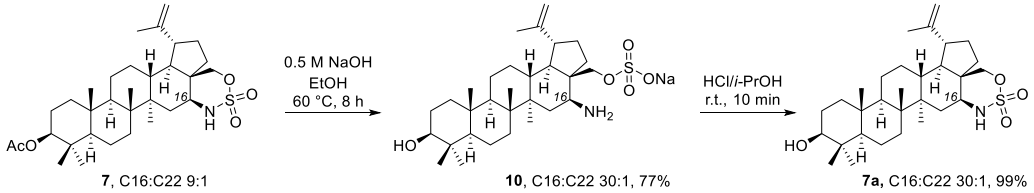
Finally, reductive cleavage conditions using diisobutylaluminium hydride (DIBAL-H) solution in toluene, were found to be useful to achieve formation of desired 1,3-amino alcohol motif **11** with 68% yield. In order to shorten reaction time, higher temperature was tried, which resulted in reduction of double bond as a side reaction to give product **11a** (**Scheme 3**). Also compound **7** provides amino diol **11** upon treatment with DIBAL-H, however, in that case, the initial C16:C22 ratio 9:1 is retained. Therefore, the described sequence **7** → **10** → **7a** → **11** (or **11a**) provides products **7a**, **11**, and **11a** with excellent regioisomeric purity.




**Scheme 3.** Reductive ring opening of 1,2,3-oxathiazinane-2,2-dione **7a**.

To increase electrophilicity of oxathiazinane ring, two different carbamoylations of the –NH moiety were accomplished. Then, the ring opening of *N*-Cbz oxathiazinane **12** with previously discussed nucleophiles resulted mostly with Cbz deprotection and the desired ring opening product was formed only in trace amounts. Thus, in the betulin-derived 1,2,3-oxathiazinane-2,2-dione competitive *N*-Cbz deprotection proceeds faster than nucleophile attack at sulfur center. It is interesting to note that in the case of iodide nucleophile, we have observed Cbz-group transformation of into *N*-benzyl group. It can be explained by in situ benzyl iodide formation from Cbz, which leads to the decarboxylation of the intermediate followed by *N*-benzylation. The structure of *N*-benzyl side product **13** was determined unambiguously by X-ray diffraction analysis[50] (**Scheme 4**).

Switching *N*-Cbz group to *N*-Boc group improved selectivity toward the formation of the desired 1,3-substituted product **15** in the case of azide nucleophile. Nevertheless, other nucleophilic reagents (e.g., NaI, acetate, thiophenolate, morholine, cyanide, thiocyanate, phenolate, and methoxide) still resulted in *N*-Boc group cleavage keeping the 1,2,3-oxathiazinane-2,2-dione ring intact. The poor reactivity of nucleophiles can be explained by C28 of betulin core being neopentyl position, which is sterically hindered by quaternary center at C17 atom.[51] Optimal conditions for synthesis of aminoazide **15** used 2 equivalents of $NaN_3$ at 80 °C in DMSO solution for 24 h. Next, the obtained azide **15** was employed in copper-catalyzed azide–alkyne 1,3-dipolar




**Scheme 2.** Synthesis of sulfate **10** and its cyclization to **7a** in acidic media. EtOH = ethanol and *i*-PrOH = isopropanol.

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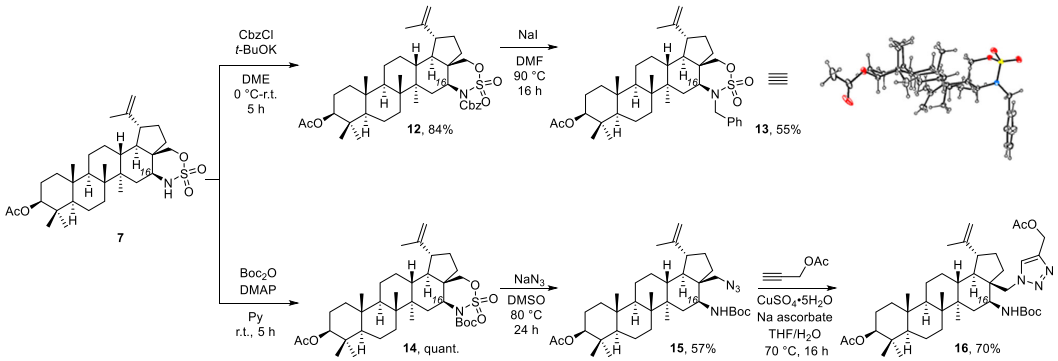
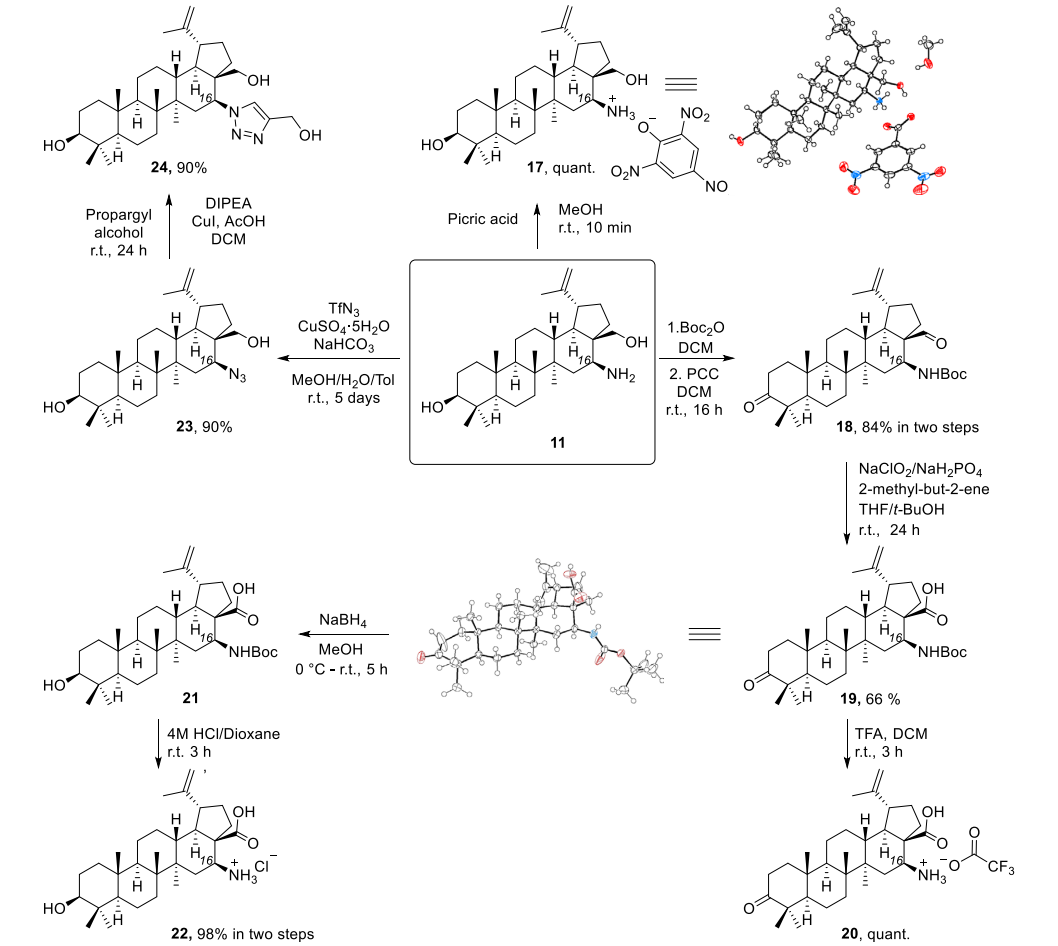
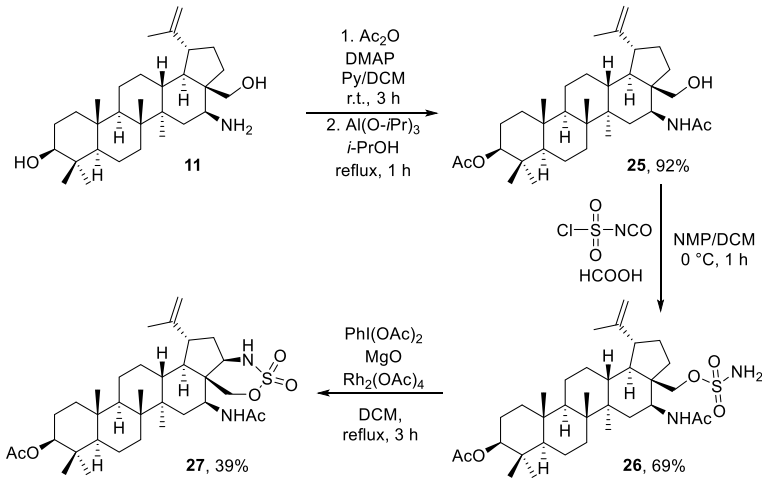



**Scheme 4.** Nucleophilic ring opening studies of *N*-protected oxathiazinanes **12** and **14**, and ORTEP representation of molecular structure **13**. *t*-BuOK = potassium *tert*-butoxide, DME = dimethoxyethane, Py = pyridine, DMF = *N, N*-dimethylformamide, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, and THF = tetrahydrofuran.




**Scheme 5.** Synthetic transformations of 1,3-aminoalcohol **11** and ORTEP representations of molecular structures **17** and **19**. DIPEA = *N,N*-diisopropylethylamine, Tol = toluene, PCC = pyridinium chlorochromate, *t*-BuOH = *tert*-butanol, and TFA = trifluoroacetic acid.




**Scheme 6.** Synthesis of sulfamate **26** and its application in C—H amination at C22.

cycloaddition reaction with propargylic acetate in the presence of $CuSO_4 \cdot 5H_2O$ to yield triazole **16** (Scheme 4).

Afterwards, we examined the synthetic utility of 1,3-aminoalcohol **11**. Reaction of the latter with picric acid afforded picrate salt **17**, the structure of which was proved by single-crystal X-ray analysis (**Scheme 5**).[52] *N*-Boc protection and the following two-step oxidation of **11** furnished *N*-Boc-$\beta$-amino-betulonic acid **19**. We have also tried to achieve the formation of corresponding acid in one-step process from the primary alcohol using PDC/DMF,[53] but optimal reaction conditions were not found. Thus, we turned to synthesis of intermediary aldehyde **18**, followed by Pinnick oxidation, which gave carboxylic acid **19**.[54,55] The latter can be diastereoselectively reduced at C3 to give *N*-Boc-$\beta$-amino-betulinic acid **21**. Treatment of both amino acids with TFA causes a facile Boc deprotection to give corresponding $\beta$-amino acids in their trifluoroacetate salt form. However, in the case of 3-OH derivative **21**, a formation of 3-*O*-trifluoroacetate side product was detected. Therefore, 4M HCl/dioxane was found to be more efficient for selective *N*-Boc deprotection to yield $\beta$-amino acid **22** in its hydrogen chloride salt form. Next, 16-azido-betulin **23** can be easily synthesized from the corresponding amine via diazotransfer reaction, employing trifluoromethanesulfonyl azide in the presence of copper (II) additive. With compound **23** in hand, copper(I)-catalyzed azide–alkyne cycloaddition furnished C16-triazolyl betulin **24** as a model compound for a virtually endless library of novel betulin–triazole conjugates (Scheme 5).

At this point of method development, we were intrigued whether it would be possible to introduce the second amino functionality at the triterpenoid core using the same sulfamate ester linker one more time. For that purpose, diacetate **25** was prepared via protection/deprotection sequence, and then, carefully treated with in situ prepared sulfamoyl chloride at 0 °C furnishing sulfamate ester **26**. The latter was subjected to previously used C—H amination conditions. The expected oxathiazinane **27** at betulin C22 was obtained with moderate yield (**Scheme 6**). It is expected that oxadiazinane cycle in compound **27** can be further transformed in a similar fashion to that of compound **7**, which opens further derivatization opportunities for betulin core.

## 3. Conclusion

We have developed synthetic approach toward previously unexplored site-selective C16—N bond formation at betulin D-ring via rhodium-catalyzed nitrene C—H insertion. The required sulfamate ester as strategic starting material was obtained from naturally available betulin in a few steps. C28-Position of betulin core bears neopentylic character, and thus, is both sterically hindered due to quaternary C17-atom and prone to cationic rearrangements in the presence of external nucleophiles. Nevertheless, the neopentylic nature of C28 within the oxathiazinane ring was overcome and several ring opening reactions were developed: 1) treatment with NaOH afforded aminosulfate salt; 2) treatment with $NaN_3$ afforded 1,3-aminoazide, which can be converted to betulin-derived $\gamma$-amino C28-triazoles; and 3) reductive ring opening gave access to 1,3-aminoalcohol, which was converted into 16-amino-betulinic and betulonic acids. Following another pathway, 16-amino-betulin can be transformed into 16-azido-betulin by the diazotransfer reaction. It was also demonstrated that once the C16-position of betulin is functionalized, the second nitrene C—H insertion is still possible and occurs at C22 position in the betulin E-ring. The developed methodology provides several novel functionalized derivatives of lupane type pentacyclic triterpenoids—16-amino-betulin, 16-azido-betulin, 16-amino-betulinic, and betulonic acids—that due to the presence of either amino or azido group in their structures constitute important starting materials for further derivatization in terms of medicinal chemistry. The possibility to attach the prospective substituents to the triterpenoid core

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by a virtually novel linker and at novel position will open new horizons for their biological activity evaluation.

## 4. Experimental Section

### General Information

Solvents for the reactions were dried over standard drying agents and freshly distilled prior to use. All purchased chemicals (Fluka, Aldrich) were used as received. All reactions were followed by thin-layer chromatography on E. Merck Kieselgel 60 $F_{254}$ and visualized by using UV lamp. Column chromatography was performed on silica gel (60 Å, 35–70 μm, Upasil). Flash column chromatography was performed on a Büchi Sepacore system (Büchi-Labortechnik GmbH, Essen, Germany) with a Büchi Control Unit C-620, an UV detector Büchi UV photometer C-635, Büchi fraction collector C-660, and two Pump Modules C-605. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 300 and 500 MHz in $CDCl_3$, [$D_6$]DMSO, or [$D_4$]MeOD at 25 °C. Chemical shifts (δ) values were reported in ppm. The residual solvent peaks were used as internal reference ($CDCl_3$) 7.26 ppm, [$D_6$]DMSO 2.50 ppm, [$D_4$]MeOD 3.31 ppm for $^1$H NMR, $CDCl_3$ 77.16 ppm, [$D_6$] DMSO 39.52 ppm, [$D_4$]MeOD 49.00 ppm for $^{13}$C NMR, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and *J* in hertz. High-resolution mass spectra (electrospray ionization) were performed on Agilent 1290 Infinity series UPLC connected to Agilent 6230 TOF mass spectrometer (calibration at *m/z* 121.050873 and *m/z* 922.009798). Fourier transform infrared (FT-IR, Nicolet iS50) spectra were recorded in the attenuated total reflectance mode. Spectra were obtained at 4 $cm^{-1}$ resolution coadding 64 scans over a range of wavenumbers from 400 to 4000 $cm^{-1}$. Before every sample measurement, a background spectrum was taken (64 scans) and deducted from the sample spectrum.

### 28-Sulfamoyloxy-Lup-20(29)ene-3β-yl Acetate 3

Formic acid (247 mg, 5.36 mmol, 1.3 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (759 mg, 5.36 mmol, 1.3 equiv.) at 0 °C. After solidification of the reaction mixture, anh. DCM (15 mL) was added dropwise at 0 °C and the obtained solution was warmed up to room temperature and stirred for 12 h. Freshly prepared solution of sulfamoyl chloride was added dropwise to a solution of 3-*O*-acetyl betulin **2** (2000 mg, 4.12 mmol, 1.0 equiv.) in anh. NMP (13 mL) at 0 °C. The resulting mixture was warmed up to room temperature, stirred for 2 h, and quenched with water (10 mL). Then EtOAc (100 mL) was added, and the organic layer was subsequently washed with water (5 × 10 mL), saturated aq. $NH_4Cl$ (5 × 10 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:1) to yield sulfamate ester **3** as a white amorphous solid (1980 mg, 85%).

### 28-Carbamoyloxy-Lup-20(29)ene-3β-yl Acetate 4

To a solution of alcohol **2** (1000 mg, 2.06 mmol, 1 equiv.) in anh. DCM (20 mL), trichloroacetyl isocyanate (427 mg, 2.27 mmol, 1.1 equiv.) was added dropwise at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 16 h. Solvent was evaporated under reduced pressure and the solid residue was redissolved in MeOH (15 mL), and solid $K_2CO_3$ (28 mg, 0.206 mmol, 0.1 equiv.) was added. The resulting mixture was stirred for 3 h, then DCM (50 mL) was added, and the organic layer was subsequently washed with saturated aq. $NH_4Cl$ (3 × 15 mL), 1% NaOH aq. (3 × 15 mL), and brine (1 × 15 mL) and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo to yield product **4** as an amorphous solid, which was further used without additional purification (1.06 g, 98%).

### (17S)-17-Cyano-28-Norlup-20(29)ene-3β-yl Acetate 5

Suspension of compound **4** (100 mg, 0.189 mmol, 1.0 equiv.), MgO (18 mg, 0.435 mmol, 2.3 equiv.), $PhI(OAc)_2$ (86 mg, 0.265 mmol, 1.4 equiv.), and $Rh_2(OAc)_4$ (8 mg, 0.019 mmol, 0.1 equiv.) in anh. DCM (2 mL) was heated at 60 °C for 3 h in a pressure flask. The resulting suspension was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes-EtOAc 9:1 → 1:1) to yield the unreacted starting material **4** (71 mg) and product **5** as white amorphous solid (8 mg, 9% or 30% based on the recovered starting material). $^1$H and $^{13}$C NMR spectra of product **5** are matching those reported in literature.[56]

### 28-Carbamoyloxy-30-Acetoxy-Lup-20(29)ene-3β-yl Acetate 6

Suspension of compound **4** (100 mg, 0.189 mmol, 1.0 equiv.), MgO (30 mg, 0.435 mmol, 4 equiv.), $PhI(OAc)_2$ (122 mg, 0.265 mmol, 2.0 equiv.), AgOTf (5 mg, 0.019 mmol, 0.1 equiv.), and 3,4,7,8-tetramethyl-1,10-phenanthroline (5 mg, 0.019 mmol, 0.1 equiv.) in anh. DCM (2 mL) was heated at 60 °C for 16 h in a pressure flask. The resulting suspension was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:1) to yield the unreacted starting material **4** (57 mg) and product **6** as white amorphous solid (23 mg, 21% or 48% based on the recovered starting material).

### Oxathiazinane 7

Suspension containing compound **3** (6.15 g, 10.90 mmol, 1.0 equiv.), MgO (1.00 g, 25.07 mmol, 2.3 equiv.), $PhI(OAc)_2$ (3.98 g,12.00 mmol, 1.1 equiv.), and $Rh_2(OAc)_4$ (96 mg, 0.218 mmol, 0.02 equiv.) in DCM (65 mL) was heated at 40 °C for 3 h. The resulting suspension was filtered through the celite pad. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:1) to yield the desired product **7** as white amorphous solid (5.34 g, 88%) with regioisomer C16:C22 ratio 9:1. The reaction proceeds with the same yield also with 1 mol-% of $Rh_2(OAc)_4$ catalyst, which was practically verified on 2.5 gram scale.

### Lup-20(29)ene-3β,28-Diyl Disulfamate 8

Formic acid (415 mg, 9 mmol, 4 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (1274 mg, 9 mmol, 4 equiv.) at 0 °C. After solidification of the reaction mixture, anh. DCM (6 mL) was added dropwise at 0 °C and the obtained solution was warmed up to room temperature and stirred for 12 h. Freshly prepared solution of sulfamoyl chloride was added dropwise to a suspension of betulin (1000 mg, 2.25 mmol,1.0 equiv.) in anh. NMP (8 mL) at 0 °C. The resulting mixture was warmed up to room temperature, stirred for 3 h, and quenched with water (10 mL). Then EtOAc (60 mL) was added and the organic layer was subsequently washed with water (5 × 10 mL), saturated aq. $NH_4Cl$ (5 × 10 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:1) to yield bis-sulfamate ester **8** as white amorphous solid (950 mg, 70%).

### Bis-Oxathiazinane 9

Suspension containing compound **8** (676 mg, 1.13 mmol, 1.0 equiv.), MgO (271 mg, 6.78 mmol, 6.0 equiv.), $PhI(OAc)_2$ (825 mg, 2.49 mmol, 2.2 equiv.). and $Rh_2(OAc)_4$ (50 mg, 0.113 mmol, 0.1 equiv.) in DCM (10 mL) was heated at 40 °C for 5 h. The resulting suspension was filtered through a celite pad. The filtrate was concentrated

in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:2) to yield desired product **9** as white amorphous solid (443 mg, 66%).

### Sodium (16S)-3β-Hydroxy-16-Amino-Lup-20(29)en-28-yl Sulfate 10

Oxathiazinane **7** (1000 mg, 1.78 mmol, 1 equiv., with regioisomer ratio C16:C22 = 9:1) in 0.5 M NaOH ethanolic solution (14 mL) was heated at 60 °C for 8 h. The obtained suspension was cooled down to room temperature and filtered. The precipitate was washed on the filter with EtOH (3 × 4 mL) and dried at 70 °C for 24 h to give product **10** as a white amorphous solid (769 mg, 77%) with improved C16:C22 ratio 30:1.

### Oxathiazinane 7a

Sulfate **10** (769 mg, 1.37 mmol, 1 equiv.) was suspended in EtOAc (30 mL) and 1M HCl aq. was added. The obtained biphasic mixture was stirred for 10 min, and then, the organic layer was separated and subsequently washed with water (3 × 20 mL) and brine (1 × 20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo to give **7a** as a white amorphous solid (710 mg, 99%, with C16:C22 ratio 30:1).

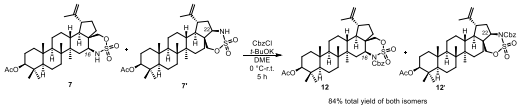
### (16S)-16-Amino-Lup-20(29)en-3β,28-Diol 11

Compound **7a** (1000 mg, 1.92 mmol) was slowly dissolved in 1.2 M DIBAL-H solution in toluene (15 mL) at 0 °C. Then the reaction mixture was stirred for 72 h at 70 °C. Then, the reaction mixture was cooled to 0 °C and subsequently MeOH (3 mL) and water (1 mL) were added dropwise. Next, MeOH (15 mL) was added and the obtained mixture was vigorously stirred and let to reach room temperature. Finally, additional water (5 mL) was added and the obtained suspension was evaporated to dryness. The residue was directly subjected to silica gel column chromatography (dry loading, DCM–MeOH 100:0 → 90:10) to yield product **11** as white amorphous solid (599 mg, 68%).

### (16S)-16-Amino-Lupan-3β,28-Diol 11a

Compound **7a** (1000 mg, 1.92 mmol) was slowly dissolved in 1.2 M DIBAL-H solution in toluene (15 mL) at 0 °C. Then the reaction mixture was stirred for 16 h at 120 °C. Then, the reaction mixture was cooled to 0 °C and subsequently MeOH (3 mL) and water (1 mL) were added dropwise. Next, MeOH (15 mL) was added and the obtained mixture was vigorously stirred and let to reach room temperature. Finally, additional water (5 mL) was added and the obtained suspension was evaporated to dryness. The residue was directly subjected to silica gel column chromatography (dry loading, DCM–MeOH 100:0 → 85:15) to yield product **11a** as white amorphous solid (449 mg, 51%).

### Synthesis of N-Cbz Oxathiazinanes 12 and 12′




To solution of **7** + **7′** (543 mg, 0.97 mmol, 1 equiv.; C16:C22 ratio = mixture of isomers **7**:**7′** = 9:1) in DME (11 mL), *t*-BuOK (120 mg, 1.07 mmol, 1.1 equiv.) was added portionwise, followed by dropwise addition of benzyl chloroformate (418 mg, 2.44 mmol. 2.5 equiv.) at 0 °C. The resulting suspension was warmed up to room temperature and stirred for 5 h. Then water (20 mL) was added and the resulting reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL) and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 2:1) to yield a 9:1 mixture of regioisomeric products **12** and **12′** as white amorphous solid (565 mg, total yield 84%). $R_f = 0.37$ (EtOAc/Hexanes 1:5). Minor isomer **12′** was isolated with preparative high-performance liquid chromatography on C18 reverse phase column by gradient A/B (50/50) → A/B (0/100)*. *A: 95 parts of 0.1% aqueous solution of trifluoroacetic acid and 5 parts of acetonitrile and B: acetonitrile.

### N-Benzyl Oxathiazinane 13

A solution of compound **12** (100 mg, 0.14 mmol, 1 equiv.) and NaI (108 mg, 0.70 mmol, 5 equiv.) in anh. DMF (1.4 mL) was heated at 90 °C for 16 h. EtOAc (20 mL) was added and the resulting solution was subsequently washed with water (3 × 20 mL), saturated $NH_4Cl$ aq. (3 × 20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 8:1) to yield product **13** as white amorphous solid (51 mg, 55%).

### N-Boc Oxathiazinane 14

A solution of compound **7** (1000 mg, 1.78 mmol, 1 equiv.), $Boc_2O$ (1050 mg, 4.82 mmol. 2.7 equiv.), and DMAP (25 g, 0.20 mmol, 0.12 equiv.) in pyridine (13 mL) was stirred at room temperature for 5 h. Then, 0.01 M HCl aq. (50 mL) was slowly added, while vigorously stirring the reaction mixture at 0 °C. The obtained suspension was extracted with EtOAc (3 × 30 mL) and the combined organic layers were subsequently washed with 1M HCl aq. (3 × 30 mL), brine (2 × 20 mL), dried over anhydrous $Na_2SO_4$, and filtered. The filtrate was concentrated in vacuo to yield product **14** as a white amorphous solid, which was used further without additional purification (1.18 g, quant. yield).

### (16S)-28-Azido-16-(Tert-Butoxycarbonyl)Amino-Lup-20(29) en-3β-yl Acetate 15

A solution of compound **14** (50 mg, 0.09 mmol, 1 equiv.) and $NaN_3$ (10 mg, 0.15 mmol, 1.67 equiv.) in anh. DMSO (0.6 mL) was heated at 80 °C for 24 h. Then, EtOAc (20 mL) was added and the organic layer was subsequently washed with saturated $NH_4Cl$ aq. (3 × 20 mL) and brine (20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 8:1) to yield product **15** as white amorphous solid (27 mg, 57%).

### Betulin Triazole Conjugate 16

To a solution of azide **15** (46 mg, 0.07 mmol, 1 equiv.) and propargyl acetate (9 mg, 0.09 mmol, 1.3 equiv.) in THF (0.7 mL), a solution of sodium ascorbate (3 mg, 0.015 mmol, 0.2 equiv.) in THF (0.7 mL) was added followed by addition of $CuSO_4{\cdot}5H_2O$ (2 mg, 0.013 mmol, 0.17 equiv.) solution in water (0.7 mL). The resulting mixture was stirred at 70 °C for 16 h. Water 10 (mL) was added, and the reaction mixture was extracted with DCM (3 × 15 mL). The combined organic layers were subsequently washed with 5% NaSH aq. (2 × 25 mL), brine (1 × 20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 8:1) to yield product **16** as white amorphous solid (37 mg, 70%).

### (16S)-3β,28-Dihydroxy-Lup-20(29)en-16-Aminium Picrate 17

A solution of compound **11** (20 mg, 0.044 mmol, 1 equiv.) and picric acid (10 mg, 0.044 mmol, 1 equiv.) in MeOH (0.5 mL) was stirred for

10 min at room temperature. Then, the solvent was evaporated in vacuo to give **17** as an off-white to yellowish amorphous solid (30 mg, quant.).

### (16S)-3-Oxo-16-(Tert-Butoxycarbonyl)Amino-Lup-20(29) en-28-al 18

A solution of $Boc_2O$ (22 mg, 0.12 mmol, 1.1 equiv.) in DCM (0.5 mL) was added dropwise to a solution of compound **11** (50 mg, 0.11 mmol, 1 equiv.) and $Et_3N$ (10 mg, 0.12 mmol, 1.1 equiv.) in DCM (0.5 mL) at room temperature, and the resulting solution was stirred for 1 h. Then, the reaction mixture was diluted with DCM (20 mL) and subsequently washed with water (20 mL) and brine (20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo to yield Boc-protected amine as a white amorphous solid (60 mg, 99%). The latter was redissolved in DCM (1 mL) and PCC (70 mg, 0.33 mmol, 3 equiv.) was added to this solution portionwise at room temperature. The resulting suspension was stirred for 16 h at room temperature, then, the reaction mixture was filtered through a pad of silica gel. The filtrate was evaporated to dryness and the residue was purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 8:1) to yield product **18** as white amorphous solid (50 mg, 84%).

### (16S)-3-Oxo-16-(Tert-Butoxycarbonyl)Amino-Lup-20(29) en-28-oic Acid 19

To a solution of aldehyde **18** (100 mg, 0.18 mmol, 1 equiv.) and 2-metylbut-2-ene (176 mg, 2.52 mmol, 14 equiv.) in 1:1 THF/*t*-BuOH (8 mL), a solution of $NaClO_2$ (131 mg, 1.44 mmol, 8 equiv.) and $NaH_2PO_4$ (196 mg, 1.26 mmol, 7 equiv.) in water (3 mL) was added at room temperature, and the resulting solution was stirred for 24 h. Then the reaction mixture was evaporated to dryness and purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 2:1) to afford product **19** (67 mg, 66%) as white amorphous solid.

### (16R,17R)-3-Oxo-17-Carboxy-28-Norlup-20(29)-en-16-Aminium Trifluoroacetate 20

A solution of **19** (15.0 mg, 0.026 mmol, 1 equiv.) in 1:1 TFA/DCM (1 mL) was stirred for 3 h at room temperature, and then, evaporated to dryness to yield product **20** (12.4 mg, quant. yield) as a white amorphous solid.

### (16R,17R)-3β-Hydroxy-17-Carboxy-28-Norlup-20(29)-en-16-Aminium Chloride 22

To a solution of **19** (79 mg, 0.14 mmol, 1 eq.) in MeOH (1 mL), solid $NaBH_4$ (21 mg, 0.56 mmol, 4 eq.) was added portionwise at 0 °C, and the reaction mixture was stirred at ambient temperature for 5 h. The resulting reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (1 mL) and evaporated to dryness. The obtained residue was dissolved in EtOAc (20 mL) and washed with water (10 mL) and brine (10 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo to yield *N*-Boc amino-betulinic acid, which was directly dissolved in 4M HCl/Dioxane (3 mL), stirred for 3 h at room temperature, and evaporated to dryness to yield salt **22** (64 mg, 99%) as a white amorphous solid.

### (16S)-16-Azido-Lup-20(29)en-3β,28-Diol 2

Solid $NaHCO_3$ (405 mg, 4.82 mmol, 8 equiv.) was added to a solution of compound **11** (276 mg, 0.60 mmol, 1 equiv.) and $TfN_3$ (1309 mg, 7.48 mmol, 12.4 equiv.) in MeOH (30 mL), and water (5 mL). Then, solid $CuSO_4{\cdot}5H_2O$ (15 mg, 0.06 mmol, 10 mol%) was added at room temperature. The resulting mixture was stirred for 5 days at room temperature. Then, it was diluted with water (30 mL) and extracted with DCM (4 × 30 mL). The combined organic layers were subsequently washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography. (Hexanes–EtOAc 9:1 → 1:5) to afford product **23** (264 mg, 90%) as a white amorphous solid.

### Betulin Triazole Conjugate 24

A suspension of compound **23** (82 mg, 0.17 mmol, 1 equiv.), propargyl alcohol (13 mg, 0.24 mmol, 1.4 equiv.), DIPEA (22 mg, 0.17 mmol, 1.0 equiv.), acetic acid (10 mg, 0.17 mmol, 1.0 equiv.), and CuI (6 mg, 0.03 mmol, 0.2 equiv.) in DCM (3 mL) was protected from light and stirred for 24 h at room temperature. Then the reaction mixture was diluted with EtOAc (25 mL) and subsequently washed with water (2 × 20 mL) and brine (2 × 20 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and purified by silica gel column chromatography (DCM–MeOH 99:1 → 90:10) to yield triazole **24** as white amorphous solid (82 mg, 90%).

### (16S)-16-Acetamido-28-Hydroxy-Lup-20(29)en-3β-yl Acetate 25

Acetic anhydride (734 mg, 7.2 mmol, 6 equiv.) was added dropwise at 0 °C to a solution of compound **11** (550 mg, 1.20 mmol, 1 equiv.), DMAP (15 mg, 0.12 mmol. 0.1 equiv.), and pyridine (567 mg, 7.2 mmol, 6 equiv.) in DCM (7 mL). The resulting reaction mixture was warmed up to room temperature and stirred for 3 h. Then, the reaction mixture was diluted with DCM (30 mL) and subsequently washed with 1 M HCl aq. (3 × 20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), water (20 mL), and brine (1 × 20 mL). Then it was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to yield crude triacetate. The latter was directly dissolved in anh. *i*-PrOH (17 mL) and solid aluminum isopropoxide was added (520 mg, 2.55, mmol, 2.1 equiv.). The resulting suspension was heated to 120 °C and stirred for 1 h. Then, the reaction mixture was cooled to room temperature and evaporated to dryness. The residue was redissolved in DCM (20 mL). Next, water (3 mL) was added and the resulting suspension was stirred for additional 10 min. The obtained precipitate was filtered, washed with DCM (3 × 10 mL), and the filtrate was concentrated in vacuo to give compound **25** (600 mg, 92%) as a white amorphous solid, which was used further without additional purification.

### (16S)-16-Acetamido-28-Sulfamoyloxy-Lup-20(29)en-3β-yl Acetate 26

Formic acid (11 mg, 0.23 mmol, 1.3 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (33 mg, 0.23 mmol, 1.3 equiv.) at 0 °C. After solidification of reaction mixture, anh. DCM (1 mL) was added dropwise at 0 °C and the obtained solution was warmed up to room temperature and stirred for 12 h. Freshly prepared solution of sulfamoyl chloride was added dropwise to a solution of compound **25** (100 mg, 0.18 mmol, 1 equiv.) in anh. NMP (1 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 1 h. Then, the reaction mixture was quenched with water (5 mL) and EtOAc (20 mL) was added. Organic layer was subsequently washed with water (5 × 10 mL) and saturated aqueous $NH_4Cl$ solution (5 × 10 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (Hexanes–EtOAc 9:1 → 1:1) to yield sulfamate ester **26** as white amorphous solid (79 mg, 69%).

**Synthesis of Oxathiazinane 27**

A suspension of compound **26** (175 mg, 0.28 mmol, 1.0 equiv.), MgO (26 mg, 0.65 mmol, 2.3 equiv.), $PhI(OAc)_2$ (103 mg, 0.31 mmol, 1.2 equiv.), and $Rh_2(OAc)_4$ (6 mg, 0.014 mmol, 0.05 equiv.) in DCM (3 mL) was heated at 40 °C for 3 h. The resulting suspension was filtered through a celite pad and the filtrate was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (Hexanes–EtOAc 3:1 → 0:1) to yield product **27** as white amorphous solid (68 mg, 39%).

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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**Vladislavs Kroškins** dzimis 1996. gadā Gusj Hrustalnijā, Krievijā. Rīgas Tehniskajā universitātē (RTU) ieguvis bakalaura (2019) un maģistra (2021) grādu ķīmijas tehnoloģijā. Patlaban ir RTU Dabaszinātņu un tehnoloģiju fakultātes Ķīmijas un ķīmijas tehnoloģijas institūta pētnieks. Zinātniskās intereses saistītas ar jaunu bioloģiski aktīvu dabasvielu atvasinājumu sintēzi, kā arī procesu ķīmiju un patentbrīvu farmaceitisko preparātu sintēzes metožu izstrādi.

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