RĪGAS TEHNISKĀ UNIVERSITĀTE

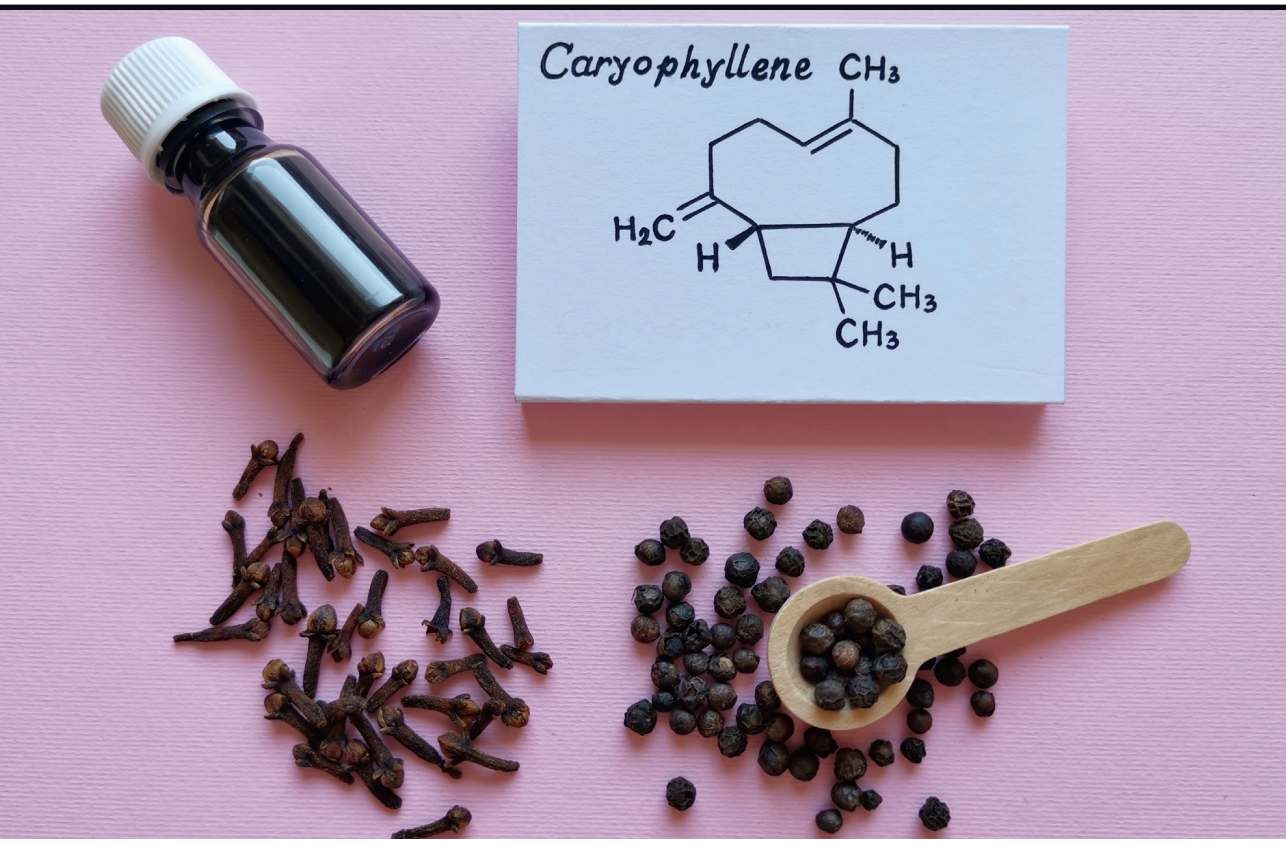
Georgijs Stakanovs

EKSOTISKU TERPENOĪDU SINTĒZE NO (–)-β-KARIOFILĒNA

Promocijas darbs

SEMISYNTHESIS OF EXOTIC TERPENOIDS FROM (–)-β-CARYOPHYLLENE

Doctoral Thesis



RTU Izdevniecība
RTU Press
Rīga 2024

RĪGAS TEHNISKĀ UNIVERSITĀTE
Dabaszinātņu un tehnoloģiju fakultāte
Ķīmijas un ķīmijas tehnoloģijas institūts

RIGA TECHNICAL UNIVERSITY
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Zinātniskie vadītāji
Scientific supervisors

Profesors / Professor *Dr. chem.* AIGARS JIRGENSONS
Dr. chem. DACE RASIŅA

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Stakanovs G. Eksotisku terpenoīdu sintēze no
(–)-β-kariofilēna.
Promocijas darbs.
Rīga.: RTU Izdevniecība, 2024. – 89 lpp.

Stakanovs G. Semisynthesis of exotic terpenoids from
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Doctoral Thesis.
Riga.: RTU Press, 2024. – 89 p.

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PROMOCIJAS DARBS IZVIRZĪTS ZINĀTNES DOKTORA GRĀDA IEGŪŠANAI RĪGAS TEHNISKĀJĀ UNIVERSITĀTĒ

Promocijas darbs zinātnes doktora (*Ph. D.*) grāda iegūšanai tiek publiski aizstāvēts 2024. gada 12. decembrī Rīgas Tehniskās universitātes Dabaszinātņu un tehnoloģiju fakultātē, Rīgā, Paula Valdena ielā 3, 272. auditorijā.

OFICIĀLIE RECENZENTI

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Tallinas Tehnoloģiju universitāte, Igaunija

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Georgijs Stakanovs ……. (paraksts)

Datums …….

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa. Tas ietver kopsavilkumu un četras publikācijas. Publikācijas uzrakstītas angļu valodā, to kopējais apjoms, ieskaitot elektroniski pieejamo informāciju, ir 466 lpp.

SATURS/CONTENTS

SAĪSINĀJUMI/ABBREVIATIONS AND ACRONYMS

Ac	acetil-/acetyl
acac	acetilacetonāts/acetylacetonate
brsm	rēķinot pēc atgūtās izejvielas daudzuma/based on recovered starting material
*n*Bu	*n*-butil-/*n*-butyl
*t*Bu	*terc*-butil-/*tert*-butyl
CSA	10-kamparsulfonskābe/10-camphorsulfonic acid
DBU	1,8-diazabiciklo[5.4.0]undec-7-ēns/1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dihloretāns/1,2-dichloroethane
DFT	blīvuma funkcionāļa teorija/density functional theory
DMAP	4-(*N*,*N*-dimetilamino)piridīns/4-(*N*,*N*-dimethylamino)pyridine
DMEDA	*N*,*N'*-dimetiletān-1,2-diamīns/*N*,*N'*-dimethylethane-1,2-diamine
DMF	*N*,*N*-dimetilformamīds/*N*,*N*-dimethylformamide
dr	diastereomēru attiecība/diastereomeric ratio
DMSO	dimetilsulfoksīds/dimethyl sulfoxide
EDCI	1-etil-3-(3-(*N*,*N*-dimetilamino)propil)karbodiimīds/1-ethyl-3-(3-(*N*,*N*-dimethylamino)propyl)carbodiimide
EDTA	etilēndiamīntetraacetāts/ethylenediaminetetraacetate
Et	etil-/ethyl
HFIP	1,1,1,3,3,3-heksafluorpropān-2-ols/1,1,1,3,3,3-hexafluoropropan-2-ol
HOBT	1*H*-1,2,3-benzotriazol-1-ols/1*H*-1,2,3-benzotriazol-1-ol
iPr	izopropil-/isopropyl
i.t.	istabas temperatūra
KMR	kodolu magnetiskā rezonanse
LC/MS	šķidruma hromatogrāfija-masspektrometrija/liquid chromatography-masspectrometry
LDA	litija diizopropilamīds/lithium diisopropylamide
*m*CPBA	3-hlorperoksibenzoskābe/3-chloroperoxybenzoic acid
Me	metil-/methyl
Ms	mezil- (metānsulfonil-)/mesyl (methanesulfonyl)
NCS	*N*-hlorsukcinimīds/*N*-chlorosuccinimide
NMO	*N*-metilmorfolīna *N*-oksīds/*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ORTEP	*Oak Ridge Thermal Ellipsoid Plot*
Ph	fenil-/phenyl
PPTS	piridīnija 4-toluolsulfonāts/pyridinium 4-toluenesulfonate
rt	room temperature
TBAF	tetra-*n*-butilamonija fluorīds/tetra-*n*-butylammonium fluoride
TBS	*terc*-butildimetilsilil-/*tert*-butyldimethylsilyl
TCCA	trihlorizocianūrskābe/trichloroisocyanuric acid
TEMPO	(2,2,6,6-tetrametilpiperidīn-1-il)oksilradikālis/(2,2,6,6-tetramethylpiperidin-1-yl)oxyl free radical
TES	trietilsilil-/triethylsilyl
Tf	triflil- (trifluormetānsulfonil-)/triflyl (trifluoromethanesulfonyl)
TFA	trifluoretiķskābe/trifluoroacetic acid
THF	tetrahidrofurāns/tetrahydrofuran
Ts	tozil- (4-toluolsulfonil-)/tosyl (4-toluenesulfonyl)

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

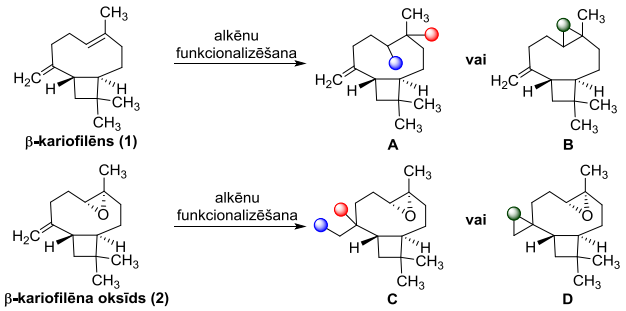
Tēmas aktualitāte

Dabasvielu sintēze ir organiskās sintēzes apakšnozare, kura ir mērķēta uz strukturāli sarežģītu dabā sastopamu savienojumu (piemēram, terpenoīdu, poliketīdu, alkaloīdu un peptīdu) iegūšanu. Šo mērķsavienojumu iegūšanai bieži izmanto totālās sintēzes pieeju, kurai raksturīga gara reakciju sekvence, reaģentu kontrolēta asimetriskā sintēze nepieciešamās stereocentru konfigurācijas ieviešanai, kā arī salīdzinoši mazi galaprodukta daudzumi. Alternatīva totālajai sintēzei ir semisintēze, kas ir dabasvielu iegūšana no citas dabasvielas. Izmantojot semisintēzes pieeju, ir iespēja būtiski saīsināt reakciju sekvenci, nereti tādējādi palielinot galaprodukta daudzumu.[1,2] Turklāt izejas dabasvielas definētie stereocentri ļauj iegūt arī stereotīru mērķsavienojumu. Biomimētisku reakciju izmantošana semisintēzes procesā sniedz priekšstatu par ķīmiskajām pārvērtībām dabā un izskaidro sarežģītu dabasvielu biosintētisko ceļu (1. att.).

1. att. Dabasvielu iegūšana, izmantojot totālo sintēzi un semisintēzi.

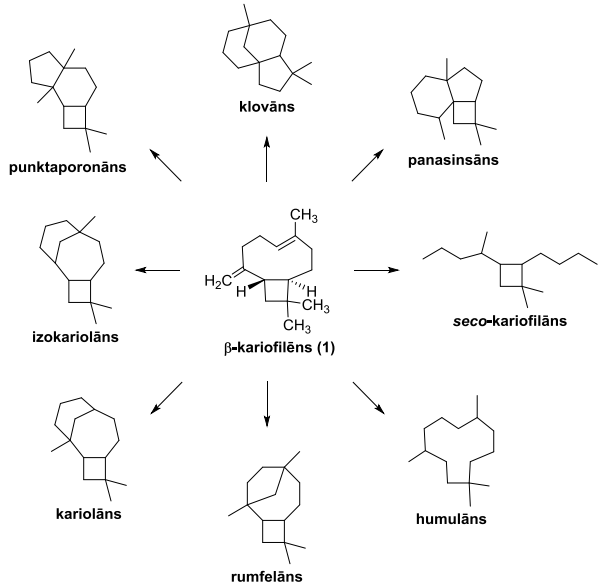
Semisintēzes pieeja promocijas darba ietvaros tika pielietota terpenoīdu bibliotēkas izveidei, kā izejvielu izmantojot vienu no vispieejamākajiem seskviterpēniem – β-kariofilēnu (**1**, 1 kg par 100 EUR ķīmisko reaģentu katalogā), kuru iegūst no dažādiem augiem, piemēram, nagliņkoka,[3] melnajiem pipariem,[4] raudenes,[5] bazilika[6] un rozmarīna.[7] β-Kariofilēna (**1**) iegūšana no biomasas piešķir tam vēl neapgūtu atjaunīgā resursa potenciālu.

E-Ciklononēna sprieguma dēļ β-kariofilēna (**1**) endocikliskā dubultsaite ir reaģētspējīgāka par eksociklisko dubultsaiti, tādējādi ir iespēja to selektīvi modificēt. Radniecīgais β-kariofilēna oksīds (**2**, 100 g par 132 EUR ķīmisko reaģentu katalogā) ļauj paplašināt produktu daudzveidību, jo tajā endocikliskā *trans*-dubultsaite ir epoksidēta, tādējādi virzot funkcionalizēšanu uz eksociklisko alkēnu (2. att.). Šī pieeja ļauj iegūt stratēģiskus būvblokus **A**–**D**, kurus var izmantot relatīvi īsu dabasvielu sintētisko ceļu izveidei. Iegūtās dabasvielas var kalpot kā references standarti augu ekstraktu analīzē vai bioloģiskās aktivitātes profilēšanā medicīnas ķīmijā.



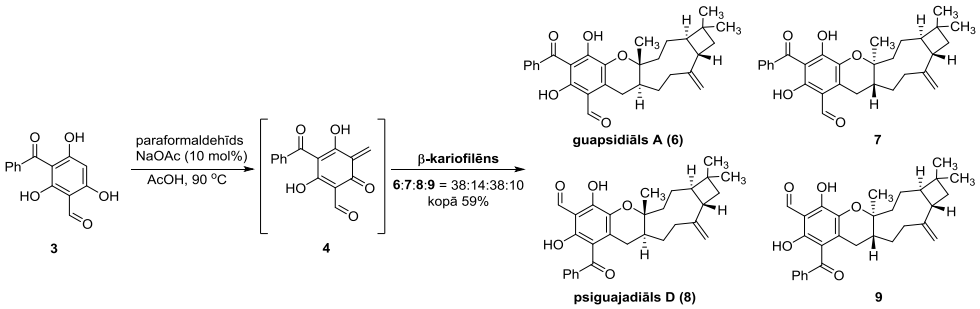
2. att. Stratēģisko būvbloku **A**–**D** iegūšana no β-kariofilēna (**1**) un tā oksīda (**2**).

Pateicoties β-kariofilēna struktūrai (kondensēti ciklobutāna un *E*-ciklononēna fragmenti, divi stereodefinēti hirālie centri) un spējai pārgrupēties, veidojot citus oglekļa skeletus, β-kariofilēnam ir augsts potenciāls kā izejvielai strukturāli daudzveidīgu seskviterpēnu iegūšanai (3. att.).[8–17]



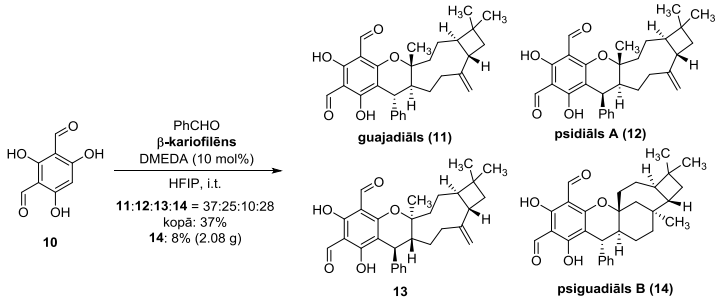
3. att. Pieejamā strukturālā daudzveidība no β-kariofilēna.

Pirms promocijas darba izstrādes β-kariofilēnu un tā oksīdu samērā reti izmantoja kā izejvielu dabasvielu sintēzē. Pamatā biomimētiski tika sintezēti meroterpenoīdi, kas izolēti no guavas (*Psidium guajava*), izmantojot β-kariofilēna reaģētspējīgāko endociklisko dubultsaiti kā dienofīlu hetero-Dīlsa–Aldera reakcijās.[18,19] Piemēram, *o*-hinona metīds **4**, kas tika ģenerēts no floroglucīna atvasinājuma **3** un paraformaldehīda Knēvenāgela tipa reakcijā, reaģēja ar β-kariofilēnu, veidojot meroterpenoīdus **6**–**9**, tostarp guapsidiālu A (**6**) un psiguajadiālu D (**8**, 1. shēma).[18]



1. shēma. Guapsidiāla A (**6**) un psiguajadiāla D (**8**) sintēze.

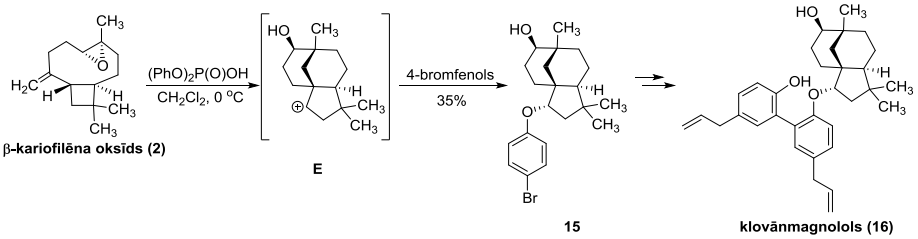
Līdzīga pieeja tika izmantota psiguadiāla B (**14**) grama apjoma sintēzē. β-Kariofilēns reaģēja ar diformilfloroglucīnu (**10**) benzaldehīda un DMEDA klātienē, veidojot psiguadiālu B (**14**) kopā ar guajadiālu (**11**), psidiālu A (**12**) un diastereomēru **13** (2. shēma).[19]



2. shēma. Guajadiāla (**11**), psidiāla A (**12**) un psiguadiāla B (**14**) sintēze.

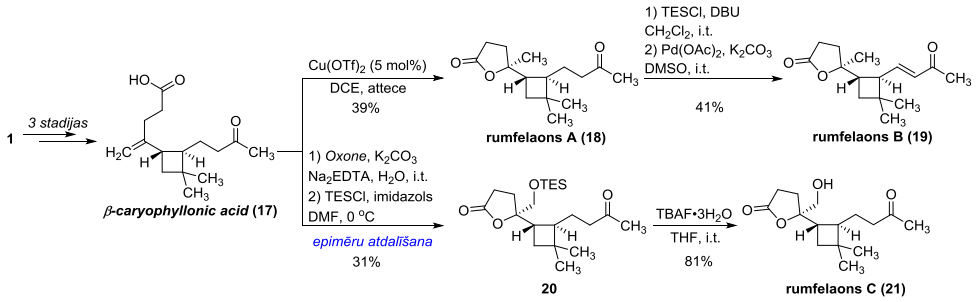
Atšķirībā no vairākuma meroterpenoīdu, kas ir klasiski Dīlsa–Aldera adukti, psiguajadiālu B (**14**) veido pārgrupētais kariolāna karkass. Ar nolūku izskaidrot psiguadiāla B veidošanās mehānismu, tika veikti kontroleksperimenti un datoraprēķini, kas parādīja, ka tas ietver Maikla pievienošanos starp *o*-hinona metīdu un β-kariofilēnu ar sekojošu ciklizēšanos, iesaistot eksociklisko dubultsaiti. Šī pārvērtība lieliski demonstrē β-kariofilēna tieksmi veidot citus karbocikliskus karkasus.[19]

β-Kariofilēna oksīds (**2**) uzrāda analoģisku tendenci uz pārgrupēšanos, kura tika pielietota klovānmagnolola sintēzē.[20] Luisa un Brensteda skābes veicina β-kariofilēna oksīda (**2**) pārgrupēšanos, veidojot klovāna karkasu. Otrējais karbkatjons **E** reaģēja ar ārējo nukleofīlu (4-bromfenolu), iegūstot arilēteri **15**, kurš tika pārvērsts par klovānmagnololu (**16**) tālākās stadijās (3. shēma).[20]



3. shēma. Klovāna tipa arilētera **15** un klovānmagnolola (**16**) sintēze.

Mūsu grupā iepriekš veiktajos pētījumos tika izstrādāta relatīvi īsa *seco*-kariofilānu rumfelaonu A–C sintēze (4. shēma).[21] Sākumā β-kariofilēns tika pārvērsts par karbonskābi **17**, kura pēc laktonizēšanās veidoja rumfelaonu A (**18**). Pakļaujot to *Saegusa–Ito* α,β-dehidrogenēšanai, tika iegūts rumfelaons B (**19**). Karbonskābes **17** epoksidēšana ar tai sekojošu laktonizēšanos veidoja rumfelaonu C (**21**). Jāpiebilst, ka epimēru veiksmīgai atdalīšanai papildus tika iegūts sililēteris **20**.[21]



4. shēma. Rumfelaonu A–C semisintēze no β-kariofilēna (**1**).

Promocijas darbs izklāsta turpmāko β-kariofilēna vai tā oksīda izmantošanu semisintēzes procesā. Darbs ir veltīts retāk sastopamu dabasvielu iegūšanai, fokusējoties uz bi-, tri- un tetracikliskiem terpenoīdiem.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir izstrādāt eksotisku dabasvielu semisintēzes ceļus, kā izejvielu izmantojot β-kariofilēnu (**1**) un/vai tā oksīdu (**2**). Lai sasniegtu šo mērķi, tika izvirzīti divi uzdevumi:

1. Izpētīt literatūru un izvēlēties piemērotus mērķsavienojumus (strukturāli sarežģītus bioloģiski aktīvus kariofilāna tipa terpenoīdus);

2. Veikt mērķsavienojumu semisintēzi un veikt to struktūru apstiprināšanu vai labojumus.

Zinātniskā novitāte un galvenie rezultāti

Promocijas darbā izstrādāta:

1. Karbonskābes *rumphellaoic acid A*, 4β,8β-epoksikariofilān-5-ola un to estera rumfelolīda J sintēze;

2. Linariofilēnu A–C un rumfelolīda H sintēze, kā arī linariofilēnu A un C struktūras labojumi;

3. Izo-eiforanīna E sintēze, kas ietver [4.3.2]propelāna saturošās dabasvielas (4,4-dimetiltetraciklo[6.3.0^{2,5}.0^{1,8}]tridekān-9-ola) iegūšanu un propelāna fragmenta katjonās šķelšanas pētījumus, kā arī (1*R*,2*S*,5*R*)-4,4-dimetiltriciklo[6.3.2.0^{2,5}]tridec-8-ēn-1-ola sintēzi;

4. Hloru saturošu hemiketālu rumfelatīnu A–C un norseskviterpenoīda rumfelolīda C sintēze, kā arī rumfelatīna A un C struktūras labojumi.

Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa par β-kariofilēna un/vai tā oksīda izmantošanu eksotisku dabasvielu semisintēzē.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti četrās zinātniskajās oriģinālpublikācijās. Pētījuma rezultāti prezentēti piecās zinātniskajās konferencēs.

Zinātniskās publikācijas:

1. Stakanovs, G.; Belyakov, S.; Jirgensons, A.; Rasina, D. Convergent Biomimetic Semisynthesis of Disesquiterpenoid Rumphellolide J. *Org. Biomol. Chem.* **2022**, *20* (12), 2455–2461. DOI: 10.1039/D2OB00238H
2. Stakanovs, G.; Blazevica, A.; Belyakov, S.; Rasina, D.; Jirgensons, A. Semisynthesis of Linariophyllenes A–C and Rumphellolide H, Structure Revisions and Proposed

Biosynthesis Pathways. *J. Nat. Prod.* **2023**, *86* (10), 2368–2378. DOI: 10.1021/acs.jnatprod.3c00574

3. Stakanovs, G.; Rasina, D.; Belyakov, S.; Kinens, A.; Jirgensons A. Bridgehead Epoxide Iso-Euphoranin E from β-Caryophyllene Oxide *via* Sequential Cationic Formation and Scission of [4.3.2]Propellane. *Org. Chem. Front.* **2024**, *11* (18), 5086–5092. DOI: 10.1039/D4QO00940A
4. Stakanovs, G.; Blazevica, A.; Rasina, D.; Belyakov, S.; Jirgensons, A. Bioinspired Semisynthesis and Structure Revisions of Chlorinated Norsesquiterpenoids Rumphellatins A–C. *Org. Lett.* **2024**, *26* (38), 8074–8078. DOI: 10.1021/acs.orglett.4c02942

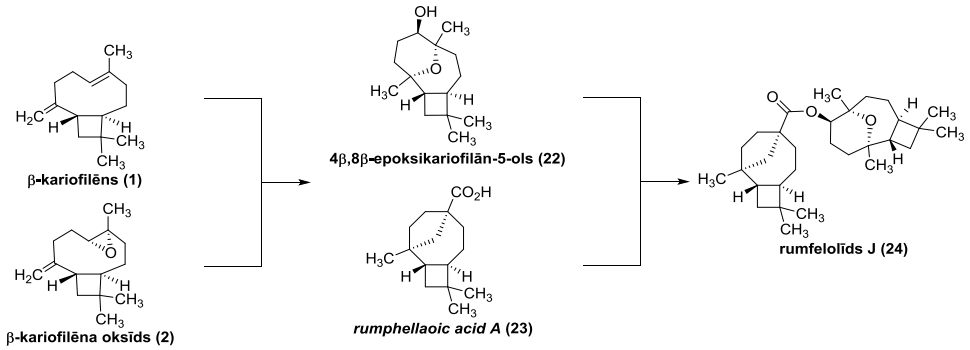
Zinātniskās konferences, kurās prezentēti darba rezultāti:

1. Rasina, D.; Stakanovs, G. Semisynthesis of Rumphellaones A–C and Rumphellolide J from Caryophyllene. *3rd Online International Conference of Biocatalysis & Green Chemistry*. Tiešsaistē, 4.–5. aprīlis **2022**.
2. Stakanovs, G.; Rasina, D. Semisynthesis of Natural Products from (–)-β-Caryophyllene. *Balticum Organicum Syntheticum (BOS 2022).* Viļņa, Lietuva, 3.–6. jūlijs **2022**.
3. Stakanovs, G.; Rasina, D.; Jirgensons A. Synthesis of Low-Abundance Sesquiterpenoids from β-Caryophyllene. *International Scientific Conference of the University of Latvia.* Rīga, Latvija, 17. marts **2023**.
4. Stakanovs, G.; Rasina, D.; Jirgensons, A. Semisynthesis and Structure Revision of Linariophyllenes A–C and Rumphellolide H. *Paul Walden 13th Symposium on Organic Chemistry*. Rīga, Latvija, 14.–15. septembris **2023**.
5. Stakanovs, G.; Rasina, D.; Jirgensons, A. Synthesis and Structure Revision of Linariophyllenes A–C. *Balticum Organicum Syntheticum (BOS 2024).* Rīga, Latvija, 7.–10. jūlijs **2024**.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

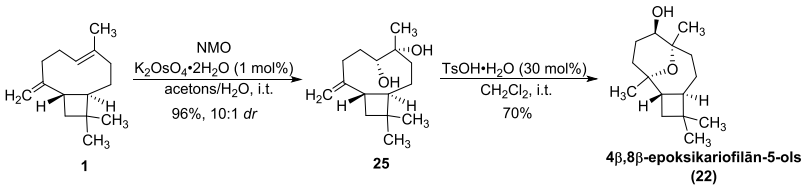
1. Diseskviterpenoīda rumfelolīda J semisintēze

Diseskviterpenoīdi jeb seskviterpenoīdu dimēri ir reta dabasvielu klase, kuras savienojumi sastāv no divu dažādu seskviterpenoīdu fragmentiem.[22] No *Rumphella antipathies* koraļļiem izdalīta rumfelolīda J (**24**) divi karkasi – karbonskābes **23** un 4β,8β-epoksikariofilān-5-ola (**22**) – ir savienoti ar estera saiti,[23] tādēļ tā bioģenētiskais ceļš visdrīzāk ietver esterificēšanu starp spirtu **22** un skābi **23** (4. att.). Rumfelolīda J (**24**) bioloģiskā aktivitāte netika noteikta, taču karbonskābe **23** uzrāda pretiekaisuma aktivitāti, inhibējot elastāzes izdalīšanu,[24] savukārt, spirts **22** paaugstina superoksīdanjona ģenerēšanu.[25]



4. att. Rumfelolīda J (**24**) iespējamais bioģenētiskais ceļš.

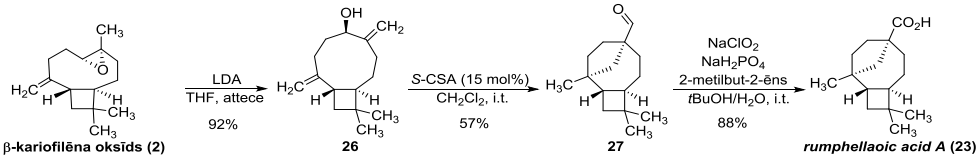
Spirts **22** ir iepriekš identificēts kā viens no daudzajiem β-kariofilēna oksīda (**2**) ciklizēšanas/pārgrupēšanas produktiem skābā vidē ūdens klātienē.[26] Darbā tika noskaidrots, ka produkta **22** iznākumu var krietni uzlabot, izmantojot divu reakciju sekvenci. Sākumā β-kariofilēns (**1**) tika dihidroksilēts, veidojot vicinālo diolu **25**, kurš pēc tam tika pārvērsts par vēlamo spirtu **22**, izmantojot katalītisku daudzumu $TsOH \cdot H_2O$ (5. shēma). Zīmīgi, ka ciklizēšanās notika selektīvi ar tetrahidropirāna cikla veidošanos, neveidojot arī iespējamo tetrahidrofurāna ciklu.



5. shēma. Spirta **22** divu stadiju sintēze no β-kariofilēna (**1**).

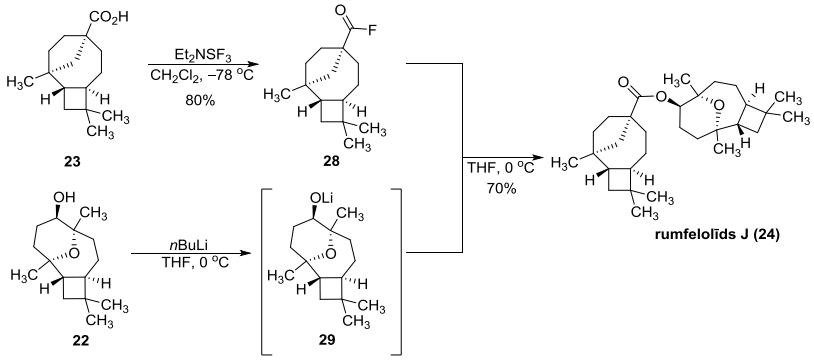
Lai iegūtu karbonskābi **23**, β-kariofilēna oksīds (**2**) tika izomerizēts par alilspirtu **26** LDA klātienē. Tālāka skābes katalizēta ciklizēšanās, iekļaujot pinakola pārgrupēšanos, veidoja aldehīdu **27**. Variējot Brensteda skābes (H_2SO_4, $TsOH \cdot H_2O$, *S*-CSA) un šķīdinātājus (MeOH,

CH_2Cl_2, DCE, C_6H_6), tika noteikts, ka visoptimālākie apstākļi aldehīda **27** iegūšanai no spirta **26** ir katalītisks daudzums *S*-CSA benzola vai CH_2Cl_2 šķīdumā. Savienojums **27** tālāk tika oksidēts līdz karbonskābei **23**, izmantojot Pinnika oksidēšanu (6. shēma).



6. shēma. Karbonskābes **23** sintēze no β-kariofilēna oksīda (**2**).

Grama apjoma rumfelolīda J (**24**) sintēze tika veikta, no sākuma pārvēršot karbonskābi **23** par acilfluorīdu **28**. Tas reaģēja ar litija alkoksīdu **29**, kurš tika iegūts no spirta **22** (7. shēma). Rumfelolīda J (**24**) struktūra tika pierādīta ar tā monokristāla rentgendifraktometriju.

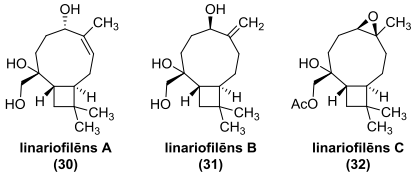


7. shēma. Rumfelolīda J (**24**) sintēze.

Tika pārbaudītas arī alternatīvas esterificēšanas stratēģijas, kas iekļāva *Steglich* reakciju ar HOBt/EDCI, taču šajos apstākļos tika novērota tikai starpproduktu (acilizourīnvielas un no HOBt atvasināta estera, kā arī acilpiridīnija jona) veidošanās, kas tika detektēta ar LC/MS. Attiecīgā acilhlorīda sintēze no karbonskābes **23** ar Vilsmeijera reaģentu ($(COCl)_2$ + DMF), $SOCl_2$ vai PCl_3 arī nebija veiksmīga, un vēlamie produkti tika novēroti tikai zīmju līmenī.

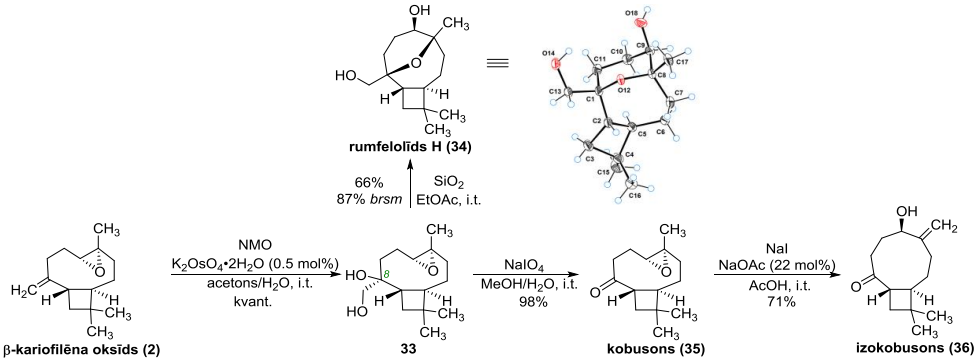
2. Linariofilēnu A–C semisintēze

Par nākamo pētījuma posmu tika izvēlēta linariofilēnu A–C (piedāvātās izolēto savienojumu struktūras **30**–**32**, 5. att.) semisintēzes ceļa izveide. Šie kariofilāna tipa seskviterpenoīdi, kas tika izolēti no sauszemes auga *Evolvulus linaroides*, uzrāda pretiekaisuma aktivitāti, inhibējot slāpekļa monoksīda ģenerēšanu un citokīnu IL-1*β*.[27] No pētītajiem savienojumiem visaugstāko bioloģisko aktivitāti uzrāda linariofilēns B (**31**).[27]



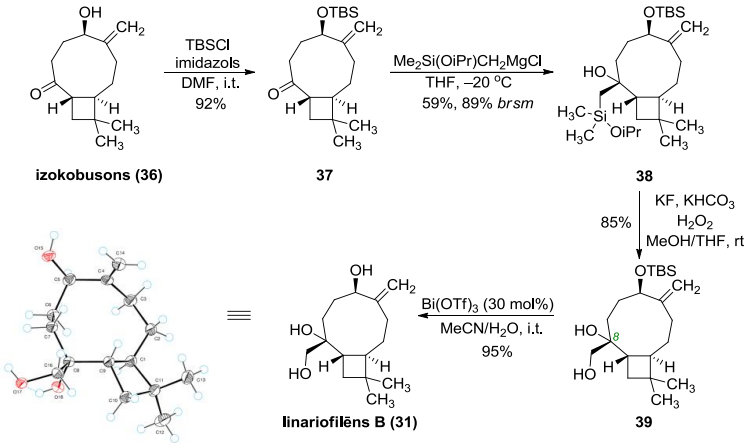
5. att. Piedāvātas linariofilēnu A–C struktūras.

Sākumā tika izstrādāta eksociklisko dubultsaiti saturošā triola – linariofilēna B (**31**) sintēze (8. un 9. shēma). β-Kariofilēna oksīda dihidroksilēšana veidoja epoksidiolu **33**, taču ar pretēju C-8 konfigurāciju nekā mērķsavienojumiem **30**–**32** (8. shēma). Vēlamā C-8 konfigurācija tika izveidota tālākajās stadijās, izmantojot izokobusonu (**36**), kas tika iegūts, pārvēšot epoksidiolu **33** par kobusonu (**35**) un to izomerizējot skābā vidē. Jāpiebilst, ka diols **33** spontāni ciklizējās SiO_2 klātienē, veidojot dabasvielu no *Rumphella antipathies* – rumfelolīdu H (**34**).[28] Savienojuma **34** struktūra tika pierādīta ar tā monokristāla rentgendifraktometriju (8. shēma).



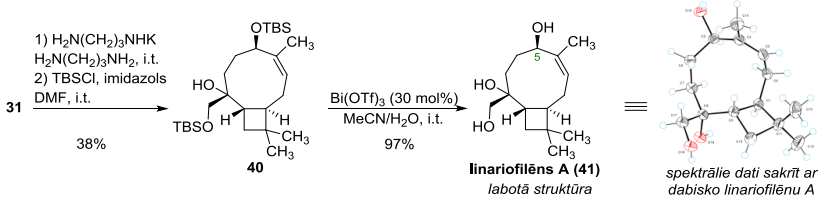
8. shēma. Rumfelolīda H (**34**) un izokobusona (**36**) sintēze, kā arī rumfelolīda H ORTEP attēlojums ar 50% kontūru varbūtību.

Izokobusons (**36**) tika sililēts, veidojot sililēteri **37**, kurš reaģēja ar $Me_2Si(OiPr)CH_2MgCl$. Izveidotais β-sililspirts **38** tika uzreiz pakļauts *Tamao* oksidēšanai, kas ļāva iegūt vicinālo diolu **39** ar vēlamo C-8 konfigurāciju. Savienojuma **39** epimērs netika detektēts, liecinot par stereoselektīvu Griņjāra pievienošanos ketonam **37**. Sililētera **39** TBS grupas nošķelšanai tika izmantots $Bi(OTf)_3$ ūdens vidē (9. shēma). Linariofilēna B (**31**) struktūra tika pierādīta ar rentgenstruktūranalīzi, tā spektrālie dati sakrita ar paraugu, kas izolēts no *Evolvulus linaroides*.[27]



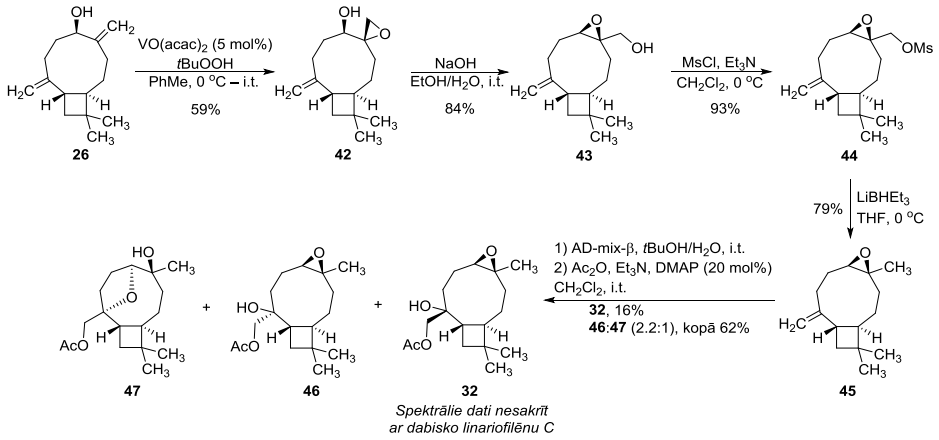
9. shēma. Linariofilēna B (**31**) sintēze un tā ORTEP attēlojums ar 50% konturu varbūtību.

Lai izomerizētu linariofilēna B (**31**) eksociklisko dubultsaiti uz endociklisko, tika izmantots kālija 3-aminopropilamīds (10. shēma). Lai atdalītu neizreaģējušo izejvielu no vēlamā produkta, maisījums tika sililēts. Pēc TBS grupu nošķelšanas no sililētera **40** tika noteikts, ka linariofilēna A īstajā struktūrā (**41**) C-5 konfigurācija ir tāda pati kā linariofilēnam B (**31**).



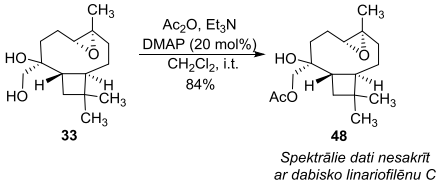
10. shēma. Linariofilēna A (**41**) sintēze un tā ORTEP attēlojums ar 50% konturu varbūtību.

Savienojums ar literatūrā piedāvāto linariofilēna C struktūru (**32**) tika iegūts no alilspirta **26**. No tā $VO(acac)_2$ katalizētā epoksidēšanā diastereoselektīvi tika iegūts epoksispirts **42**, kurš pēc tam tika pakļauts *Payne* pārgrupēšanās reakcijai, veidojot pirmējo spirtu **43**. Tālāka mezilēšana un sulfonāta **44** reducēšana ar $LiBHEt_3$ ļāva iegūt *cis*-epoksīdu **45**. Pēc dihidroksilēšanas un acetilēšanas reakciju sekvences tika iegūti diastereomērie epoksiacetāti **32** un **46**, kā arī tetrahidrofurāns **47**, taču neviens no šo produktu KMR spektriem nesakrita ar dabisko linariofilēnu C (11. shēma).



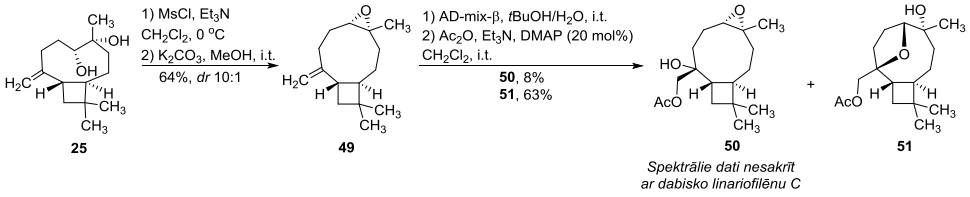
11. shēma. Piedāvātās linariofilēna C struktūras (**32**) iegūšana.

Tika izvirzīta hipotēze, ka īstā linariofilēna C struktūra varētu būt savienojuma **32** diastereomērs. Lai pārbaudītu šo hipotēzi, epoksidiols **33** tika acetilēts, taču arī epoksiacetāta **48** spektrālie dati nesakrita ar dabiskā linariofilēna C datiem (12. shēma).



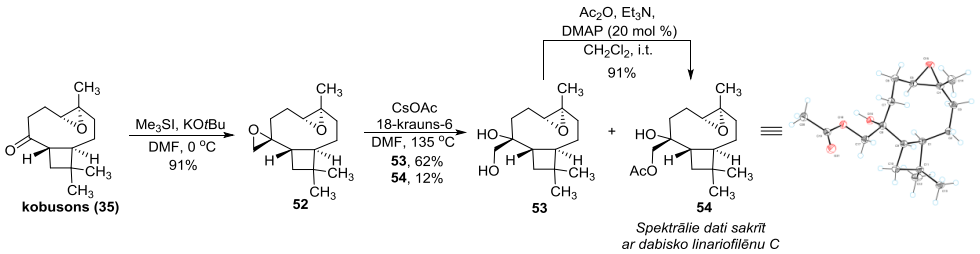
12. shēma. Epoksiacetāta **48** sintēze.

Cita epoksiacetāta **32** diastereomēra sintēzei diols **25** no sākuma tika pārvērsts par *cis*-epoksīdu **49**, izmantojot Viljamsona epoksīdu sintēzi. Pēc dihidroksilēšanas un acetilēšanas sekvences tika izolēts epoksiacetāts **50**, kā arī tetrahidrofurāns **51**, taču to ^{1}H un ^{13}C KMR spektri arī nesakrita ar dabisko linariofilēnu C (13. shēma).



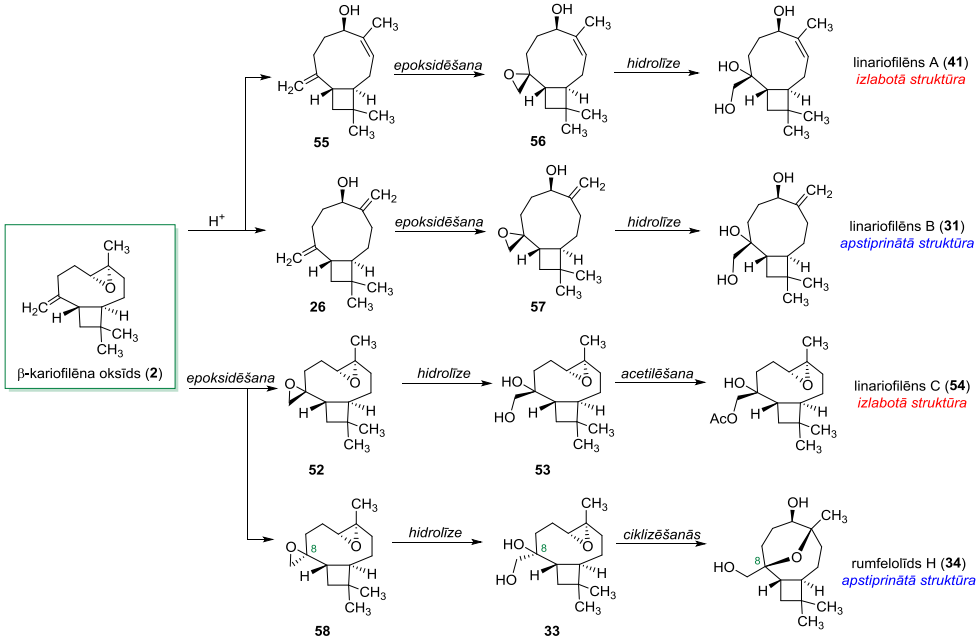
13. shēma. Epoksiacetāta **50** iegūšana.

Linariofilēns C ar īsto struktūru visbeidzot tika iegūts, pārvēršot kobusonu (**35**) par diepoksīdu **52**, izmantojot Korija–Čaikovska reakciju. Selektīvas 1,1-diaizvietotā epoksīda uzslēgšanas rezultātā izveidojās diols **53** un acetāts **54**. Lai iegūtu maksimāli iespējamo acetāta **54** daudzumu, diols **53** tika acetilēts iepriekš izmantotajos apstākļos (14. shēma). Acetāta **54** spektrālie dati pilnībā sakrita ar dabisko linariofilēnu C.



14. shēma. Linariofilēna C (**54**) sintēze, tā struktūras noteikšana un ORTEP attēlojums ar 50% konturu varbūtību.

Pēc linariofilēnu A (**41**) un C (**54**) struktūras labojumiem, kā arī linariofilēna B (**31**) struktūras apstiprināšanas iespējams piedāvāt šo dabasvielu vienotu biosintētisko ceļu (6. att.), sākot no β-kariofilēna oksīda (**2**).

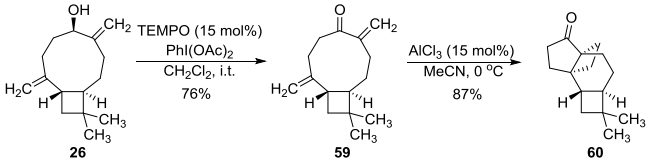


6. att. Linariofilēnu A–C un rumfelolīda H piedāvātais biosintētiskais ceļš.

Sākotnēji, β-kariofilēna oksīdam (**2**) izomerizējoties skābā vidē, var veidoties alilspirti **26** un **55** ar ekso- vai endociklisko dubultsaiti attiecīgi. Pēc epoksidēšanas[29] un spiroepoksīdu **56** un **57** hidrolīzes no šiem spirtiem var veidoties linariofilēni A un B (6. att.). Linariofilēns C (**54**) un rumfelolīds H (**34**) var veidoties no diepoksīdiem **52** un **58**. Epimērs **52** var veidot linariofilēnu C pēc hidrolīzes un pirmējā spirta acetilēšanas. Savukārt, epimēra **58** hidrolīze un ciklizēšanās skābā vidē noved pie rumfelolīda H (**34**), kas arī tika parādīts izstrādātajā sintēzes pieejā (8. shēma). Epoksidēšanas pretējo diastereoselektivitāti rumfelolīda H (**34**) biosintēzē var izskaidrot ar atšķirīgiem enzīmiem, kas veicina šo pārvērtību jūras un sauszemes organismos.

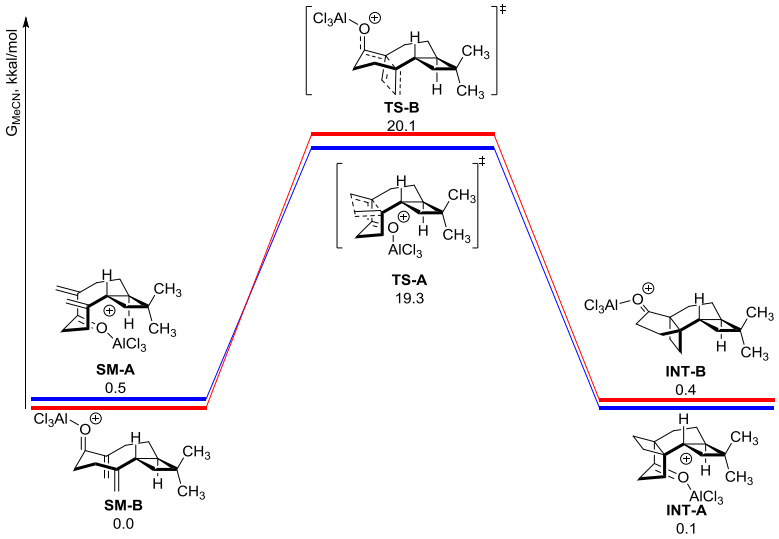
3. [4.3.2]Propelānu un epoksīdu saturošu dabasvielu sintēze

Tālāk tika izpētīta α,β-nepiesātinātā ketona **59**, kas iegūstams no alilspirta **26**, pārgrupēšanās skābā vidē. Atšķirībā no izejvielas **26**, kurai ir zināmas skābju katalizētas pārvērtības, ketonam **59** analoģiskās reakcijas nav publicētas. Pētījuma ietvaros tika atklāts, ka Luisa skābes ($AlCl_3$, $BF_3{\cdot}OEt_2$, $TiCl_4$ un Me_3SiOTf) katalizē [2 + 2] ciklopievienošanos, veidojot [4.3.2]propelānu saturošu ketonu **60** (15. shēma).



15. shēma. Ketona **60** sintēze.

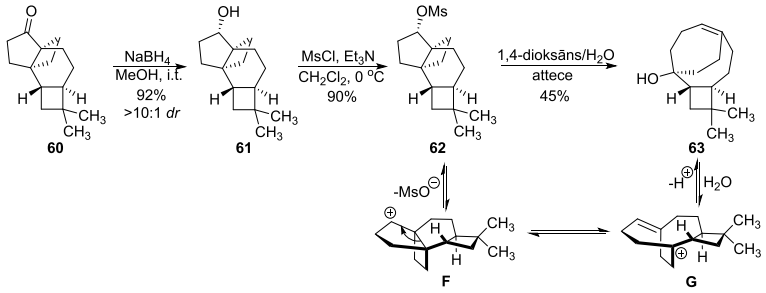
Blīvuma funkcionāļa teorijas aprēķini parādīja, ka šīs ciklopievienošanās mehānisms ir saskaņots, taču diastereoselektivitātes cēlonis netika līdz galam izprasts, jo aprēķinātā enerģijas starpība starp enona–$AlCl_3$ kompleksa konformācijām **SM-A** un **SM-B** ir tikai 0,5 kkal/mol (7. att.). *Gassman et al.* ziņoja par līdzīgu reakciju,[30,31] taču, atšķirībā no šīm pārvērtībām, ciklopievienošanās un ketona **60** veidošanās notiek bez 1,3-dioksolāna aizsarggrupas. Jāuzsver arī, ka šis ir pirmais gadījums, kad [4.3.2]propelāna fragments ir iegūts skābes katalizētā reakcijā.



7. att. α,β-Nepiesātinātā ketona **59** [2 + 2] ciklopievienošanās potenciālās enerģijas virsmas profils (aprēķini tika veikti sadarbībā ar *Dr. chem.* Arti Kinēnu).

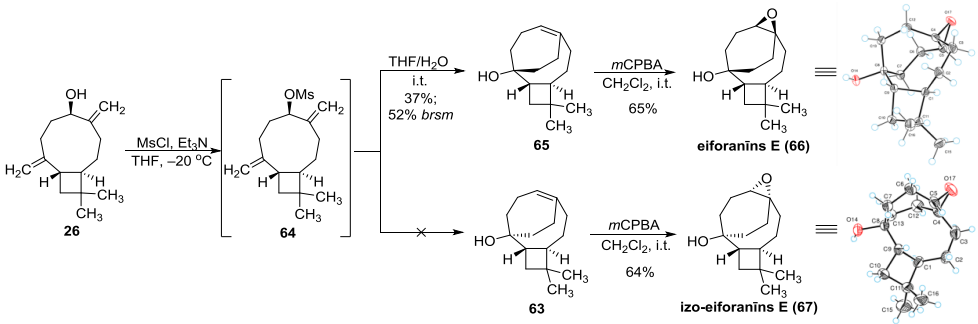
Ketons **60** tika reducēts līdz spirtam **61** (16. shēma), kurš ir detektēts vairāku augu (*Tagetes lucida*, *Psidium guajava*) ekstraktos.[32,33] Pēc spirta **61** mezilēšanas iegūtais sulfonāts

62 tika pakļauts solvolīzei, veidojot olefīnu **63** (16. shēma). Šīs pārvērtības mehānisms visdrīzāk ietver otrējā karbkatjona **F** veidošanos un tā pārgrupēšanos par katjonu **G**, kurš reaģē ar ūdeni, veidojot produktu **63.**



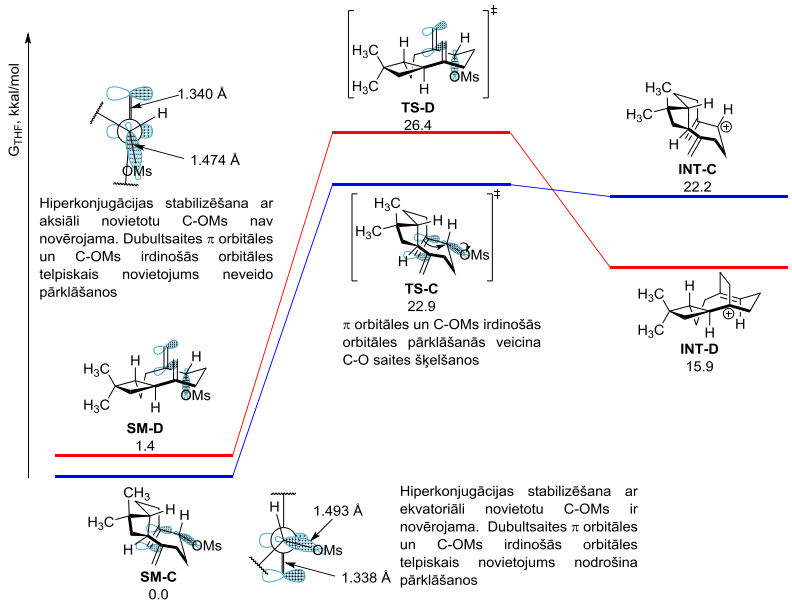
16. shēma. Spirta **61** un olefīna **63** sintēze.

Olefīns **63** ir dabasvielas **65** diastereomērs,[34] kuru var iegūt no alilmezilāta **64** (17. shēma). Zīmīgi, ka savienojuma **64** solvolīzes rezultātā produkts **63** netika detektēts. Abi alkēni **63** un **65** tika epoksidēti, stereoselektīvi veidojot epoksispirtus **66** un **67**. Pēc salīdzināšanas ar literatūras datiem tika noteikts, ka epoksīda **66** KMR dati sakrīt ar eiforanīnu E, kas tika izolēts no sauszemes auga *Euphorbia wangii*.[35] Līdz šim nav ziņots par savienojumu **63** un **67** esamību dabā, bet pastāv augsta varbūtība, ka tie ir sastopami dzīvajos organismos, jo tos var iegūt no [4.3.2]propelānu saturošās dabasvielas **60**.



17. shēma. Epoksīdu **66** un **67** sintēze un to ORTEP attēlojums ar 50% kontūru varbūtību.

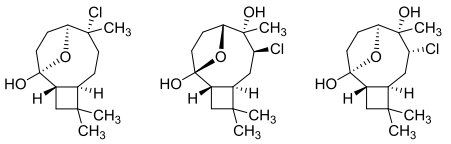
Blīvuma funkcionāļa teorijas aprēķini (8. att.) tika pielietoti arī alilmezilāta **64** solvolīzes diastereoselektivitātes noteikšanai. Mezilāta **SM-C** konformācijā –OMs grupa novietota ekvatoriāli, kas nodrošina dubultsaites π orbitāles pārklāšanos ar C–O saites irdinošo orbitāli. Šī konformācija ir enerģētiski izdevīgāka par **SM-D** konformāciju, kurai –OMs grupai ir aksiālais novietojums. Šis hiperkonjugācijas efekts izraisa 3,5 kkal/mol starpību starp pārejas stāvokļiem **TS-C** un **TS-D**, nodrošinot > 99:1 *dr*, kas sakrīt ar eksperimentāliem rezultātiem.



8. att. Mezilāta **64** solvolīzes potenciālās enerģijas virsmas profils (aprēķini tika veikti sadarbībā ar *Dr. chem.* Arti Kinēnu).

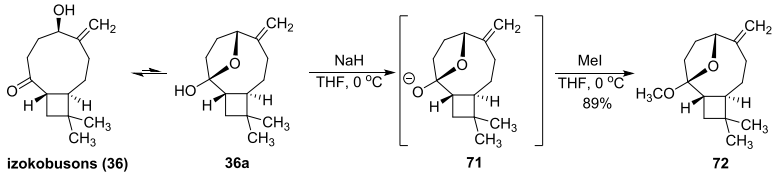
4. Hloru saturošu hemiketālu rumfelatīnu A–C sintēze

No *Rumphella antipathies* izdalīti rumfelatīni A–C (piedāvātās izolēto savienojumu struktūras **68–70**) ir hloru saturošie norseskviterpenoīdi, kas satur hemiketāla fragmentu (9. att.).[36,37] Halogēnu un hemiketāla funkcionālo grupu klātbūtne padara tos par strukturāli eksotiskām dabasvielām kariofilāna tipa terpenoīdu klāstā. Rumfelatīnam A un B (**68** un **69**), saskaņā ar iespriekšējiem pētījumiem, piemīt antibakteriālā aktivitāte.[36,37] Jāuzsver, ka neveiksmīgie mēģinājumi iegūt šīs dabasvielas totālās sintēzes ceļā[38] iedrošināja izstrādāt rumfelatīnu A–C semisintētisku iegūšanu.



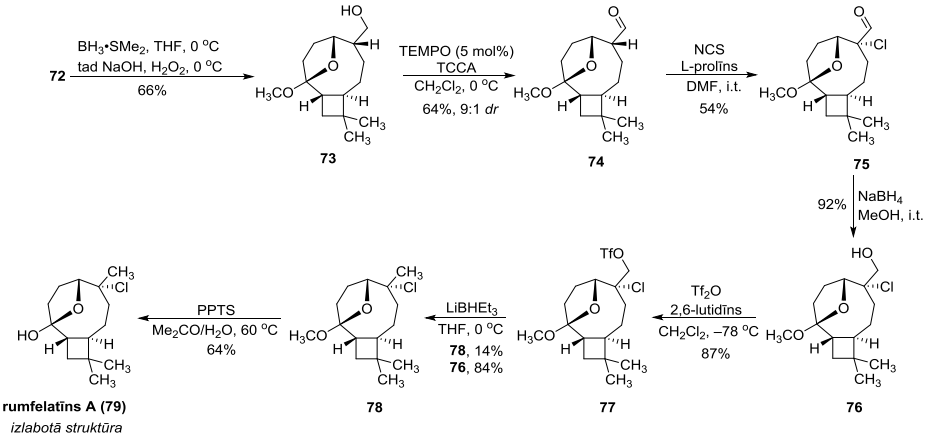
9. att. Rumfelatīnu A–C piedāvātās struktūras (**68–70**).

Iepriekš tika novērots, ka izokobusons (**36**) $CDCl_3$ šķīdumā eksistē kā tautomēru maisījums, kurš sastāv no ketoformas **36** un minorās hemiketāla formas **36a** (18. shēma). Šis novērojums iedvesmoja veikt rumfelatīnu A–C sintēzi, izmantojot izokobusonu (**36**) kā starpproduktu. Izokobusona (**36**) deprotonēšana ar NaH veidoja alkoksīdu, kurš ciklizējās, izveidojot hemiketāla anjonu **71**, un reaģēja ar MeI kā ārējo elektrofīlu. Tādējādi tika iegūts ketāls **72** ar teicamu iznākumu (18. shēma).



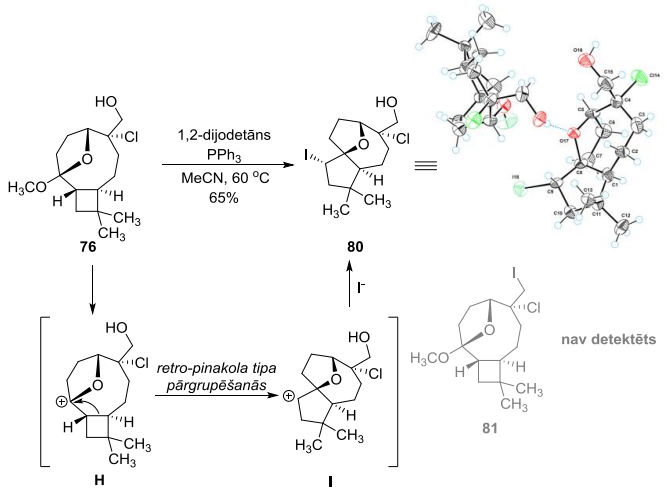
18. shēma. Izokobusona tautomērija un ketāla **72** sintēze.

Sākotnēja rumfelatīna A sintēze (19. shēma) iekļāva ketāla **72** hidroborēšanu-oksidēšanu ar pirmējā spirta **73** izveidi. Tas tika oksidēts tālāk līdz aldehīdam **74**, kurš tika pakļauts α-hlorēšanai ar NCS un L-prolīnu. α-Hloraldehīds **75** tika reducēts līdz hlorhidrīnam **76**, kurš tika pārvērsts par triflātu **77**. Savienojuma **77** reakcija ar $LiBHEt_3$ veidoja ketālu **78**, kam tika nošķelta metilgrupa ūdens un PPTS klātienē. Galaprodukta **79** spektrālie dati pilnībā sakrita ar rumfelatīnu A, kas parādīja, ka dabasvielas tetrahidrofurāna fragmenta konfigurācija tika noteikta nepareizi, izolējot šo savienojumu no *Rumphella antipathies* koraļļiem.



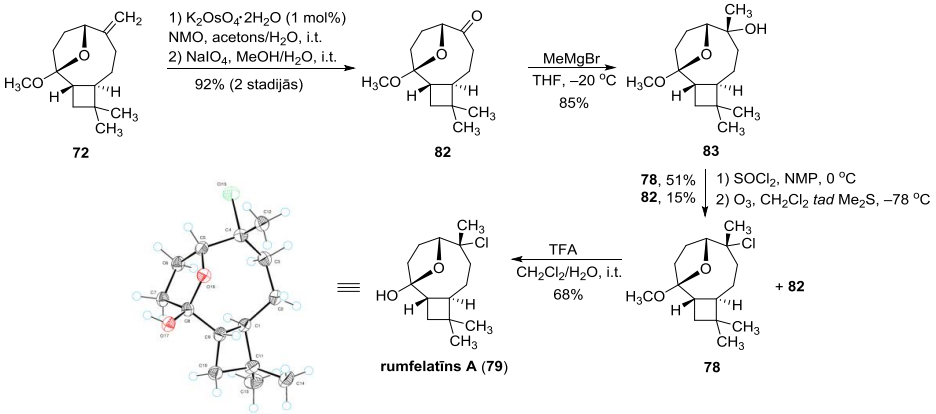
19. shēma. Rumfelatīna A (**79**) sākotnēja sintēze.

Šīs shēmas galvenie trūkumi ir gara lineāra sekvence un zems triflāta **77** reducēšanas iznākums, kur kā pamatprodukts veidojās spirts **76**. Iespējams, ka stēriski apgrūtinātās neopentilpozīcijas dēļ hidrīda uzbrūkums notiek sēra nevis oglekļa atomam. Jāpiebilst, ka no spirta **76** atvasinātā mezilāta vai tozilāta reducēšana ar $LiBHEt_3$ nenotiek arī paaugstinātās temperatūrās. Spirts **76** tika pakļauts *Appel* jodēšanai alternatīvas aizējošās grupas ieviešanai (20. shēma), taču kā pamatprodukts tika izolēts jodciklopentāns **80** konkurējošās retro-pinakola pārgrupēšanās dēļ.



20. shēma. Jodciklopentāna **80** sintēze un tā ORTEP attēlojums ar 50% kontūru varbūtību.

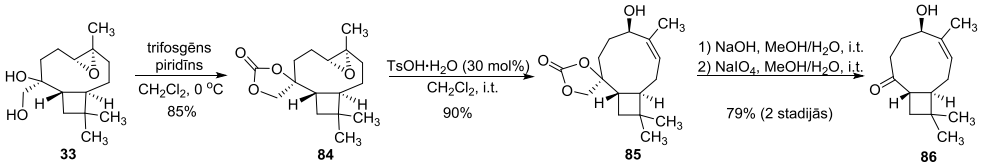
Rumfelatīna A (**79**) uzlabota sintēze ietvēra ketāla **72** dihidroksilēšanu un sekojošu diola oksidējošu šķelšanu (21. shēma). Ketons **82** tālāk reaģēja ar MeMgBr, veidojot trešējo spirtu **83** ar izcilu diastereokontroli. Pēc spirta **83** hlorēšanas ar $SOCl_2$ NMP šķīdumā tika iegūts vēlamais hlorīds **78** un ketāls **72** kā eliminēšanas reakcijas blakusprodukts. Savienojumu **78** un **72** maisījumu nebija iespējams hromatogrāfiski atdalīt, tāpēc tas tika pakļauts ozonolīzei, kura pārvērta alkēnu **72** par ketonu **82**, atvieglojot savienojumu savstarpēju atdalīšanu un attīrīšanu. Hlorīda **78** reakcija ar TFA ūdens šķīdumu ļāva iegūt rumfelatīnu A (**79**) ar teicamu iznākumu.



21. shēma. Rumfelatīna A (**79**) uzlabota sintēze un tā ORTEP attēlojums ar 50% kontūru varbūtību.

Rumfelatīna B un C sintēze tika veikta no epoksidiola **33**, kurš tika aizsargāts ar karbonāta funkciju, izmantojot trifosgēnu un piridīnu (22. shēma). Epoksikarbonāts **84** tika izomerizēts par alilspirtu **85**, kurš satur endociklisko dubultsaiti. Pēc karbonāta hidrolīzes

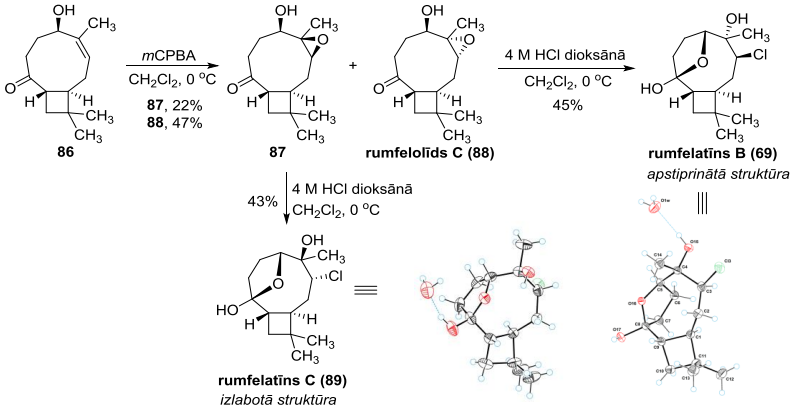
sārmainā vidē un iegūtā vicinālā diola oksidējošās šķelšanas tika iegūts ketospirts **86** (22. shēma), no kura tālāk tika sintezēti rumfelatīni B un C.



22. shēma. Ketospirta **86** sintēze.

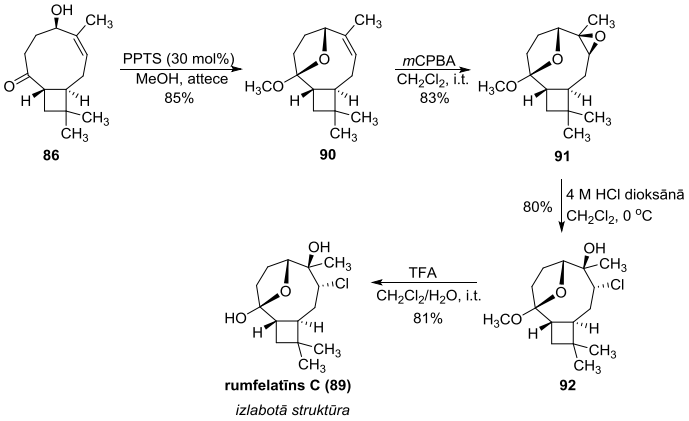
Rumfelatīns B tika iegūts alilspirta **86** epoksidēšanas rezultātā (23. shēma), kā starpproduktu veidojot rumfelolīdu C (**88**),[39] kura struktūra tika pierādīta ar tā monokristāla rentgendifraktometriju. Reaģējot rumfelolīdam C ar HCl, tika iegūts rumfelatīns B. Savukārt, pakļaujot diastereomēru **87** analoģiskiem reakcijas apstākļiem, tika iegūts rumfelatīns C. Rumfelolīda C pārvēršana par rumfelatīnu B parāda, ka šī reakcija varētu notikt arī *Rumphella antipathies* koraļļos.

Rumfelatīna B struktūra tika apstiprināta, taču rumfelatīna C struktūra tika izlabota, pierādot, ka tam ir analoģiska tetrahidrofurāna konfigurācija kā hemiketāliem **79** un **69**. Turklāt rumfelatīna C trešējā spirta konfigurācija arī tika izlabota.



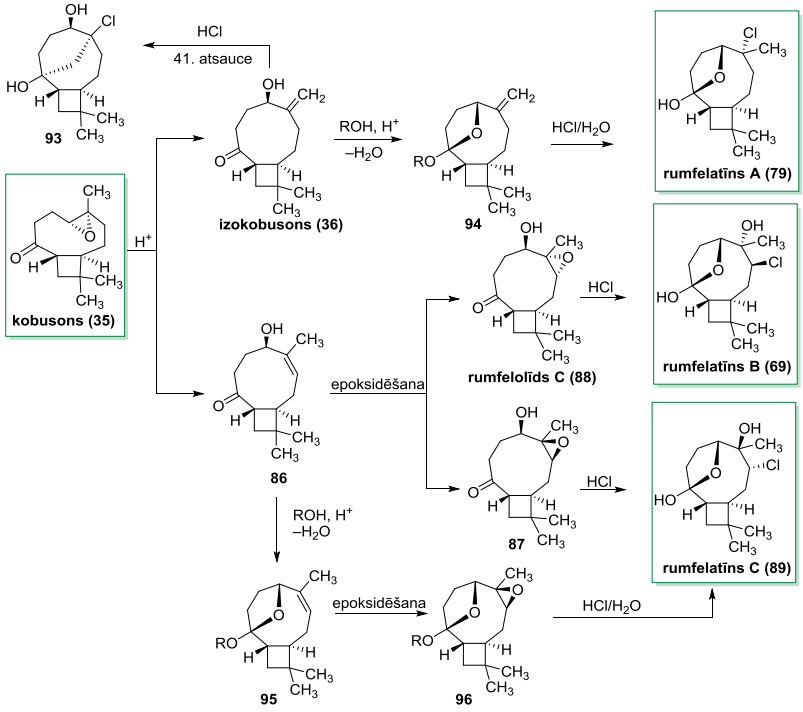
23. shēma. Rumfelolīda C (**88**), rumfelatīna B (**69**) un C (**89**) sintēze un to monohidrātu ORTEP attēlojums ar 50% kontūru varbūtību.

Alternatīva diastereoselektīva rumfelatīna C (**89**) sintēze tika izstrādāta, ketalizējot ketospirtu **86** MeOH šķīdumā, iegūstot ketālu **90** (24. shēma). Tā diastereoselektīva epoksidēšana ar *m*CPBA veidoja epoksīdu **91**, kura apstrāde ar HCl ļāva iegūt hlorhidrīnu **92**. Analoģiski rumfelatīna A sintēzei (19. shēma), demetilēšana tika veikta ar TFA ūdens šķīdumu.



24. shēma. Diastereoselektīva rumfelatīna C (**89**) sintēze.

Pēc visu dabasvielu struktūru **69**, **79**, **88** un **89** apstiprināšanas vai labošanas tika piedāvāti to biosintēzes ceļi (10. att.). Literatūrā zināms, ka kobusons (**35**) ir detektēts *Rumphella antipathies* koraļļos,[40] padarot to par potenciālo sākumposmu rumfelatīnu A−C un rumfelolīda C bioģenēzē.



10. att. Piedāvātie rumfelatīnu A−C biosintēzes ceļi.

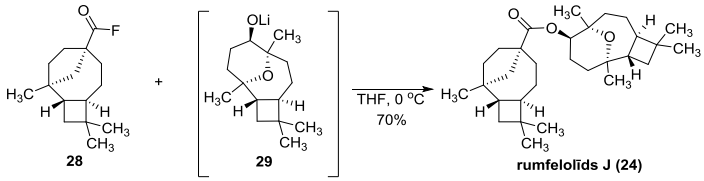
Analoģiski linariofilēna A un B (6. att.) biosintēzei, pirmā stadija varētu ietvērt *trans*-epoksīda izomerizēšanos skābā vidē par alilspitiem **36** un **86**, kuru klātbūtne *Rumphella antipahies* koraļļos šobrīd vēl nav apstiprināta. Zināms, ka, izokobusonam (**36**) reaģējot ar HCl, kvantitatīvi veidojas hlorīds **93**,[41] kas liecina par to, ka izokobusona hidrohlorēšanas reakcija visticamāk nav iesaistīta rumfelatīna A (**79**) biosintēzē. Turpretī izokobusona ketalizēšana varētu notikt, veidojot savienojumu **94**, kurš tad reaģē ar HCl ūdens vidē, veidojot rumfelatīnu A (**79**).[42] Alternatīvs vienas stadijas biosintētiskais ceļš arī varētu notikt, uzslēdzot kobusona *trans*-epoksīda ciklu ar halohidrīndehidrogenāzēm.[43]

Rumfelatīns B (**69**) varētu veidoties no alilspirta **86**, kurā notiek epoksidēšana, veidojot rumfelolīdu C (**88**). Rumfelatīns B (**69**) varētu rasties, epoksīda ciklam reaģējot ar HCl. Arī šī stadija varētu tikt katalizēta ar halohidrīndehidrogenāzēm.[43] Gadījumā, ja alilspirta **86** epoksidēšana nenotiek diastereoselektīvi, analoģisko ceļu var piedāvāt arī attiecībā uz rumfelatīnu C (10. att.).

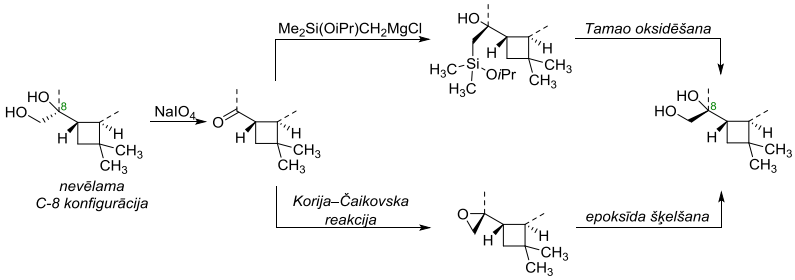
Rumfelatīna C biosintēzes ceļš varētu arī ietvert alilspirta **86** ketalizēšanos un epoksidēšanu, veidojot epoksiketālu **96**. Tā hidrohlorēšana un ketāla hidrolīze skābā vidē var veidot rumfelatīnu C.

SECINĀJUMI

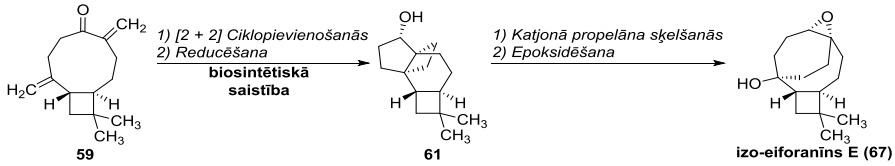
1. Reakcija starp acilfluorīdu un litija alkoksīdu ir visefektīvāka metode biomimētiskai rumfelolīda J estera saites veidošanai, nodrošinot mērķsavienojuma sintēzi grama mērogā.



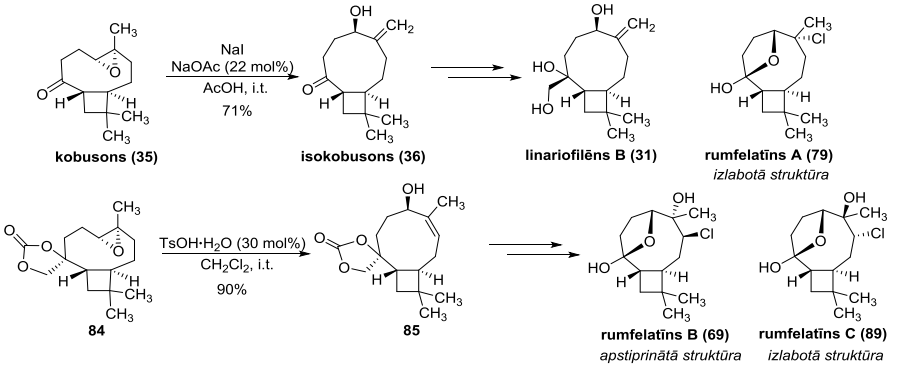
2. Ketona funkcijas nukleofīlā hidroksimetilēšana ir efektīva metode vicinālo diolu konfigurācijas apgriešanai kariofilāna tipa terpenoīdos. Šī pieeja tika veiksmīgi pielietota linariofilēnu A−C sintēzē.



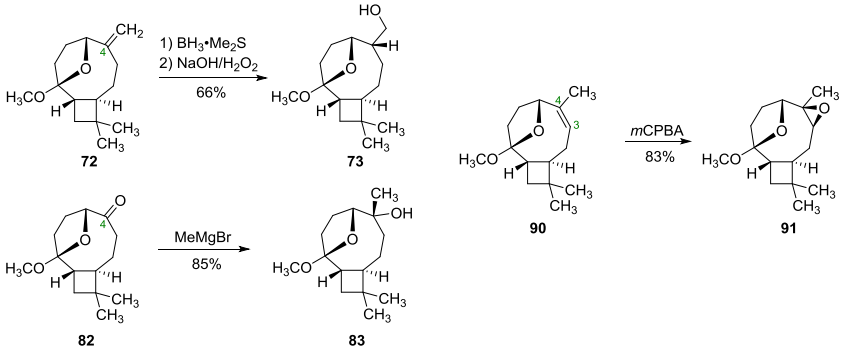
3. Saskaņotā α,β-nepiesātinātā ketona **59** Luisa skābju katalizētā [2 + 2] ciklopievienošanās atklāja biosintētisko ceļu, kas savieno ketonu **59** ar dabā sastopamo [4.3.2]propelānu saturošu spirtu **61**, no kura katjonās šķelšanās un epoksidēšanas rezultātā tika iegūta iespējamā dabasviela izo-eiforanīns E (**67**).



4. Selektīva *trans*-epoksīda izomerizēšanās skābā vidē, veidojot endo- vai eksocikliskos alilspirtus, ir efektīva metode linariofilēna B un hloru saturošu norseskviterpenoīdu rumfelatīnu A−C iegūšanai.



5. 12-Oksatriciklo[7.2.1.0^{2,5}]dodekāna skelets ļauj diastereoselektīvi funkcionalizēt olefīnu vai karbonilu C-3 un/vai C-4 pozīcijās, nodrošinot ārējā elektrofīla/nukleofīla uzbrukumu no skābekļa tiltiņa puses. Tas ļauj diastereoselektīvi iegūt hidroborēšanas-oksidēšanas, Griņjāra pievienošanas un epoksidēšanas produktus.



6. Semisintēze, kā izejvielu izmantojot (–)-β-kariofilēnu vai tā oksīdu, ir efektīva eksotisku dabasvielu iegūšanas pieeja, kas ļauj iegūt mērķsavienojumus grama mērogā un ļauj veikt to struktūru apstiprināšanu vai labošanu. Šie galaprodukti tālāk varētu tikt izmantoti to bioloģiskās aktivitātes testēšanai vai kā references standarti sauszemes vai jūras organismu metabolisma pētījumiem.

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

To be granted the scientific degree of Doctor of Sciences (*Ph. D.*), the present Doctoral Thesis will be defended at a public session on December 12, 2024 at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena Street 3, Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

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

Georgijs Stakanovs ……. (signature)

Date …….

The Doctoral Thesis has been prepared as a thematically united collection of scientific publications. It consists of a Summary and 4 scientific publications. Publications are written in English. The total number of pages is 466, including electronic supporting information.

GENERAL OVERVIEW OF THE THESIS

Introduction

Natural product synthesis represents a branch of organic synthesis aimed at obtaining structurally complex representatives of naturally occurring compounds, i.e., terpenoids, polyketides, alkaloids, and peptides. An access of natural products by means of total synthesis is associated with long reaction sequences, small amount of acquired target compound, and often a need for a reagent-controlled asymmetric induction to install the desired stereoconfiguration. In turn, semisynthesis – a transformation from one natural product into another – provides an opportunity to shorten the longest linear sequence, thus increasing the amount of final product.[1,2] Additionally, the stereodefined starting material facilitates the preparation of a stereomerically pure target compound. Finally, this approach enables the elucidation of biosynthetic routes of complex natural products by applying biomimetic reactions (Fig. 1).

Fig. 1. Synthesis of natural products using total synthesis and semisynthesis

In the Doctoral Thesis, semisynthetic strategy was applied to generate terpenoid library starting from one of the most abundant sesquiterpenes – β-caryophyllene (**1**, 1 kg for 100 EUR at chemical reagent supplier catalog), which can be isolated from various plant extracts, i.e., cloves,[3] black pepper,[4] oregano,[5] basil,[6] rosemary.[7] The availability of β-caryophyllene from biomass renders it an unexplored renewable resource.

Due to the strain of *E*-cyclononene, the endocyclic double bond of β-caryophyllene (**1**) is more reactive than the exocyclic double bond, thus allowing for the selective functionalization of the former. The natural oxidation product of β-caryophyllene (**1**), β-caryophyllene oxide (**2**, 100 g for 132 EUR at chemical reagent supplier catalog), enables the further diversity in functionalization. In β-caryophyllene oxide, the endocyclic *trans*-double bond is epoxidized, thus driving the alkene functionalization towards exocyclic double bond (Fig. 2). This approach allows for the swift generation of strategic building blocks **A–D**, which can be used for the design of concise routes towards rare natural products. The natural products obtained by semisynthesis can be further used as reference standards in the analysis of plant extracts or in medicinal chemistry for detailed profiling of biological activity.

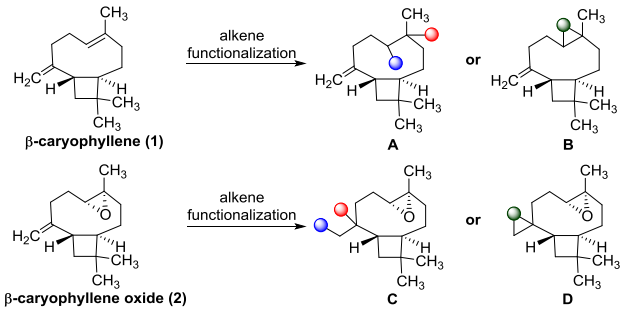


Fig. 2. Generation of building blocks **A**–**D** from β-caryophyllene (**1**) and its oxide (**2**)

Owing to its structure (fused cyclobutane and *E*-cyclononene), two stereodefined chiral centers, and intrinsic ability to rearrange forming various complex carbon frameworks, β-caryophyllene (**1**) possesses the potential to serve as a common starting material (Fig. 3), generating a diverse array of other sesquiterpenes and their derivatives.[8–17]

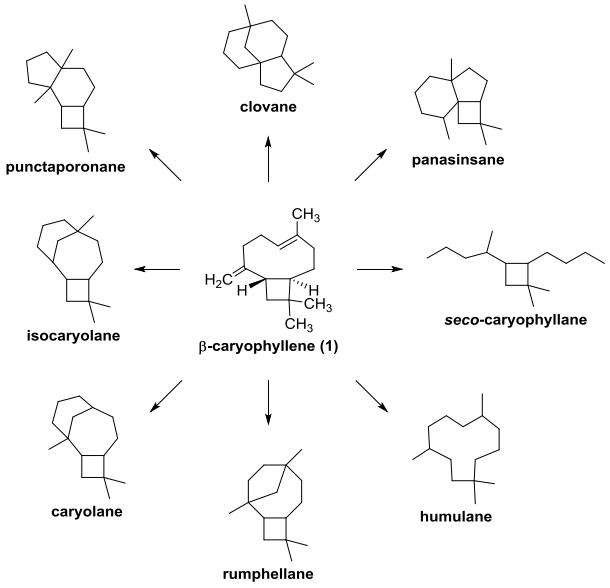
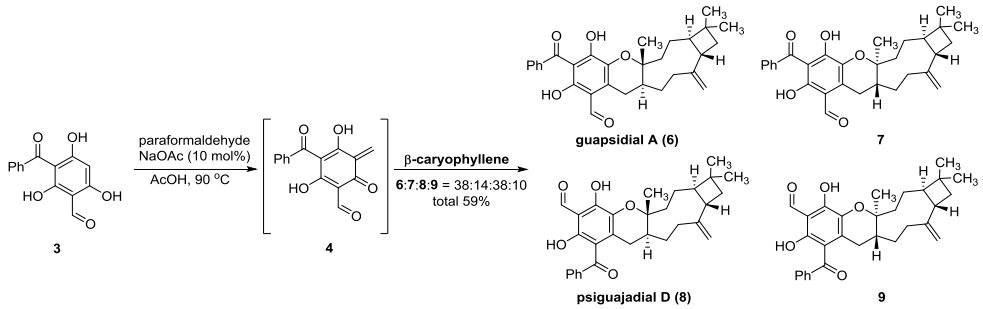


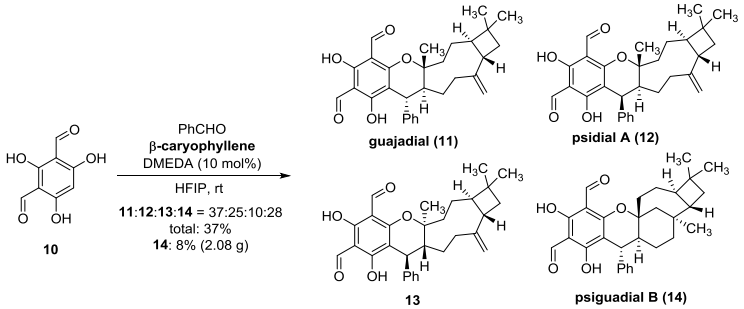
Fig. 3. Scaffold-based diversity available from β-caryophyllene

Prior to this work, β-caryophyllene and its oxide were sporadically used as chiral pool starting materials for the synthesis of exotic natural products. The studies were mainly limited to the biomimetic generation of meroterpenoids from *Psidium guajava*, using the strained endocyclic double bond as a dienophile in hetero-Diels−Alder reactions.[18,19] Thus, Knoevenagel condensation between phloroglucinol derivative **3** and paraformaldehyde afforded *o*-quinone methide **4**, which *in situ* reacted with β-caryophyllene, affording meroterpenoids guapsidial A (**6**), psiguajadial D (**8**) as well as other two diastereomers **7** and **9** (Scheme 1).[18]



Scheme 1. Synthesis of guapsidial A (**6**) and psiguajadial D (**8**)

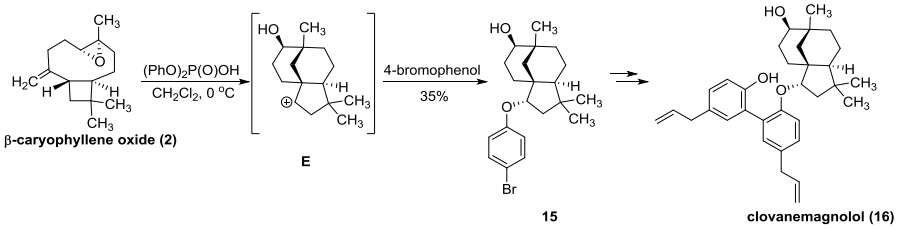
A similar approach was used in one-step multigram-scale synthesis of psiguadial B (**14**). β-Caryophyllene reacted with diformylphloroglucinol (**10**) in the presence of benzaldehyde and DMEDA, yielding the target psiguadial B (**14**) along with guajadial (**11**), psidial A (**12**), and diastereomer **13** (Scheme 2).[19]



Scheme 2. Synthesis of guajadial (**11**), psidial A (**12**) and psiguadial B (**14**)

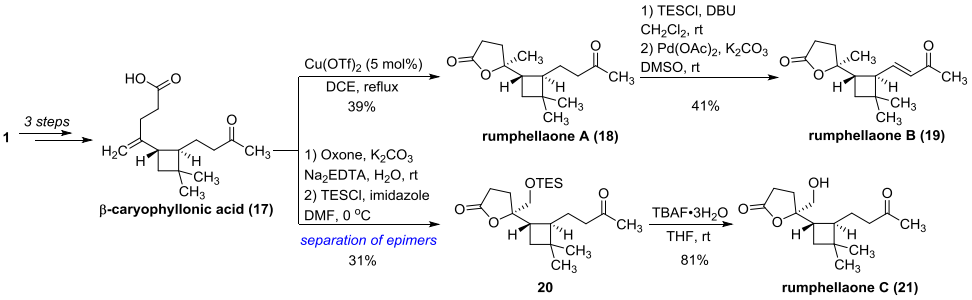
In contrast to the majority of meroterpenoids, which represent classical hetero-Diels−Alder adducts, psiguadial B (**14**) possesses a rearranged caryolane-type scaffold. A combination of computational and synthetic studies revealed that the mechanism of formation of psiguadial B (**14**) involves Michael addition between β-caryophyllene endocyclic double bond and *o*-quinone methide, followed by subsequent transannular cyclization involving exocyclic olefin moiety.[19] This demonstrates the propensity of β-caryophyllene towards the generation of other carbocyclic frameworks.

β-Caryophyllene oxide (**2**) can behave in a comparable fashion, which was demonstrated in the synthesis of clovanemagnolol, a natural product with potential neuroregenerative properties.[20] Lewis and Brønsted acids are able to rearrange β-caryophyllene oxide (**2**) into clovane-type scaffold. The intermediate secondary carbocation **E** was captured by an outer nucleophile (4-bromophenol), and the resultant aryl ether **15** was further functionalized to give clovanemagnolol (**16**, Scheme 3).[20]



Scheme 3. Synthesis of clovane-type aryl ether **15** *en route* to clovanemagnolol (**16**)

The previous research in our group resulted in the development of a concise semisynthesis of *seco*-caryophyllanes rumphellaones A–C (Scheme 4).[21] Initially, β-caryophyllene was converted into β-caryophyllonic acid (**17**), which underwent lactonization, furnishing rumphellaone A (**18**). It was then subjected to Saegusa–Ito α,β-dehydrogenation, providing rumphellaone B (**19**). Epoxidation-lactonization of acid **17** gave rumphellaone C (**21**) after desilylation of compound **20**, whose synthesis was necessary for the efficient separation of epimers.[21]



Scheme 4. Semisynthesis of rumphellaones A–C (**18**, **19** and **21**) from β-caryophyllene (**1**)

The Doctoral Thesis presents further development of semisynthesis approach using β-caryophyllene (**1**) and its oxide (**2**) as starting materials. The studies are devoted to access low-abundant natural products, focusing on bi-, tri- and tetracyclic terpenoids.

Aims and objectives

The aim of the thesis is to develop efficient semisyntheses of rare natural products starting from β-caryophyllene (**1**) and/or its oxide (**2**). In order to achieve this aim, the following tasks were set:

1. Analyze the literature and determine appropriate synthetic targets (biologically active caryophyllane-type terpenoids possessing structural complexity);

2. Design and perform the semisyntheses towards chosen targets with confirmation/revision of their proposed structures.

Scientific novelty and main results

Completion of the thesis led to the following results:

1. Synthesis of rumphellaoic acid A, 4β,8β-epoxycaryophyllan-5-ol and their corresponding ester, disesquiterpenoid rumphellolide J, in a convergent manner;

2. Synthesis of linariophyllenes A–C and rumphellolide H as well as structure revision for linariophyllenes A and C;

3. Synthesis of [4.3.2]propellane-containing natural product (4,4-dimethyltetracyclo-[6.3.0^{2,5}.0^{1,8}]tridecan-9-ol) as well as investigation of cationic scission of [4.3.2]propellane moiety with formation of eventual natural products (bridgehead epoxide iso-euphoranin E and bridgehead olefin (1*R*,2*S*,5*R*)-4,4-dimethyltricyclo[6.3.2.0^{2,5}]tridec-8-en-1-ol;

4. Synthesis of chlorinated hemiketals rumphellatins A–C as well as norsesquiterpenoid rumphellolide C with structure revisions for rumphellatins A and C.

Structure of the thesis

The thesis is a collection of scientific publications on the application of β-caryophyllene and/or its oxide in semisynthesis of rare natural products.

Publications and approbation of the thesis

Main results of the thesis were summarized in four scientific publications. Results of the research were presented at five conferences.

Scientific publications:

1. Stakanovs, G.; Belyakov, S.; Jirgensons, A.; Rasina, D. Convergent Biomimetic Semisynthesis of Disesquiterpenoid Rumphellolide J. *Org. Biomol. Chem.* **2022**, *20* (12), 2455–2461. DOI: 10.1039/D2OB00238H

2. Stakanovs, G.; Blazevica, A.; Belyakov, S.; Rasina, D.; Jirgensons, A. Semisynthesis of Linariophyllenes A–C and Rumphellolide H, Structure Revisions and Proposed Biosynthesis Pathways. *J. Nat. Prod.* **2023**, *86* (10), 2368–2378. DOI: 10.1021/acs.jnatprod.3c00574
3. Stakanovs, G.; Rasina, D.; Belyakov, S.; Kinens, A.; Jirgensons A. Bridgehead Epoxide iso-Euphoranin E from β-Caryophyllene Oxide *via* Sequential Cationic Formation and Scission of [4.3.2]Propellane. *Org. Chem. Front.* **2024**, *11* (18), 5086–5092. DOI: 10.1039/D4QO00940A
4. Stakanovs, G.; Blazevica, A.; Rasina, D.; Belyakov, S.; Jirgensons, A. Bioinspired Semisynthesis and Structure Revisions of Chlorinated Norsesquiterpenoids Rumphellatins A–C. *Org. Lett.* **2024**, *26* (38), 8074–8078. DOI: 10.1021/acs.orglett.4c02942

Results of the thesis were presented at the following conferences:

1. Rasina, D.; Stakanovs, G. Semisynthesis of Rumphellaones A–C and Rumphellolide J from Caryophyllene. *3rd Online International Conference of Biocatalysis & Green Chemistry*. Online, 4–5 April **2022**.
2. Stakanovs, G.; Rasina, D. Semisynthesis of Natural Products from (–)-β-Caryophyllene. *Balticum Organicum Syntheticum (BOS 2022).* Vilnius, Lithuania, 3–6 July **2022**.
3. Stakanovs, G.; Rasina, D.; Jirgensons A. Synthesis of Low-Abundance Sesquiterpenoids from β-Caryophyllene. *International Scientific Conference of the University of Latvia.* Riga, Latvia, 17 March **2023**.
4. Stakanovs, G.; Rasina, D.; Jirgensons, A. Semisynthesis and Structure Rrevision of Linariophyllenes A–C and Rumphellolide H. *Paul Walden 13th Symposium on Organic Chemistry*. Riga, Latvia, 14–15 September **2023**.
5. Stakanovs, G.; Rasina, D.; Jirgensons, A. Synthesis and Structure Revision of Linariophyllenes A–C. *Balticum Organicum Syntheticum (BOS 2024).* Riga, Latvia, 7–10 July **2024**.

MAIN RESULTS OF THE THESIS

1. Semisynthesis of disesquiterpenoid rumphellolide J

Disesquiterpenoids (sesquiterpenoid dimers) are a rare class of natural products, which consist of two different sesquiterpenoid fragments.[22] Rumphellolide J (**24**), disesquiterpenoid isolated from *Rumphella antipathies*, contains scaffolds of rumphellaoic acid A (**23**) and 4β,8β-epoxycaryophyllan-5-ol (**22**), which are connected with ester bond,[23] hence, the proposed biogenetic pathway (Fig. 4) involves esterification of alcohol **22** and acid **23**. Furthermore, while rumphellaoic acid A (**23**) shows anti-inflammatory activity, inhibiting the elastase release by human neutrophils,[24] and alcohol **22** enhances generation of superoxide anion,[25] the biological activity of rumphellolide J (**24**) has not been yet determined.

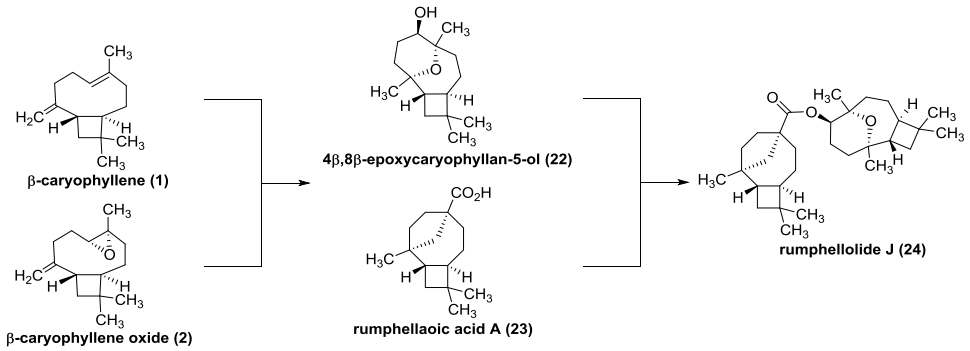
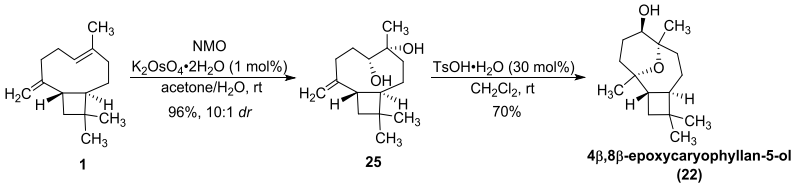


Fig. 4. Plausible biogenetic pathway towards rumphellolide J (**24**)

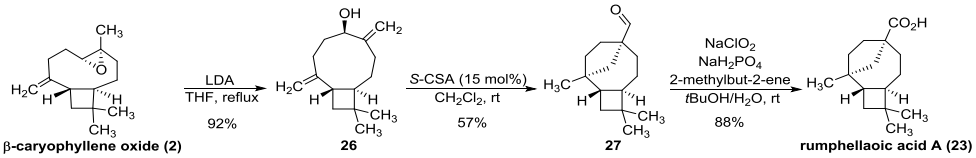
Alcohol **22** is known as one of the products of acid-promoted non-selective transformation of β-caryophyllene oxide (**2**).[26] Fortunately, the selectivity towards the desired product **22** can be driven by employing two-step protocol. Initially, β-caryophyllene (**1**) was dihydroxylated, and the resultant vicinal diol **25** furnished alcohol **22** with catalytic amounts of $TsOH{\cdot}H_2O$ (Scheme 5). Noteworthy, the cyclization proceeded with an exclusive formation of tetrahydropyran cycle with no detectable amount of tetrahydrofuran-containing isomer.



Scheme 5. Two-step synthesis of alcohol **22** from β-caryophyllene (**1**)

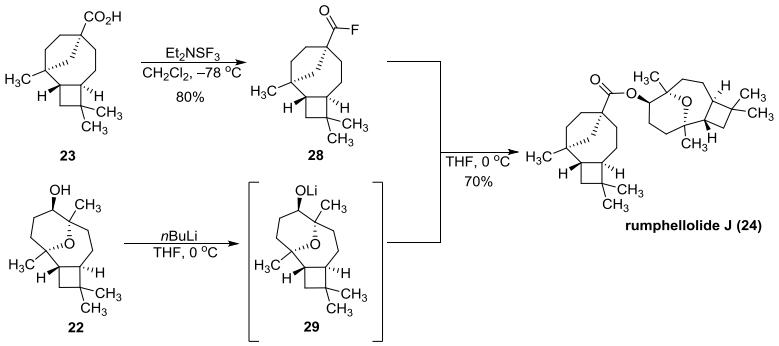
In order to obtain rumphellaoic acid A (**23**), β-caryophyllene oxide (**2**) was isomerized to allylic alcohol **26** in the presence of LDA. Then, acid-catalyzed tandem transannular cyclization with pinacol rearrangement furnished aldehyde **27** (Scheme 6). Varying Brønsted

acids (H_2SO_4, $TsOH \cdot H_2O$, *S*-CSA) and solvents (MeOH, CH_2Cl_2, DCE, C_6H_6), it was found that the most optimal conditions for the synthesis of aldehyde **27** from alcohol **26** were catalytic amounts of *S*-CSA in either benzene or CH_2Cl_2 solution. Afterwards, aldehyde **27** was oxidized under Pinnick conditions (Scheme 6) to yield target rumphellaoic acid A (**23**).



Scheme 6. Synthesis of rumphellaoic acid A (**8**) from β-caryophyllene oxide (**2**)

Rumphellolide J (**24**) was prepared on a gram-scale by conversion of rumphellaoic acid A (**23**) to acyl fluoride **28**, which reacted with lithium alkoxide **29** derived from alcohol **22** (Scheme 7). The structure of rumphellolide J (**24**) was unambiguously confirmed by single-crystal X-ray diffraction.



Scheme 7. Synthesis of rumphellolide J (**24**)

Alternative strategies, such as Steglich esterification with HOBt/EDCI, did not form the ester bond between compounds **22** and **23**. Instead, only intermediates (acyl isourea, HOBt-derived ester and acyl pyridinium ion) were detectable in LC/MS. The conversion of acid **23** into acyl chloride with Vilsmeier reagent ($(COCl)_2$ + DMF), $SOCl_2$ or PCl_3 gave only trace amounts of the desired chloride.

2. Semisynthesis of linariophyllenes A–C

The next step of our study involved the semisynthesis of linariophyllenes A–C (proposed structures **30**–**32**, Fig. 5), caryophyllane-type terrestrial natural products from *Evolvulus linaroides* that possess anti-inflammatory activity by inhibiting nitrogen monoxide production and the pro-inflammatory cytokine IL-1β.[27] Among these compounds, linariophyllene B (**31**) displays the most potent biological activity.[27]

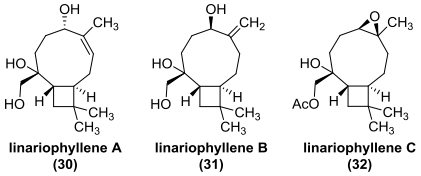
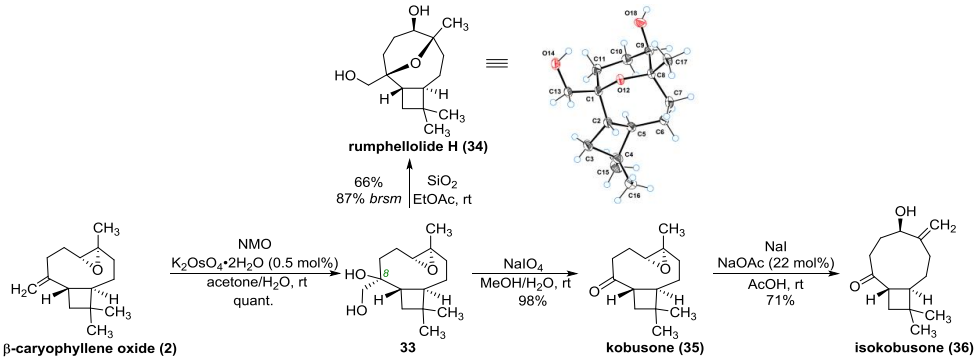


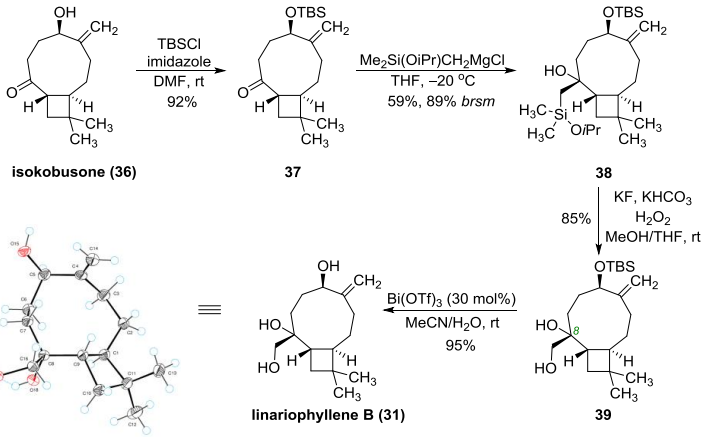
Fig. 5. Proposed structures of linariophyllenes A–C

Firstly, we developed the synthesis of linariophyllene B (triol **31**), bearing exocyclic double bond (Schemes 8 and 9). Dihydroxylation of β-caryophyllene oxide (**2**) gave epoxydiol **33**, albeit with opposite configuration of C-8 in comparison with the target compounds **30**–**32** (Scheme 8). The installation of the desired C-8 configuration was achieved downstream by converting epoxydiol **33** to kobusone (**35**), which was then isomerized in acidic media to isokobusone (**36**). Diol **33** underwent cyclization in the presence of SiO_2, furnishing rumphellolide H (**34**), a marine natural product isolated from *Rumphella antipathies*,[28] whose structure was confirmed by X-ray crystallography (Scheme 8).



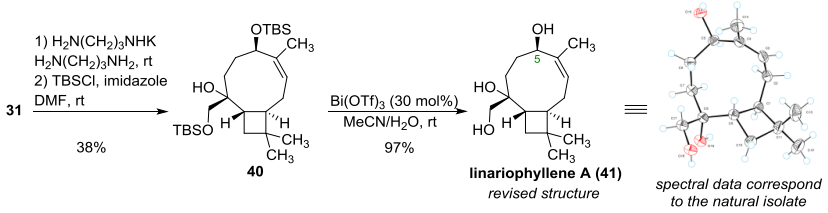
Scheme 8. Synthesis of rumphellolide H (**34**), kobusone (**35**) and isokobusone (**36**) and ORTEP image of rumphellolide H with 50% contour probability

Isokobusone (**36**) was then silylated, furnishing silyl ether **37**, which then reacted with $Me_2Si(OiPr)CH_2MgCl$ (Scheme 9). The resultant β-silyl alcohol **38** was immediately converted to vicinal diol **39** using Tamao oxidation. This approach resulted in the stereoselective installation of desired configuration of C-8, as no formation of C-8 epimer of **39** was detected, indicating perfect diastereocontrol during Grignard addition step. The final desilylation of compound **39** was performed using catalytic amounts of $Bi(OTf)_3$ in aqueous media (Scheme 9). The structure of linariophyllene B (**31**) was confirmed by X-ray crystallography, and the spectral data perfectly corresponded to those of the natural isolate.



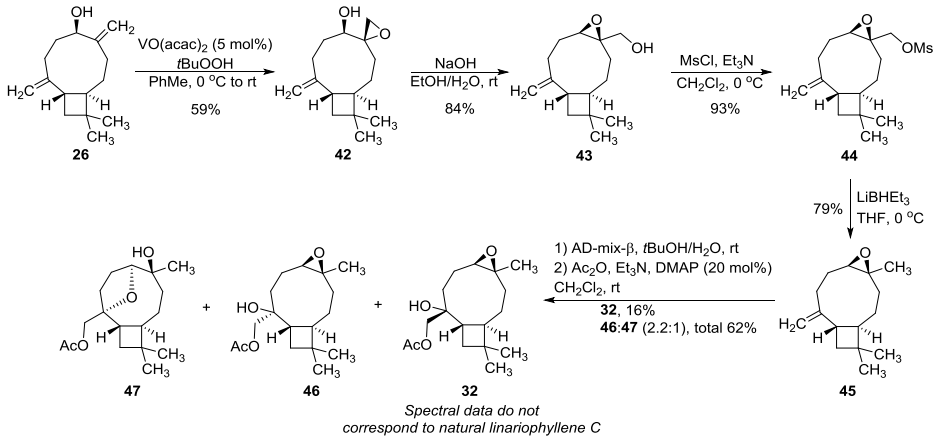
Scheme 9. Synthesis of linariophyllene B (**31**) and its ORTEP image with 50% contour probability

The isomerization of the exocyclic double bond of linariophyllene B (**31**) to the endocyclic double bond was achieved using potassium 3-aminopropylamide (Scheme 10). To facilitate the separation, the resultant mixture was silylated. After the cleavage of TBS groups from compound **40**, it was revealed (Scheme 10) that the correct structure of linariophyllene A (**41**) possesses the same configuration of C-5 as linariophyllene B (**31**).



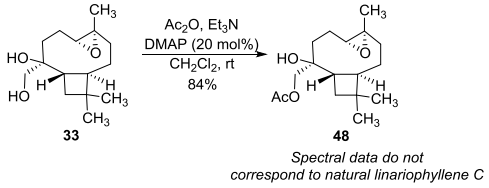
Scheme 10. Synthesis of linariophyllene A (**41**) and its ORTEP image with 50% contour probability

The proposed structure of linariophyllene C (**32**) was obtained using allylic alcohol **26** as a starting material. $VO(acac)_2$-catalyzed epoxidation resulted in the diastereoselective formation of epoxyalcohol **42**, which smoothly yielded primary alcohol **43** as a result of the Payne rearrangement. Mesylation followed by reduction of mesylate **44** with $LiBHEt_3$ gave *cis*-epoxide **45**. After a dihydroxylation/acetylation sequence, diastereomeric epoxyacetates **32** and **46** as well as tetrahydrofuran **47** were isolated. Surprisingly, the spectral data of neither of the diastereomers **46** and **32** corresponded to natural linariophyllene C (Scheme 11).



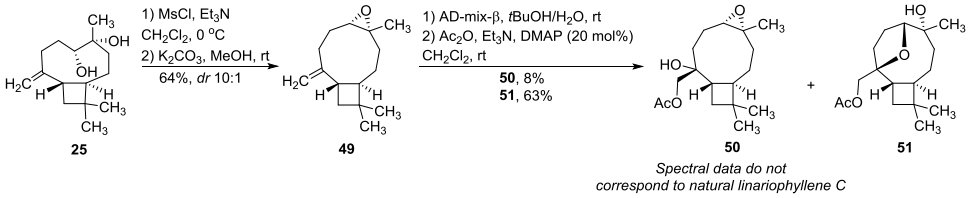
Scheme 11. Synthesis of proposed structure of linariophyllene C (**32**)

We hypothesized that the correct structure of linariophyllene C may be attributed to another diastereomer of compound **32**. Thus, epoxydiol **33** was acetylated to give acetate **48**; however, its spectral data also did not correspond to linariophyllene C (Scheme 12).



Scheme 12. Synthesis of epoxyacetate **48**

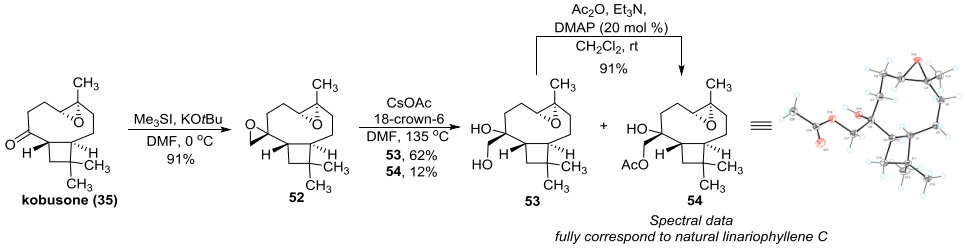
To obtain the other diastereomer of acetate **32**, diol **25** was converted to *cis*-epoxide **49** using Williamson epoxide synthesis. A dihydroxylation/acetylation sequence furnished epoxyacetate **50** and tetrahydrofuran **51**, but the ^{1}H and ^{13}C NMR spectra of compound **50** did not match with the natural linariophyllene C either (Scheme 13).



Scheme 13. Synthesis of epoxyacetate **50**

Finally, the correct structure of linariophyllene C was determined by converting kobusone (**35**) into acetate **54** (Scheme 14). Kobusone (**35**) was transformed to diepoxide **52** by using the Corey–Chaykovsky reaction. The selective cleavage of 1,1-disubstituted epoxide resulted in the formation of diol **53** and acetate **54**. The diol **53** was transformed into acetate **54** using

standard acetylation conditions (Scheme 14). Gratifyingly, the spectral data of acetate **54** completely matched those of natural linariophyllene C.



Scheme 14. Synthesis and determination of the correct structure of linariophyllene C (**54**) and its ORTEP image with 50% contour probability

Having confirmed and corrected the structures of linariophyllenes A−C and rumphellolide H, biosynthetic pathways for their formation (Fig. 6) were proposed starting from β-caryophyllene oxide (**2**).

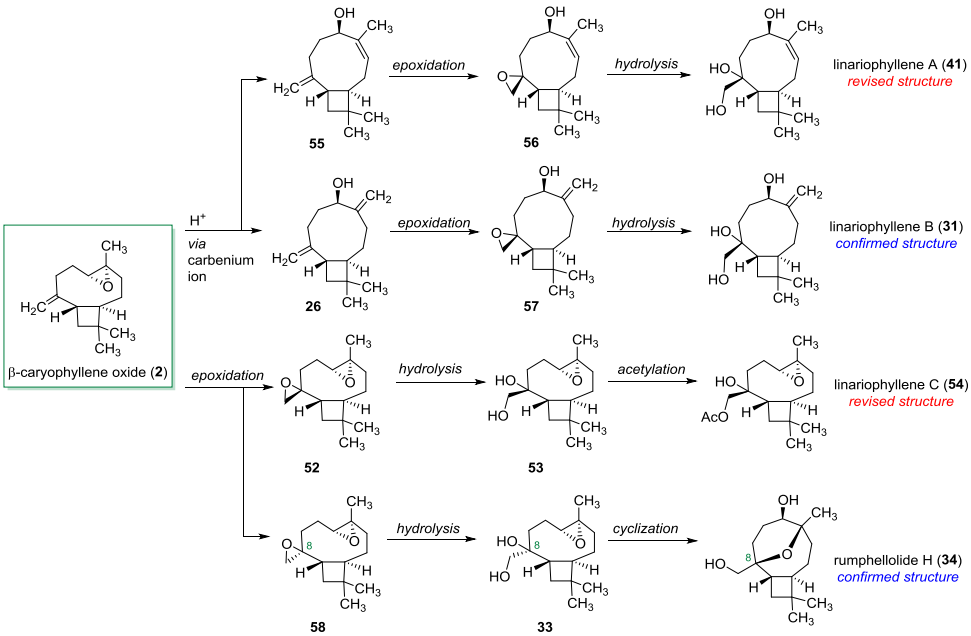


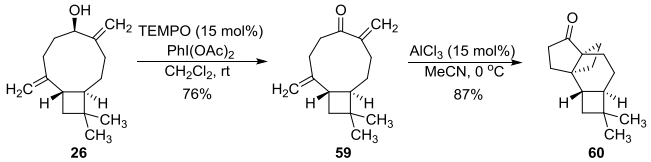
Fig. 6. Proposed biosynthetic pathway towards linariophyllenes A−C and rumphellolide H

Initially, acid-catalyzed epoxide isomerization of β-caryophyllene oxide (**2**) can form allylic alcohols with exo- (**26**) or endocyclic double bond (**55**). Linariophyllenes A and B then can be formed after epoxidation[29] and subsequent hydrolysis of spiroepoxides **56** and **57** (Fig. 6). Linariophyllene C (**54**) and rumphellolide H (**34**) may stem from diepoxides **52** and **58**. Epimer **52** can lead to linariophyllene C (**54**) after hydrolysis and acetylation of the primary alcohol, whereas hydrolysis of epimer **58** forms diol **33**, which can undergo

acid-mediated cyclization to yield rumphellolide H (**34**), as it was demonstrated in developed synthetic routes (Scheme 8). The opposite diastereoselectivity of epoxidation of C-8 (Fig. 6) *en route* to rumphellolide H (**34**) can be explained by different enzymes ensuring this transformation in marine and terrestrial organisms.

3. [4.3.2]Propellane and bridgehead epoxide-containing natural products

Next, we aimed at the investigation of acid-catalyzed rearrangements of enone **59**, which can be prepared from allylic alcohol **26** via standard oxoammonium-catalyzed oxidation. While the acid-catalyzed rearrangements of alcohol **26** are known, the analogous transformations of enone **59** have not been reported. This study revealed that Lewis acids, such as $AlCl_3$, $BF_3{\cdot}OEt_2$, $TiCl_4$ and Me_3SiOTf, initiate [2 + 2] cycloaddition, furnishing [4.3.2]propellane-containing ketone **60** (Scheme 15).



Scheme 15. Synthesis of ketone **60**

DFT calculations indicated that the mechanism of this [2 + 2] cycloaddition is concerted, however, the reason of the diastereoselectivity remains unclear, as the calculated difference between conformations **SM-A** and **SM-B** of enone−$AlCl_3$ complex is only 0.5 kcal/mol (Fig. 7). A similar reaction was discovered by Gassman,[30,31] however, the transformation from **59** to **60** does not employ the 1,3-dioxolane protection of the carbonyl, as described in the original findings.[30,31] Moreover, it is the first time when the construction of a [4.3.2]propellane motif was achieved employing acid catalysis.

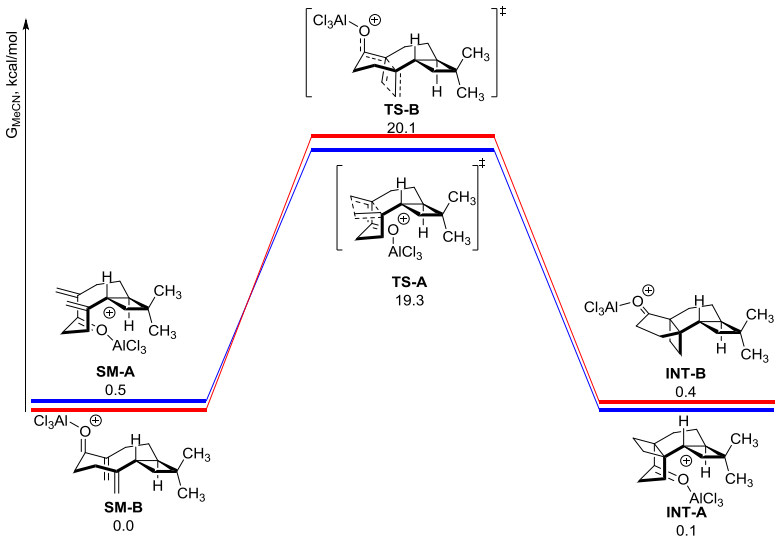
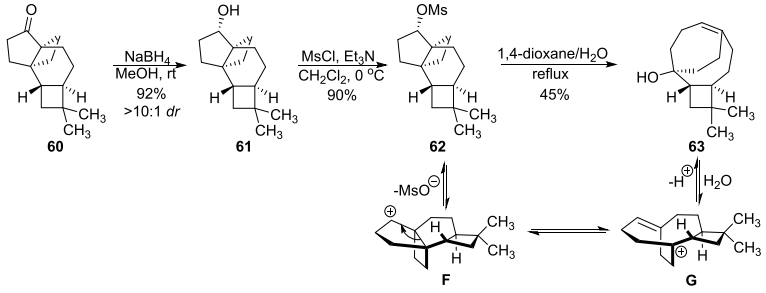


Fig. 7. Potential energy surface for the [2 + 2] cycloaddition of enone **59** (DFT calculations were performed in collaboration with *Dr. chem.* Artis Kinēns)

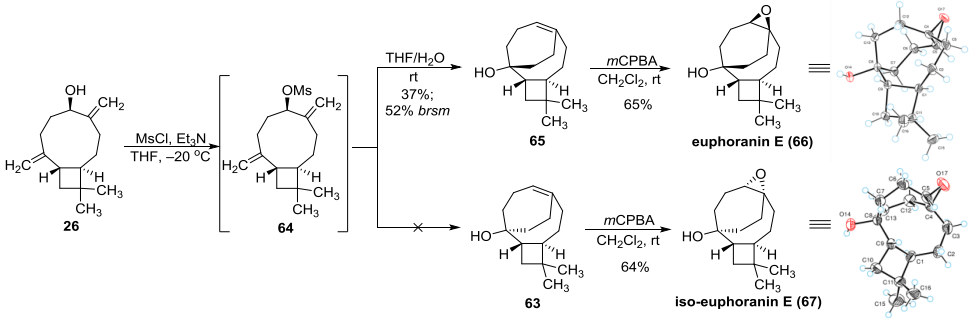
Ketone **60** was then reduced to alcohol **61** (Scheme 16), which is a natural product found in a variety of plant extracts (*Tagetes lucida*, *Psidium guajava*).[32,33] The transformation from the naturally occurring enone **60** to alcohol **61** suggests a possible biosynthetic link between two compounds and implies that similar [2 + 2] cycloaddition may occur in plants. The mesylation of alcohol **61** gave rise to the corresponding mesylate **62**, which underwent solvolysis, resulting in the formation of bridgehead olefin **63** (Scheme 16). The mechanism of this reaction most probably involves the formation of secondary carbocation **F**, which rearranges to bridgehead carbocation **G** that undergoes hydration with the formation of product **63**.



Scheme 16. Synthesis of alcohol **61** and the route towards bridgehead olefin **63**

Bridgehead olefin **63** is a diastereomer of the natural product **65**,[34] which can be synthesized from allylic mesylate **64** (Scheme 17). Interestingly, the solvolysis of compound **64** did not produce the alcohol **63**. Both olefins **63** and **65** were epoxidized to products **66** and **67** in a stereoselective fashion (Scheme 17). After comparing with the literature, the spectral

data of epoxide **66** corresponded to euphoranin E, a natural product from the terrestrial plant *Euphorbia wangii*.[35] Nevertheless, the probability of the natural occurrence of compounds **63** and **67** is also high, since they can be synthesized from the natural [4.3.2]propellane **60**.



Scheme 17. Synthesis of bridgehead epoxides **66** and **67** and their ORTEP images with 50% contour probability

The DFT calculations (Fig. 8) were also used in this case to explain the stereoselectivity of the solvolysis of mesylate **64**. The equatorial position of –OMs group in **SM-C** conformation establishes the overlap between π orbital of the double bond and antibonding orbital of C–O bond, thus, the departure of mesylate anion is more favorable compared to **SM-D** conformation, in which –OMs group is directed axially. This hyperconjugational effect results in the 3.5 kcal/mol difference between transition states **TS-C** and **TS-D**, leading to >99:1 diastereomeric ratio that corresponds to the experimental results.

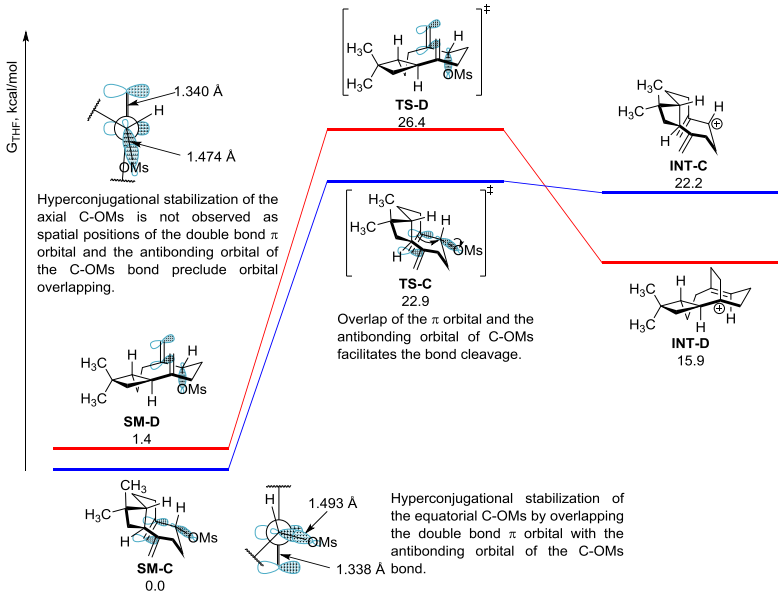


Fig. 8. Potential energy surface for the solvolysis of mesylate **64** (DFT calculations were performed in collaboration with *Dr. chem.* Artis Kinēns)

4. Synthesis of chlorinated hemiketals rumphellatins A–C

Rumphellatins A–C (proposed structures **68–70**) are chlorinated norsesquiterpenoids isolated from *Rumphella antipathies* possessing a hemiketal moiety (Fig. 9).[36,37] The presence of both halogen and hemiketal functionalities renders these natural products structurally exotic among caryophyllane-type terpenoids. Rumphellatins A and B (**68** and **69**) exhibit modest antibacterial activity according to preliminary studies.[36,37] An unsuccessful attempt of total synthesis of these natural products was made, which prompted us to explore a semisynthetic strategy.[38]

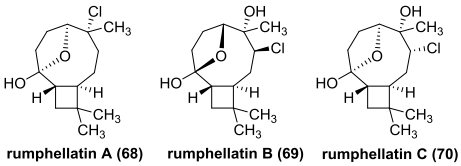
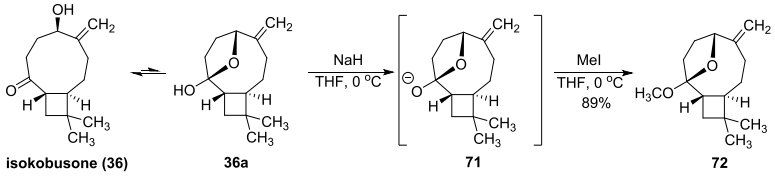


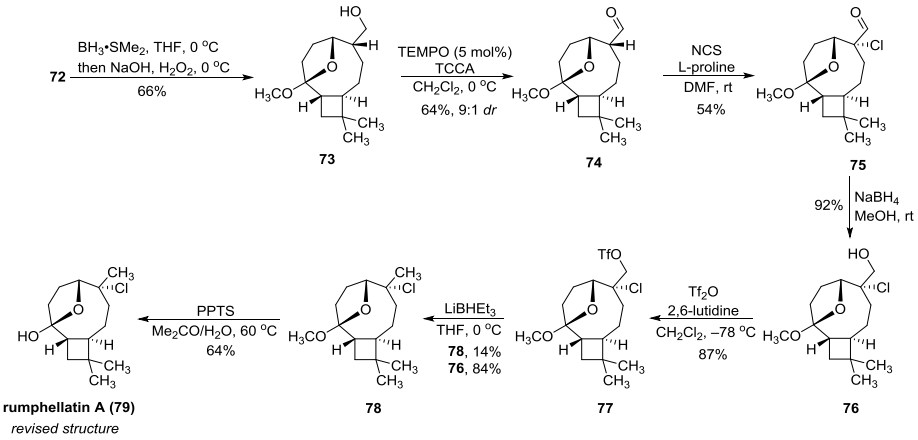
Fig. 9. Proposed structures of rumphellatins A–C (**68–70**)

During our previous studies, it was observed that isokobusone (**36**) exists as a mixture of major keto-tautomer **36** and minor (~13%) hemiketal tautomer **36a** in $CDCl_3$ solution (Scheme 18). This observation facilitated the development of a semisynthesis of rumphellatins A–C, employing isokobusone (**36**) as a key intermediate. Deprotonation of isokobusone with NaH resulted in the formation of the corresponding alkoxide, which formed a hemiketal anion **71**. It was then successfully trapped using MeI as an electrophile, producing ketal **72** in excellent yield (Scheme 18).



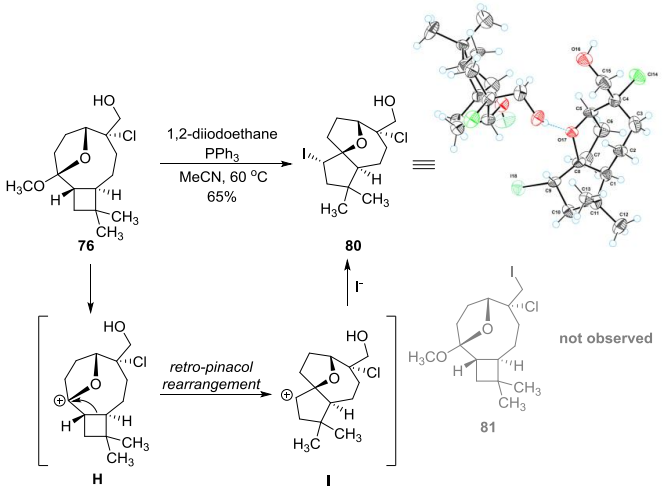
Scheme 18. Isokobusone ketone–hemiketal tautomery and synthesis of ketal **72**

The initial synthesis of rumphellatin A (Scheme 19) started with the hydroboration-oxidation of ketal **72**, resulting in primary alcohol **73**. It was oxidized to aldehyde **74**, which underwent α-chlorination in the presence of NCS and L-proline. The obtained α-chloroaldehyde **75** was reduced to chlorohydrin **76**. Subsequent triflation and reduction of triflate **77** with $LiBHEt_3$ yielded compound **78**. Demethylation of ketal **78** produced hemiketal **79**, whose spectral data fully corresponded to natural rumphellatin A; therefore, the configuration of tetrahydrofuran fragment of rumphellatin A was revised.



Scheme 19. Initial synthesis of rumphellatin A (**79**)

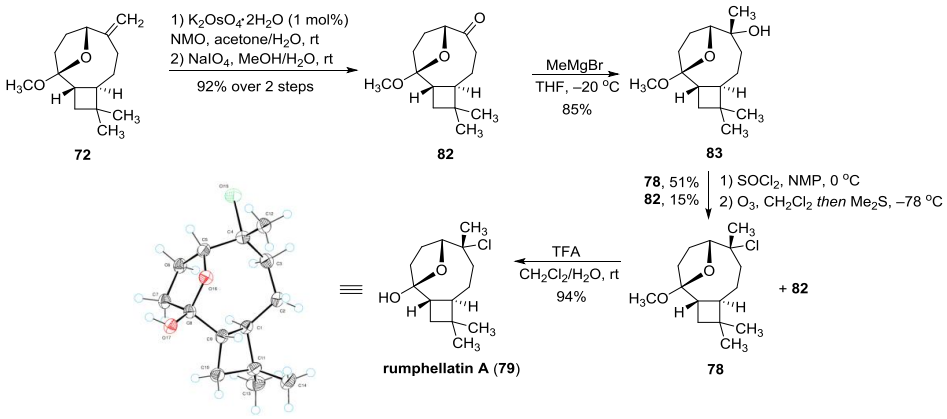
The major disadvantage of this synthesis (Scheme 19) was long linear sequence and low yield of triflate **77** reduction, in which the main product was alcohol **76**. This can originate from hydride attack on sulfur atom instead of sterically hindered neopentylic carbon atom. Importantly, $LiBHEt_3$-mediated reduction of the corresponding mesylate or tosylate derived from alcohol **76** did not occur at all. When alcohol **76** was subjected to Appel iodination to introduce iodide as an alternative leaving group, iodocyclopentane **80** was obtained instead of the primary iodide **81** as a result of competitive retro-pinacol rearrangement (Scheme 20).



Scheme 20. Synthesis of iodide **80** and its ORTEP image with 50% contour probability

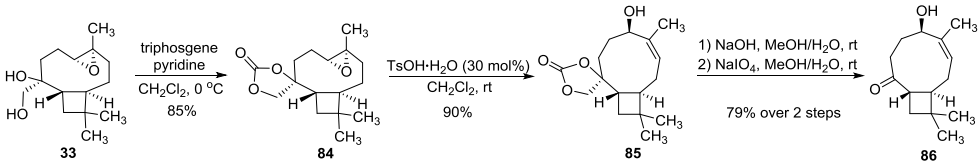
Improved synthesis of rumphellatin A (**79**) involved a dihydroxylation and diol cleavage sequence of ketal **72** (Scheme 21). Ketone **82** was subjected to a reaction with MeMgBr, diastereoselectively producing tertiary alcohol **83**. Chlorination of alcohol **83** with $SOCl_2$ in NMP afforded the desired chloride **78** and ketal **72** as a result of a competing elimination

reaction. The mixture of compounds **78** and **72** was inseparable using column chromatography; therefore, the subsequent ozonolysis was used to convert alkene **72** into ketone **82**, making the separation of tertiary chloride **78** more facile. Treatment of chloride **78** with aqueous TFA gave rumphellatin A (**79**) in excellent yield.



Scheme 21. Improved synthesis of rumphellatin A (**79**) and its ORTEP image with 50% contour probability

The synthesis of rumphellatins B and C started with the protection of epoxydiol **33** as a carbonate using triphosgene and pyridine (Scheme 22). The obtained epoxycarbonate **84** smoothly underwent acid-catalyzed isomerization to form the endocyclic double bond, producing allylic alcohol **85**. Alkali-mediated carbonate hydrolysis with subsequent vicinal diol oxidative cleavage gave keto alcohol **86**, which served as a common intermediate for the synthesis of rumphellatins B and C (Scheme 22).

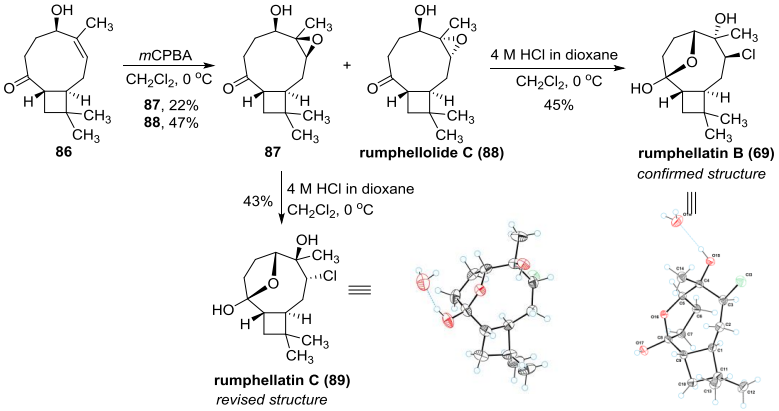


Scheme 22. Synthesis of keto alcohol **86**

The synthesis of rumphellatin B was completed (Scheme 23) by the epoxidation of allylic alcohol **86**, resulting in the formation of rumphellolide C (**88**),[39] whose structure was confirmed by single-crystal X-ray diffractometry. Treatment of rumphellolide C with HCl yielded rumphellatin B (**69**), whereas diastereomer **87** yielded rumphellatin C under analogous conditions. The facile transformation from rumphellolide C to rumphellatin B indicates that a similar transformation may occur in *Rumphella antipathies*.

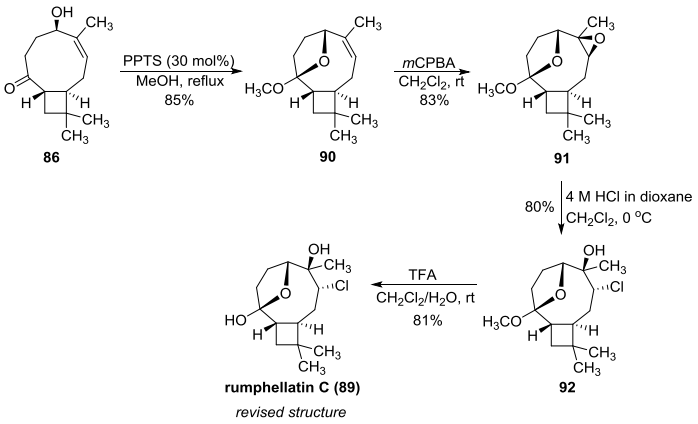
While the structure of rumphellatin B was confirmed, it was revealed that the correct structure of rumphellatin C (**89**) possesses the same configuration of tetrahydrofuran moiety as in hemiketals **79** and **69**, since the spectral data of compound **89** perfectly corresponded to

the natural isolate. Moreover, the configuration of the tertiary alcohol in rumphellatin C (**89**) was also proven to be opposite compared to the proposed structure.



Scheme 23. Synthesis of rumphellolide C (**88**), rumphellatins B (**69**) and C (**89**) with their corresponding ORTEP images as monohydrates with 50% contour probability

An alternative diastereoselective synthesis of rumphellatin C (**89**) was developed by the ketalization of keto alcohol **86** in MeOH, furnishing compound **90** (Scheme 24). Stereoselective epoxidation with *m*CPBA resulted in the formation of epoxide **91**, whose treatment with HCl afforded chlorohydrin **92**. Analogously to the synthesis of rumphellatin A (Scheme 19), demethylation was achieved by action of aqueous TFA to yield the final product **89**.



Scheme 24. Diastereoselective synthesis of rumphellatin C (**89**)

With the established structure revisions of these natural products, the biosynthetic pathway can be proposed. It is known that kobusone (**35**) is present in *Rumphella antipathies*,[40] which could be a common starting point for the biogenesis of rumphellatins A−C as well as rumphellolide C (Fig. 10).

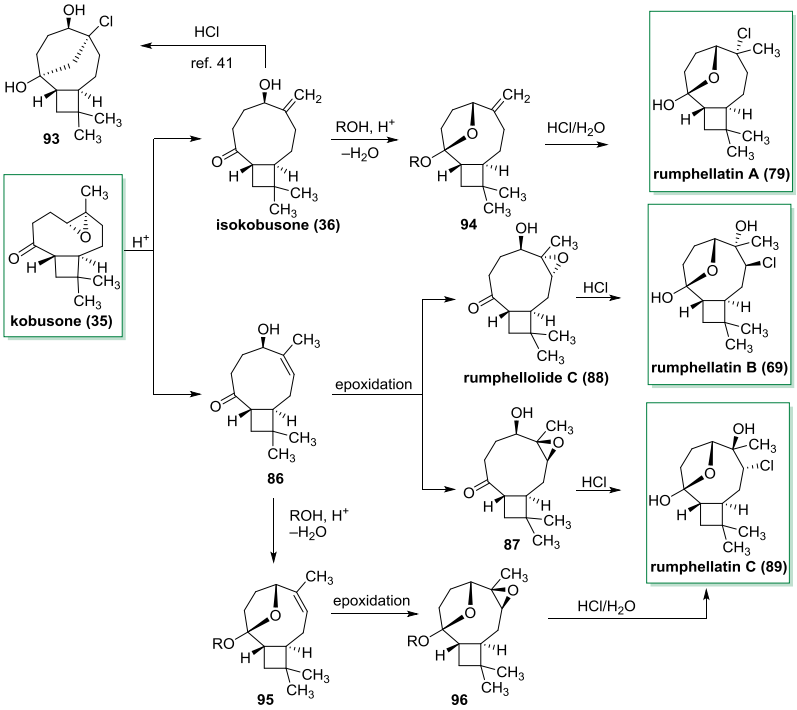


Fig. 10. Proposed biosynthetic pathways towards rumphellatins A−C

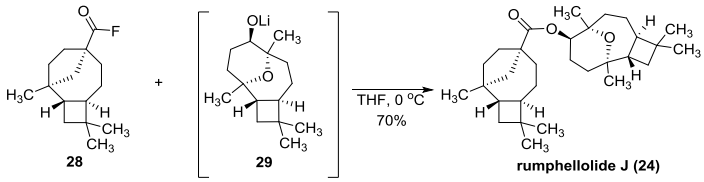
Analogously to the biosynthesis of linariophyllenes A and B (Fig. 6), the first step may involve the acid-catalyzed isomerization of *trans*-epoxide moiety to allylic alcohols **36** and **86**, whose presence in *Rumphella antipathies* still needs to be confirmed. It is reported that treatment of isokobusone with HCl quantitatively leads to chloride **93**,[41] thus making improbable the direct hydrochlorination of isokobusone in gorgonian corals. Instead, ketalization may occur with the formation of ketal **94**, followed by reaction with HCl,[42] producing rumphellatin A (**79**) after ketal cleavage. An alternative pathway involving halohydrin dehalogenase-mediated cleavage of *trans*-epoxide moiety of kobusone, producing rumphellatin A in one step, is also feasible.[43]

Rumphellatin B (**69**) may originate from allylic alcohol **86**, which undergoes epoxidation to form rumphellolide C (**88**). The epoxide is then cleaved by HCl, potentially assisted by halohydrin dehalogenases.[43] In case of non-diastereoselective epoxidation of allylic alcohol **86**, a similar pathway can be suggested for rumphellatin C (Fig. 10).

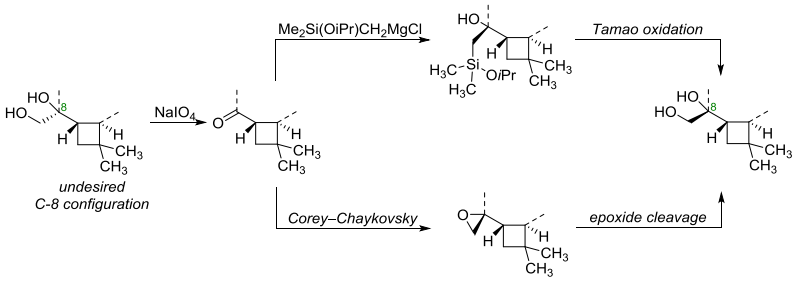
An alternative diastereoselective pathway towards rumphellatin C also can be proposed, which includes ketalization of allylic alcohol **86** and subsequent epoxidation (Fig. 10), furnishing epoxyketal **96**. Hydrochlorination-deketalization of compound **96** can then produce rumphellatin C.

CONCLUSIONS

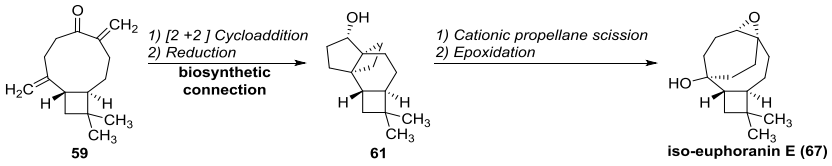
1. Acyl fluoride-lithium alkoxide coupling is the most efficient approach to form an ester bond in rumphellolide J, which successfully delivers the target product on a gram-scale in a biomimetic manner.



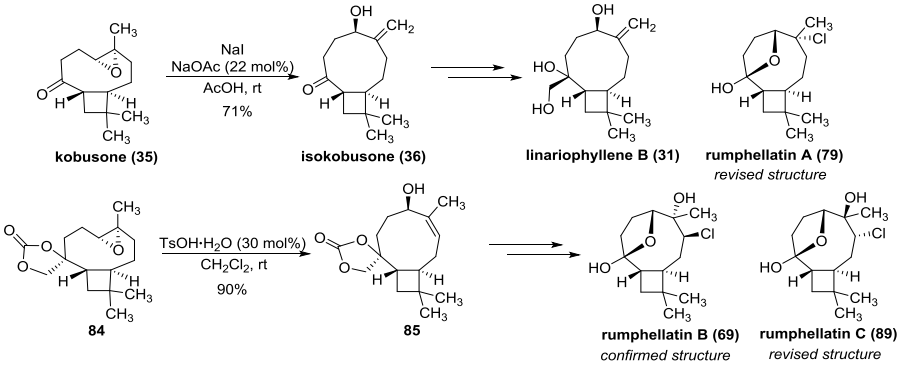
2. Nucleophilic hydroxymethylation of ketone functionality is an effective method for the stereochemical inversion of vicinal diol moiety in caryophyllane-type terpenoids. This approach was successfully employed in the synthesis of linariophyllenes A–C.



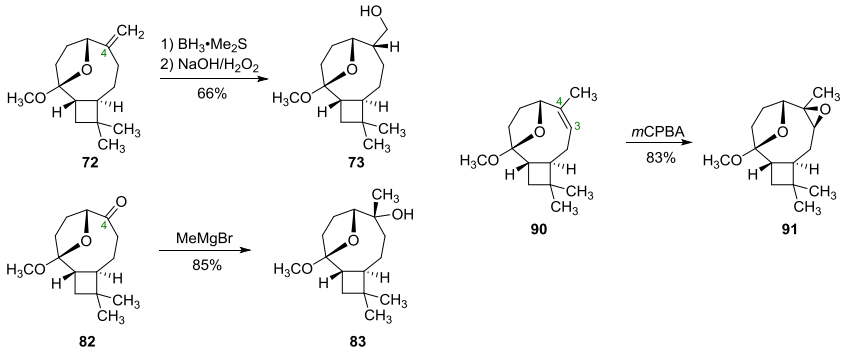
3. The concerted Lewis acid-catalyzed [2 + 2] cycloaddition of enone **59** revealed a biosynthetic link connecting it with the naturally occurring [4.3.2]propellane-containing alcohol **61**. Subsequent cationic scission and epoxidation yielded the eventual natural product iso-euphoranin E (**67**).



4. The acid-mediated selective cleavage of *trans*-epoxide to either endo- or exocyclic allylic alcohols provides an effective route towards linariophyllene B and chlorinated norsesquiterpenoids rumphellatins A–C.



5. 12-Oxatricyclo[7.2.1.0^{2,5}]dodecane scaffold enables olefin or carbonyl functionalization at C-3 and/or C-4 positions by the attack of outer electrophile/nucleophile from the face of bridging oxygen. This provides the diastereoselective formation of hydroboration-oxidation, Grignard addition, and epoxidation products.



6. Semisynthesis starting from abundant (–)-β-caryophyllene or its oxide provides an effective approach towards their more exotic congeners in ample quantities (up to gram-scale) with confirmation or revision of the originally proposed structures. These final products can be further applied for profiling their biological activity and as reference standards in studies of the metabolism of terrestrial or marine organisms.

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PIELIKUMI/PUBLICATIONS

1. pielikums/publication No. 1

Stakanovs, G.; Belyakov, S.; Jirgensons, A.; Rasina, D. Convergent Biomimetic Semisynthesis of Disesquiterpenoid Rumphellolide J.

Org. Biomol. Chem. **2022**, *20* (12), 2455−2461.

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Convergent biomimetic semisynthesis of disesquiterpenoid rumphellolide J†

Georgijs Stakanovs, Sergey Belyakov, Aigars Jirgensons and Dace Rasina *

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The convergent biomimetic gram-scale synthesis of disesquiterpenoid ester rumphellolide J is described. 4β,8β-Epoxycaryophyllan-5-ol was prepared in 67% yield (1.4 g) from naturally ambudant (−)-β-caryophyllene. (+)-Rumphellaoic acid A was obtained in 46% yield (2.2 g) from (−)-caryophyllene oxide. The synthesised (+)-rumphellaoic acid had an opposite specific rotation compared to that of (−)-rumphellaoic acid A isolated from nature, indicating possible occurrence of (+)-β-caryophyllene in *Rumphella antipathies* and *Psidium guajava*. Esterification of (+)-rumphellaoic acid A *via* acyl fluoride and alkoxide of 4β,8β-epoxycaryophyllan-5-ol gave rumphellolide J in 70% yield (1.65 g). The same structure for the synthesized product and natural isolate was proven despite the opposite specific rotation value of the intermediate acid. The short access to the terpenoids provides a material for further investigations of biological activities and valuable reference standards for the analysis of the chemical composition of various natural sources.

Introduction

Gorgonian coral *Rumphella antipathies* L. is a rich source of structurally diverse β-caryophyllene-derived terpenoids, which have been identified by detailed investigations of its chemical constituents. Such derivatives mainly possess caryophyllane- or clovane-related frameworks, as well as specific γ-lactone moieties (Fig. 1).[1] Among the isolated products, two disesquiterpenoid esters were identified: rumphellolide J (**7**)[2] – an ester of rumphellaoic acid A (**5**) and 4β,8β-epoxycaryophyllan-5-ol (**6**), and rumphellolide L (**10**)[3] – an ester of antipacid A (**8**) and clovane-2β,9α-diol (**9**) (Scheme 1).

Although rumphellaoic acid A (**5**) displayed anti-inflammatory activity by inhibiting the release of elastase by human neutrophils and 4β,8β-epoxycaryophyllan-5-ol (**6**) enhanced the generation of superoxide anions, rumphellolide J (**7**) was not tested in any bioactivity assays.[2]

The proposed biogenetic pathways indicate that all aforementioned isolated compounds might have originated from β-caryophyllene (**1**) and/or its oxide (**4**) as their relative configuration match with the parent compounds (Scheme 1).

(−)-β-Caryophyllene ((−)-**1**) can be obtained from different natural sources in large quantities and can be used not only as a cheap, renewable starting material to access more complex low-abundance natural compounds, but also to study biosynthetic connections in nature. Several natural product syntheses from (−)-β-caryophyllene have been recently demonstrated, including the biomimetic syntheses of meroterpenoids,[4–8] semisyntheses of rumphellaones A–C,[9] as well as the rearrangement of caryophyllene derivative to the tricyclic presilphiperfolan-1β-ol structure,[10] providing evidence for biosynthetic relationships in nature. Only few examples to date depict the applicability of β-caryophyllene and β-caryophyllene oxide in gram-scale syntheses of natural products of rare occurrence.[11,12]

Our ongoing research in the field of natural product semisynthesis from β-caryophyllene has resulted in the convergent biomimetic gram-scale synthesis of rumphellolide J (**7**)[2] by esterification of rumphellaoic acid A (**5**)[13,14] and 4β,8β-epoxycaryophyllan-5-ol (**6**)[15,16] (Scheme 1).

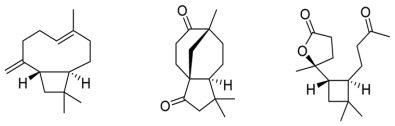

Fig. 1 Representative structures of caryophyllane, clovane and γ-lactone frameworks.

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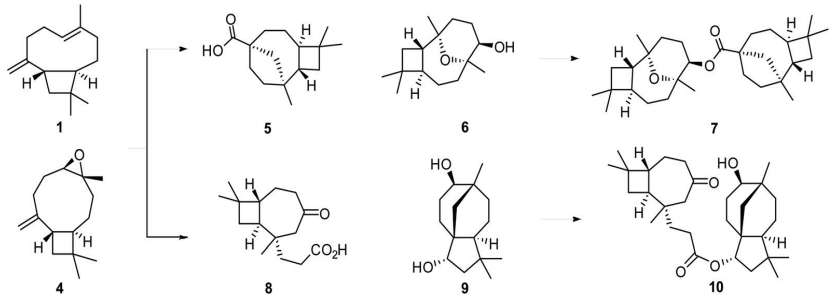
†Electronic supplementary information (ESI) available: List of compounds isolated from *Rumphella antipathies*. ^{1}H, ^{13}C NMR spectra of all compounds; 2D NMR spectra with assignments of all protons, carbons and interactions in NOESY, HMBC spectra, comparison of specific rotation values and ^{1}H, ^{13}C NMR shifts of (+)-**5**, (−)-**6** and (−)-**7**; X-ray crystallography data (CIF) for (+)-**5**, (−)-**12** and (−)-**7**. CCDC 2127464–2127466. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2ob00238h



Scheme 1 Proposed biogenetic pathways and structures of rumphellolide J (**7**) and L (**10**).

Results and discussion

Synthesis of 4β,8β-epoxycaryophyllan-5-ol (6)

4β,8β-Epoxycaryophyllan-5-ol ((−)-**6**) was first obtained as a synthetic product[16,17] and later isolated from gorgonian coral *Rumphella antipathies*.[15] Previously, caryophyllanol (−)-**6** was synthesized in low yields using an aqueous acid-catalyzed rearrangement of caryophyllene oxide ((−)-**4**), in which vicinal diol (−)-**11** was proposed as an intermediate that is formed *in situ* by acid-induced epoxide cleavage.[16] The formation of the tetrahydropyran fragment was confirmed by NMR experiments, yet the configuration of C-5 in the obtained material was not determined.[16] The C-5 configuration was determined relative to the other stereocenters in the isolated compound, although the absolute configuration remained unclear.[15]

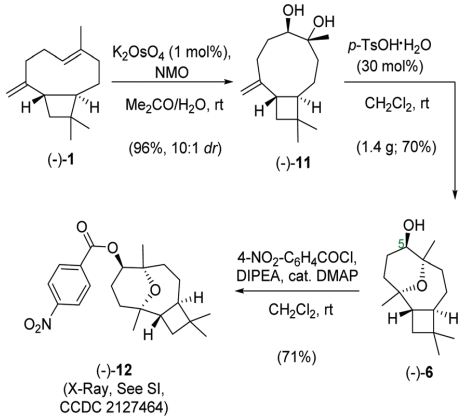
In the present work, we used a stereo- and regiocontrolled strategy for the synthesis of caryophyllanol (−)-**6** that included direct diastereoselective synthesis of diol (−)-**11**, utilizing dihydroxylation of (−)-caryophyllene ((−)-**1**),[9] followed by acid-catalyzed tetrahydropyran formation (Scheme 2). Gratifyingly, by using this approach, alcohol (−)-**6** was isolated as the major product in 70% yield, exceeding all previously reported results. Caryophyllanol (−)-**6** was fully characterized and the obtained data were consistent with literature values.[15] Crystals suitable for X-ray diffraction were obtained from the 4-nitrobenzoyl derivative (−)-**12** (CCDC 2127464†), which unambiguously confirmed the desired structure.

Synthesis of rumphellaoic acid A (5)

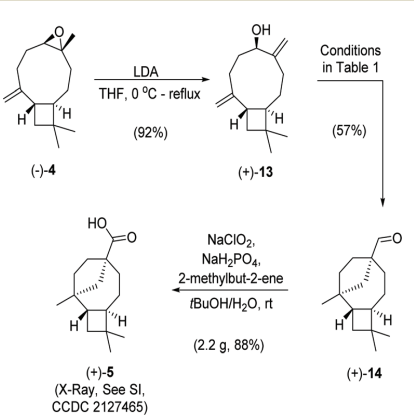
Rumphellaoic acid A ((−)-**5**) was isolated from the gorgonian coral *Rumphella antipathies*.[13] The same structure was later attributed to the guavacid A isolated from the leaves of *Psidium guajava* L.[14] It was proposed that acid (−)-**5** is naturally derived from β-caryophyllene (**1**), yet the absolute configuration of the isolated material was not assigned.

The synthesis of rumphellaoic acid A (**5**) has not been reported, however, the corresponding rumphellane carbon skeleton is present in aldehyde **14**, a product of acid-mediated cyclisation and pinacol-type rearrangement of allylic alcohol **13**.[18,19] In addition, both allylic alcohol **13**[17,20–22] and aldehyde **14**[17] have been detected in low yields as rearrangement products of caryophyllene oxide (**4**) in acidic media.

We prepared (+)-**13** by treatment of caryophyllene oxide ((−)-**4**) with lithium diisopropylamide (LDA) (Scheme 3).[23,24] Previously, aldehyde **14** was synthesised in moderate to good yields using acidic conditions (tetracyanoethylene/MeOH;



Scheme 2 Synthesis of 4β,8β-epoxycaryophyllan-5-ol ((−)-**6**).



Scheme 3 Synthesis of rumphellaoic acid A ((+)-**5**).

H_2SO_4/MeOH or H_2SO_4/Et_2O).[18,19] In our hands, the treatment (+)-**13** with H_2SO_4 in MeOH produced (+)-**14** in only 32% yield with the formation of various side products. After the evaluation of different acids and solvents, we were pleased to see that *S*-camphorsulphonic acid (CSA), in catalytic quantity, facilitated the formation of (+)-**14** with yields as high as 57% on gram scale (Table 1).[25] Subsequent Pinnick oxidation of (+)-**14** led to the target rumphellaoic acid A ((+)-**5**) in 88% yield (Scheme 3).

NMR spectra (^{1}H, ^{13}C, HSQC, HMBC, COSY, NOESY) of the synthesised acid (+)-**5** are in agreement with that of products isolated from natural sources, thus establishing the structure and relative configuration of all stereocentres, as well as the same identity of the two naturally isolated acids. These results confirm the occurrence of rumphellane carbon frameworks both in terrestrial (*Psidium guajava*)[14] and marine organisms (*Rumphella antipathies*).[13] In addition, we confirmed the relative and absolute configuration by crystallographic analysis of (+)-**5** (CCDC 2127465†). Nevertheless, specific optical rotation of isolated product (−)-**5** was assigned as negative in both isolated materials: $[\alpha]_D^{23} = -32$ (c = 0.07, $CHCl_3$)[13] and $[\alpha]_D = -11.8$ (c = 0.06, $CHCl_3$),[14] respectively, whereas the synthesised acid (+)-**5** has an opposite specific rotation $[\alpha]_D^{20} = +25.5$ (c = 1.04, $CHCl_3$). Theoretically opposite specific rotation is possible in both cases: compounds are diastereomers or enantiomers. Since NMR data established the same relative configuration, stereocentres of cyclobutane were not interfered during the synthesis, and transformation of (+)-**13** to (+)-**14**, including the formation of two new stereocentres, was fully substrate controlled, we can assume, that the (−)-rumphellaoic acid A ((−)-**5**) isolated from natural sources likely originates from less common (+)-caryophyllene ((+)-**1**) or its derivative, and is an enantiomer of (+)-**5**, obtained synthetically from (−)-caryophyllene oxide ((−)-**4**). Although β-caryophyllene and its derivatives are detected in various organisms (bacteria, plants, and corals), the absolute configuration for the majority of these products has not been described. It is known that (+)-caryophyllene ((+)-**1**) is produced by liverworts[26,27] and bacterial enzymes.[28] Contrastingly, it is assumed that specifically (−)-caryophyllene ((−)-**1**) is present in the essential oils of many different spice and food plants. We cannot exclude other circumstances, *e.g.* interfered measurements by impurities in natural samples, but in this case the error in measurements is less feasible, considering that two different natural sources provided comparable negative specific rotation data.[13,14]

Table 1 Reaction conditions for the synthesis of aldehyde (+)-**14**

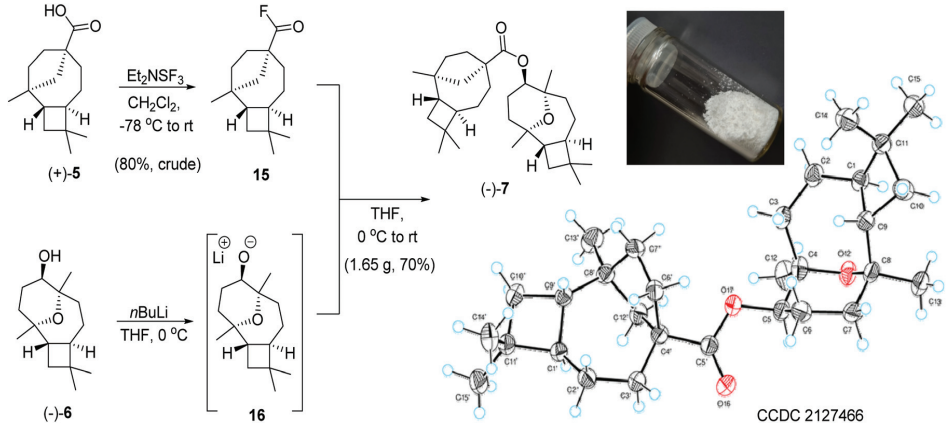
Entry	Acid (equiv.)	Conditions[a]	Isolated yield of (+)-**14** (%)
1	H_2SO_4 (150)	MeOH, 0 °C to rt	32%
2	TsOH·H_2O (1.1)	CH_2Cl_2, rt	35%
3	*S*-CSA (1.1)	$(CH_2)_2Cl_2$, 60 °C	23%
4	*S*-CSA (1.1)	MeOH, rt	10%
5	*S*-CSA (1.1)	CH_2Cl_2 or PhH, rt	50%
6	*S*-CSA (0.15)	CH_2Cl_2, rt	57% (2.4 g)
7	*S*-CSA (0.05)	CH_2Cl_2, rt	28%

[a] Reaction time: 16 h.

Synthesis of rumphellolide J (7)

With (+)-**5** and (−)-**6** in hand, we proceeded with the esterification reaction, which posed a significant challenge due to sterical hindrance of both fragments (Scheme 4). The use of coupling reagents, such as carbodiimides with catalytic or equimolar amount of 4-dimethylaminopyridine (DMAP), promoted the formation of acylisourea or acylpyridinium intermediates (as detected by LC/MS) with no further reaction with alcohol (−)-**6**. Acid (+)-**5** conversion to acyl chloride using Vilsmeier reagent, $SOCl_2$ or PCl_3 was not successful either. To overcome these difficulties, we proposed that increased nucleophilicity of alcohol (−)-**6** and electrophilicity of activated acid derivative was necessary.

Consequently, the coupling was successfully achieved by the synthesis of acyl fluoride **15** and its reaction with *in situ*



Scheme 4 Synthesis of rumphellolide J ((−)-**7**), sample of 1.65 g and ORTEP figure of (−)-**7**.

prepared alkoxide **16** (Scheme 4). The reaction produced 1.65 g (70%) of rumphellolide J ((−)-**7**), and its structure was established by the X-ray crystallography (CCDC 2127466†).

The spectral data of synthetic rumphellolide J ((−)-**7**) are consistent with reported data from isolated material. The specific optical rotation data are comparable as well.[2] Thus, we confirm that the synthesized product and natural isolate have the same structure, despite having the opposite rotation value of obtained intermediate acid (+)-**5**. Considering the associated difficulties in accessing both authentic sample of (−)-rumphellaoic acid A ((−)-**5**) and (+)-caryophyllene ((+)-**1**), we can hypothesize that (−)-rumphellaoic acid ((−)-**5**) naturally occurs in its free form, while (+)-rumphellaoic acid ((+)-**5**) forms the ester with alcohol (−)-**6**, providing rumphellolide J ((−)-**7**).

Conclusions

In summary, we have demonstrated synthesis of several naturally occurring β-caryophyllene derivatives, along with the confirmation of their structures by 2D NMR experiments and X-ray crystallography. Our presented biomimetic approach provided support to the proposed biochemical relationships in nature and assumable evidence of the existence of less explored (+)-caryophyllene, thus opening up new potential perspectives in sesquiterpene metabolism in gorgonian coral species. At the same time, we have demonstrated short access to complex structures in sufficient quantities for further investigations of biological activities. In addition, all synthesized terpenoids, including intermediates that are not yet isolated from nature, can be used as valuable reference standards in the analysis of chemical composition of various natural sources.

Experimental

Melting points were detected with an OptiMelt MPA100 melting point apparatus, with a heating rate of 3 °C min^{-1}. Specific optical rotations were measured at specified temperature on a Rudolph Research Analytical Autopol VI polarimeter, cell length 100 mm, using the solvent and concentration stated, at 589 nm. Infrared spectra (IR) were obtained using a Shimadzu IR Prestige-21 Fourier-transform IR spectrometer. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on 400 MHz Bruker spectrometer using the residual solvent peak ($CDCl_3$; 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C) as an internal reference. High-resolution molecular masses (HRMS) were determined on a Waters Synapt G2-Si hybrid quadrupole time-of-flight (TOF) mass spectrometer equipped with an electron spray ion source (ESI). Reagents were purchased from commercial sources and used as received. Commercial (−)-β-caryophyllene (CAS 87-44-5, ≥80% from Sigma-Aldrich) was purified by column chromatography using hexanes as eluent to remove humulene and oxidized material prior to use. Commercial (−)-β-caryophyllene oxide (CAS 1139-30-6, 95%) was obtained from Acros. Flash chromatography was carried out using Kieselgel (35–70 μm) silica gel. Thin layer chromatography was performed on TLC silica gel 60 F254 aluminum sheets (Merck) and was visualized by staining with $KMnO_4$ or cerium ammonium molybdate stain systems.

Crystal structure analysis

A suitable crystal was selected, and the X-ray crystal data were acquired on an XtaLAB Synergy-S, Dualflex, HyPix diffractometer (Rigaku) with Cu Kα radiation (λ = 1.541 84 Å). The crystal was kept at 150 K during data collection. The CrysAlis PRO 1.171.40.35a software package was used for intensity data acquisition. Crystal structures were solved and refined by the SHELXT 2014/4 program. Non-hydrogen atoms were refined anisotropically with the full least-squares approximation. Hydrogen-atom positions were calculated geometrically and refined using the riding-model approximation. The absolute configuration of the compounds has been determined both by the anomalous dispersion method and known chiral centers from the parent compound. Single-crystal X-Ray crystallography data, ORTEP drawings and the refinement model description are available in ESI.† Crystallographic data for the structures (+)-**5**, (−)-**7** and (−)-**12** have been deposited in the Cambridge Crystallographic Data Centre.

(1*R*,4*R*,5*R*,9*S*)-4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]-undecane-4,5-diol ((−)-11)

Preparation procedure from (−)-caryophyllene ((−)-**1**), spectral data, and HRMS can be found in our previous publication.[9] Additional data: $[\alpha]_D^{20}$ −32.8 (*c* 1.00, $CHCl_3$). FT-IR (thin film): ν_{max} 3404, 3078, 2952, 2929, 2862, 2714, 1636, 1462, 1373, 1284, 1122, 1053, 886, 755, 614 cm^{-1}.

4β,8β-Epoxycaryophyllan-5-ol ((−)-6)

To the solution of diol (−)-**11** (2.02 g; 8.50 mmol) in CH_2Cl_2 (80 mL), *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 484 mg; 2.54 mmol) was added. Reaction mixture was stirred at rt for 5 h and then quenched with saturated aqueous $NaHCO_3$ solution. Organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using hexanes/EtOAc (3 : 1 v/v) elution to obtain the title product (1.41 g, 70%) as colorless oil. $[\alpha]_D^{20}$ −65.3 (*c* 1.03, $CHCl_3$). FT-IR (thin film): ν_{max} 3393, 2966, 2944, 2861, 1449, 1364, 1285, 1247, 1109, 1059, 1005 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.45 (dd, *J* = 11.5, 4.9 Hz, 1H), 2.51 (ddd, *J* = 12.0, 9.9, 8.0 Hz, 1H), 2.07 (ddd, *J* = 12.0, 10.4, 5.9 Hz, 1H), 2.00–1.89 (m, 1H), 1.86 (dd, *J* = 14.0, 4.6 Hz, 1H), 1.78–1.70 (m, 1H), 1.69–1.62 (m, 1H), 1.62–1.53 (m, 2H), 1.48–1.40 (m, 1H), 1.42 (t, *J* = 9.9 Hz, 1H), 1.37 (br. s, 1H), 1.34 (d, *J* = 9.8 Hz, 1H), 1.32–1.27 (m, 1H), 1.18 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 76.8, 75.6, 72.9, 42.6, 36.4, 36.3, 35.3, 34.5, 30.6, 29.3, 27.2, 26.2, 25.5, 21.4, 18.6. HRMS *m*/*z*: 239.2009 $[M + H]^+$ (calcd for $C_{15}H_{27}O_2$ 239.2011).

(1*R*,2*S*,5*R*,8*R*,9*R*)-1,4,4,8-Tetramethyl-12-oxatricyclo[6.3.1.0^{2,5}]-dodecan-9-yl 4-nitrobenzoate ((−)-12)

To the mixture of 4-nitrobenzoyl chloride (146 mg; 0.78 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 0.24 ml; 1.38 mmol), and DMAP (11 mg; 0.09 mmol) in dry CH_2Cl_2 (1.5 mL) a solution of 4β,8β-epoxycaryophyllan-5-ol (−)-**6** (110 mg; 0.46 mmol) in dry CH_2Cl_2 (1.5 mL) was added. Reaction mixture was stirred at rt for 6 h, quenched with saturated aqueous $NaHCO_3$ solution. Organic layer was washed subsequently with 5% aqueous $KHSO_4$ solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using hexanes/EtOAc (8 : 1 v/v) elution to obtain the title product (127 mg, 71%) as white crystalline solid (EtOAc): mp 119–120 °C. $[\alpha]_D^{20}$ −73.4 (*c* 1.00, $CHCl_3$). FT-IR (thin film): ν_{max} 2955, 2929, 2863, 1720, 1608, 1528, 1351, 1319, 1289, 1103, 870, 717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.33–8.24 (m, 2H), 8.20–8.11 (m, 2H), 4.92 (dd, *J* = 11.5, 5.1 Hz, 1H), 2.60 (ddd, *J* = 11.9, 9.8, 8.0 Hz, 1H), 2.24–2.06 (m, 3H), 2.00 (dtd, *J* = 13.0, 4.9, 2.7 Hz, 1H), 1.81–1.70 (m, 2H), 1.69–1.63 (m, 1H), 1.55–1.44 (m, 3H), 1.38 (t, *J* = 9.9 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 164.2, 150.7, 136.0, 130.8, 123.7, 78.8, 75.5, 73.4, 42.6, 36.4, 35.7, 35.3, 34.6, 30.7, 30.6, 27.4, 26.1, 22.0, 21.5, 18.7. HRMS *m*/*z*: 388.2124 $[M + H]^+$ (calcd for $C_{22}H_{30}NO_5$ 388.2110). The structure was confirmed by single-crystal X-ray analysis. Suitable crystals were prepared by dissolving 10 mg of ester in warm (50–60 °C) EtOH (1 mL) in a screw-cap 10 mL vial. The cap was set on the top to avoid airborne dust and sealed loosely for the slow evaporation of solvent. After standing 24 h at rt appropriate crystals for the single-crystal X-ray analysis were formed. Crystal data for ester: $C_{22}H_{29}NO_5$ (*M* = 387.46 g mol^{-1}), orthorhombic, space group $P2_12_12_1$, *a* = 5.9706(8) Å, *b* = 8.0539(8) Å, *c* = 42.817(5) Å, *V* = 2058.9(4) Å^3, *Z* = 4, *T* = 150.0 (1) K, μ(CuKα) = 0.717 mm^{-1}, D_{calcd} = 1.250 g cm^{-3}, 10 856 reflections measured (8.3° ≤ 2Θ ≤ 156.0°), 4065 unique (R_{int} = 0.0853, R_{sigma} = 0.0756) which were used in all calculations. The final R_1 was 0.0789 ($I > 2\sigma(I)$) and wR_2 was 0.1965 (CCDC 2127464†).

(1*S*,5*R*,9*R*)-10,10-Dimethyl-2,6-dimethylenebicyclo[7.2.0] undecan-5-ol ((+)-13)

Diisopropylamine (3.85 ml; 27.5 mmol) was dissolved in dry tetrahydrofuran (THF, 70 mL) and the solution was cooled to 0 °C. A solution (2.0 M) of *n*BuLi in hexanes (13.7 ml, 27.5 mmol) was added dropwise to the mixture. Reaction mixture was stirred for 15 min at 0 °C and a solution of (−)-β-caryophyllene oxide ((−)-**4**) (5.50 g; 25.0 mmol) in dry THF (25 mL) was added dropwise. Reaction mixture was refluxed for 4 h. Then it was allowed to cool down to rt and quenched with saturated aqueous NH_4Cl solution. THF was evaporated *in vacuo*, mixture was extracted with Et_2O. Organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using hexanes/EtOAc (4 : 1 v/v) elution to obtain the title product (5.07 g, 92%) as light yellow oil. $[\alpha]_D^{20}$ +10 (*c* 0.93, $CHCl_3$). FT-IR (thin film): ν_{max} 3355, 3075, 2952, 2929, 2860, 1635, 1458, 1281, 1023, 884, 614 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.04 (s, 1H), 4.95 (s, 1H), 4.78 (d, *J* = 1.4 Hz, 1H), 4.76 (d, *J* = 1.4 Hz, 1H), 4.09 (ddd, *J* = 8.9, 3.9, 1.0 Hz, 1H), 2.57–2.47 (m, 1H), 2.31 (ddd, *J* = 18.2, 9.5, 5.7 Hz, 2H), 2.09–1.89 (m, 2H), 1.89–1.68 (m, 4H), 1.68–1.49 (m, 4H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 152.6, 151.4, 113.6, 109.3, 75.3, 54.4, 44.0, 37.1, 33.6, 33.0, 32.7, 32.6, 30.8, 30.2, 22.1. HRMS *m*/*z*: 221.1908 $[M + H]^+$ (calcd for $C_{15}H_{25}O$ 221.1905).

(1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo[6.2.1.0^{2,5}]undecane-8-carbaldehyde ((+)-14)

Alcohol (+)-**13** (4.40 g; 20.0 mmol) was dissolved in dry CH_2Cl_2 (180 mL) and *S*-camphorsulphonic acid (696 mg; 3.00 mmol) was added. Reaction mixture was stirred for 16 h at rt, quenched with saturated aqueous $NaHCO_3$ solution. Organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using hexanes/EtOAc (20 : 1 v/v) elution to obtain the title product (2.45 g, 57%) as colorless oil. $[\alpha]_D^{20}$ +27.8 (*c* 1.22, $CHCl_3$). FT-IR (thin film): 3456, 2952, 2929, 2860, 2803, 2686, 1723, 1459, 1364, 1286, 1110, 1063, 1005 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): ^{1}H NMR (400 MHz, $CDCl_3$, δ) δ 9.41 (s, 1H), 1.82 (ddd, *J* = 14.2, 8.8, 1.1 Hz, 1H), 1.72–1.66 (m, 2H), 1.66–1.59 (m, 3H), 1.58–1.55 (m, 1H), 1.56–1.43 (m, 3H), 1.43–1.32 (m, 4H), 0.99 (s, 6H), 0.96 (s, 3H). HRMS *m*/*z*: 221.1908 $[M + H]^+$ (calcd for $C_{15}H_{25}O$ 221.1905).

(+)-Rumphellaoic acid A ((+)-5)

Aldehyde (+)-**14** (2.38 g; 10.8 mmol) and 2-methylbut-2-ene (22.9 mL; 216 mmol) were dissolved in *t*BuOH (100 mL). Then a solution of $NaClO_2$ (12.2 g; 108 mmol) and NaH_2PO_4 (13.0 g; 108 mmol) in H_2O (50 mL) was added dropwise. After stirring for 2 h at rt, the reaction mixture was quenched with brine and extracted with Et_2O. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was partitioned between 1 M aq. NaOH solution and Et_2O. The aqueous layer was acidified by dropwise addition of 6 M aq. HCl solution until pH ∼ 3 and extracted with Et_2O. Organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to obtain acid (2.25 g, 88%) as white crystalline solid (*n*-hexane): mp 78–90 °C. $[\alpha]_D^{20}$ +25.5 (*c* 1.04, $CHCl_3$). FT-IR (thin film): 3062, 2952, 2866, 2630, 1688, 1460, 1408, 1301, 1237, 955 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 11.55 (br. s, 1H), 2.14 (dd, *J* = 8.6, 7.6 Hz, 1H), 1.93 (dd, *J* = 12.8, 2.9 Hz, 1H), 1.77 (dd, *J* = 12.8, 5.4 Hz, 1H), 1.72–1.60 (m, 4H), 1.59–1.48 (m, 4H), 1.46–1.39 (m, 1H), 1.38–1.30 (m, 2H), 0.98 (s, 6H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 185.8, 52.9, 49.1 (2C overlap), 46.1, 45.6, 42.0, 37.3, 34.4, 33.6, 30.6, 29.6, 26.0, 22.2, 20.5. HRMS *m*/*z*: 235.1709 $[M - H]^+$ (calcd for $C_{15}H_{23}O_2$ 235.1698). The structure was confirmed by single-crystal X-ray analysis. Suitable crystals were prepared by dissolving 8 mg of acid in *n*-hexane (1 mL) in a screw-cap 10 mL vial. The cap was set on the top to avoid airborne dust and sealed

loosely for the slow evaporation of solvent. After standing 24 h at rt appropriate crystals for the single-crystal X-ray analysis were formed. Crystal data for acid: $C_{90}H_{144}O_{12}$ (M = 1418.14 g mol^{-1}), triclinic, space group $P1$, a = 9.1756(2) Å, b = 15.1486(3) Å, c = 16.0961(4) Å, α = 102.879(2)°, β = 100.414(2)°, γ = 102.046(2)°, V = 2071.53(8) Å^3, Z = 1, T = 150.0(1) K, μ(Cu Kα) = 0.571 mm^{-1}, D_{calc} = 1.1367 g cm^{-3}, 37 044 reflections measured (5.8° ≤ 2Θ ≤ 155.0°), 11 863 unique (R_{int} = 0.0562, R_{sigma} = 0.0503) which were used in all calculations. The final R_1 was 0.0680 ($I > 2\sigma(I)$) and wR_2 was 0.1787 (CCDC 2127465†).

Rumphellolide J ((−)-7)

To a stirred solution of acid (+)-**5** (1.54 g; 6.52 mmol) in CH_2Cl_2 was added Et_2NSF_3 (2.52 ml; 19.5 mmol) dropwise at −78 °C. The reaction mixture was allowed to warm to 0 °C, stirred for 4 h and then quenched by dropwise addition of H_2O. Organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 5 mL of hexanes/EtOAc (40 : 1 v/v) mixture and filtered through a short pad of silica to obtain crude acyl fluoride **15** (1.24 g, 80%) as colorless oil. Then to a solution of epoxycaryophyllanol (−)-**6** (1.34 g; 5.62 mmol) in dry THF (60 mL) a solution (1.9 M) of *n*BuLi in hexanes was added (3.00 mL, 5.62 mmol) at 0 °C. Reaction mixture was stirred at 0 °C for 15 minutes and then a solution of acyl fluoride **15** (1.24 g; 5.19 mmol) in dry THF was added. Reaction mixture was allowed to warm up to rt, stirred for 2 h, and then quenched with saturated aqueous NH_4Cl solution. THF was evaporated *in vacuo*, mixture was extracted with Et_2O. Organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using hexanes/EtOAc (20 : 1 v/v) elution to obtain the title product (1.65 g, 70%) initially as colorless oil, which gave white crystals (mp 107–109 °C) upon triturating with EtOH and subsequent drying *in vacuo*. $[\alpha]_D^{20}$ −44.0 (c 1.01, $CHCl_3$). FT-IR (thin film): ν_{max} 2952, 2860, 1727, 1455, 1364, 1262, 1193, 1110, 1055, 1000, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.58 (dd, J = 11.4, 5.1 Hz, 1H), 2.55 (ddd, J = 12.0, 9.9, 8.0 Hz, 1H), 2.13 (ddd, J = 13.8, 8.2, 1.2 Hz, 1H), 2.09–2.03 (m, 1H), 2.01–1.96 (m, 1H), 1.96–1.87 (m, 2H), 1.85–1.77 (m, 1H), 1.72–1.53 (m, 10H), 1.52–1.48 (m, 1H), 1.47–1.40 (m, 4H), 1.38–1.27 (m, 4H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 178.7, 76.6, 75.6, 73.2, 53.2, 49.4, 49.1, 46.1, 45.6, 42.6, 41.9, 37.4, 36.4, 35.7, 35.3, 34.6, 34.5, 33.6, 30.64 (2C overlap), 30.56, 29.3, 27.4, 26.1, 26.0, 22.3, 21.8, 21.5, 20.5, 18.7. HRMS m/z: 457.3686 $[M + H]^+$ (calcd for $C_{30}H_{49}O_3$ 457.3682). The structure was confirmed by single-crystal X-ray analysis. Suitable crystals were prepared by dissolving 8 mg of rumphellolide J in warm (50–60 °C) EtOH/H_2O (1 : 1 v/v, 1 mL) mixture in a screw-cap 10 mL vial. The cap was set on the top to avoid airborne dust and sealed loosely for the slow evaporation of solvent. After standing 24 h at 5 °C appropriate crystals for the single-crystal X-ray analysis were formed. Crystal data for rumphellolide J: $C_{30}H_{48}O_3$ (M = 456.714 g mol^{-1}), monoclinic, space group $P2_1$, a = 8.1401(2) Å, b = 15.6385(2) Å, c = 10.9587(2) Å, β = 99.041(2)°, V = 1377.69(4) Å^3, Z = 2, T = 150.0(1) K, μ(Cu Kα) = 0.529 mm^{-1}, D_{calc} = 1.101 g cm^{-3}, 14 302 reflections measured (8.0° ≤ 2Θ ≤ 155.0°), 4645 unique (R_{int} = 0.0280, R_{sigma} = 0.0270) which were used in all calculations. The final R_1 was 0.0319 ($I > 2\sigma(I)$) and wR_2 was 0.0836 (CCDC 2127466†).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Article

Semisynthesis of Linariophyllenes A–C and Rumphellolide H, Structure Revisions and Proposed Biosynthesis Pathways

Georgijs Stakanovs,* Anastasija Blazevica, Sergey Belyakov, Dace Rasina, and Aigars Jirgensons*

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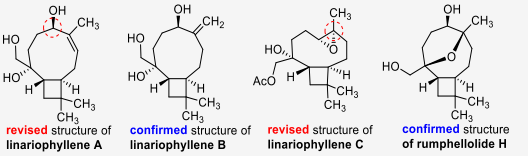
ABSTRACT: The first semisynthetic routes toward terrestrial anti-inflammatory natural products linariophyllene A–C and the refined route toward marine natural product rumphellolide H are presented. Among the synthesized target compounds, the correct structure of linariophyllene A was determined to be the diastereomer of the originally proposed structure with an inverted stereocenter at the secondary alcohol. The proposed structures of linariophyllene B and rumphellolide H were confirmed. However, the correct structure of linariophyllene C was found to be the diastereomer of the originally proposed structure with an inverted stereocenter at the tertiary carbon of the epoxide moiety. The structures of linariophyllenes A–C and rumphellolide H were unequivocally confirmed by single-crystal X-ray diffractometry. The obtained results enabled the proposal of the biosynthetic origins of the aforementioned natural products and bolstered the diversity of available sesquiterpenoids. Linariophyllenes A–C and rumphellolide H were obtained in sufficient amounts to further expand their bioactivity profile and utility as reference standards in future studies of chemical constituents of terrestrial and marine organisms.



Linariophyllenes A–C (**1**–**3**) are caryophyllane-type sesquiterpenoids (Figure 1) isolated from the aerial parts of *Evolvulus linarioides*.[1] These natural products likely result from biosynthetic modifications of *β*-caryophyllene (**5**) and/or its oxide **6**.[1] Linariophyllenes A–C exhibit anti-inflammatory activity by inhibition of NO production and pro-inflammatory cytokine IL-1*β*, with **2** showing the most potent inhibitory activity (17.8 ± 0.8 *μ*M).[1] Moreover, **2** reduced IL-1*β* levels by 93% at 10 *μ*M concentration, demonstrating greater effectiveness than the known anti-inflammatory drug dexamethasone (87%).[1] Using 2D NMR, the structure of linariophyllene A (**1**) was proposed to be a triol with an endocyclic *Z* double bond, whereas the structure of linariophyllene B (**2**) was elucidated as its isomer with an inverted stereocenter at C-5 and an exocyclic double bond.[1] The structure of linariophyllene C (**3**) was deciphered as a related acetate with a *cis*-epoxide moiety.[1]

Rumphellolide H (**4**) is a marine natural product isolated from the gorgonian coral *Rumphella antipathies* presumably also originating from *β*-caryophyllene (**5**) and/or its oxide **6**.[2] Like linariophyllenes A–C, rumphellolide H also exhibits moderate anti-inflammatory activity.[2] Interestingly, this cyclic ether **4** shares structural similarity with the terrestrial sesquiterpenoids **1**–**3** as a ring-closed analogue however with an important difference—it has an opposite stereocenter at C-8.

The relative configurations for linariophyllenes A–C (proposed structures **1**–**3**) as well as for rumphellolide H (proposed structure **4**) were assigned by NMR spectroscopy, which provides strong however not unambiguous structural proof.

Our aim was to develop a semisynthetic approach toward **1**–**4**, providing access to these biologically active terpenoids as well as their analogues for more detailed profiling of their properties. In addition, these studies would provide ample quantities of compounds for X-ray crystallography, which would allow confirmation/revision of the structures. Semisynthetic transformations together with confirmed/revised structures would also provide hints for biosynthetic pathways of terrestrial caryophyllanes, linariophyllenes A–C, and marine organism-derived rumphellolide H.

The starting materials for semisynthesis of target compounds *β*-caryophyllene (**5**) and/or *β*-caryophyllene oxide (**6**) are abundant, commercially available inexpensive sesquiterpenes that have found an application as starting materials for the semisynthesis of other natural products.[3−9]

RESULTS AND DISCUSSION

The synthesis of both linariophyllenes A and B started with dihydroxylation of *β*-caryophyllene oxide (**6**) to obtain diol **7** in quantitative yield (Scheme 1). However, single-crystal X-ray

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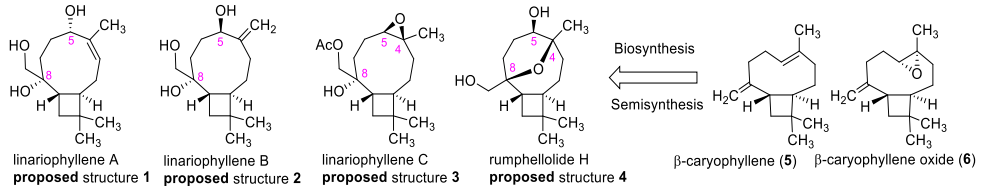
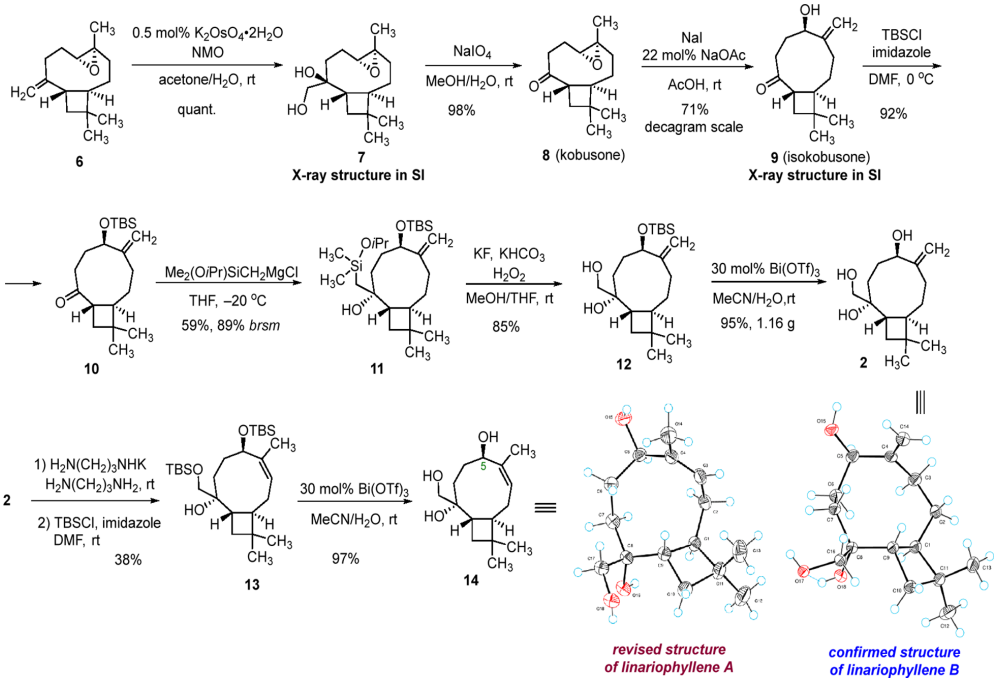


Figure 1. Proposed structures of linariophyllenes A−C (**1**−**3**), rumphellolide H (**4**), and potential precursors for their semisynthesis.

Scheme 1. Synthesis of Linariophyllene A (Revised Structure 14) and Linariophyllene B (Confirmed Structure 2)



diffraction studies of compound **7** revealed that the newly formed stereocenter at C-8 had the opposite configuration to that of **1**−**3**. An attempt to control the diastereoselectivity of the dihydroxylation reaction was made by using chiral additives AD-mix-α or AD-mix-β; however, both reagent systems provided diol **7** as the major diastereomer. The installation of a diol system with the required configuration at C-8 was achieved downstream in the synthetic route. The cleavage of diol **7** by $NaIO_4$ was performed to obtain compound **8**, known also as the natural product kobusone. The epoxide in kobusone (**8**) was then isomerized to an allylic alcohol in acidic media in the presence of NaI,[10] furnishing compound **9**, known also as isokobusone.[11] The structure of isokobusone (**9**) was confirmed by X-ray crystallography; however, it was found by NMR that ∼13% of the material exists as a cyclic hemiacetal in $CDCl_3$ solution (Supporting Information, Table S1).

With an aim to achieve the desired diastereoselectivity at C-8, we investigated the nucleophilic hydroxymethylation of isokobusone (**9**). First, the hydroxy group in **9** was TBS protected, providing silyl ether **10**. The reaction between intermediate **10** and freshly prepared Grignard reagent (Me_2(*i*PrO)$SiCH_2MgCl$) successfully gave β-silylalcohol **11**, which was immediately subjected to the next step due to its limited shelf life. Subsequent Tamao oxidation in basic media with KF and H_2O_2 yielded diol **12** in a high yield and as a single diastereomer, indicating the highly stereoselective addition of the Grignard reagent to the carbonyl group in intermediate **10**. *O*-Desilylation was done using $Bi(OTf)_3$ in aqueous media,[12,13] providing target linariophyllene B (**2**) in excellent yield in a gram scale (Scheme 1). The NMR spectra and specific rotation of compound **2** matched the natural isolate of linariophyllene B, and its structure was confirmed with X-ray diffractometry of a single crystal.

The route to linariophyllene A involved isomerization of the double bond in linariophyllene B (**2**) using potassium 3-aminopropylamide.[14] This furnished an inseparable mixture of the product and unchanged starting material (1.5:1 by ^{1}H NMR). To facilitate the separation, the components of the mixture were subjected to silylation, and silyl ether **13** was then isolated by column chromatography. Desilylation of **13** by using the previously described procedure afforded triol **14**, which turned out to be the correct structure of linariophyllene A, as its NMR spectra and specific rotation perfectly matched the natural isolate.[1] Moreover, the structure of **14** was unambiguously proven by X-ray diffractometry. Hence, we

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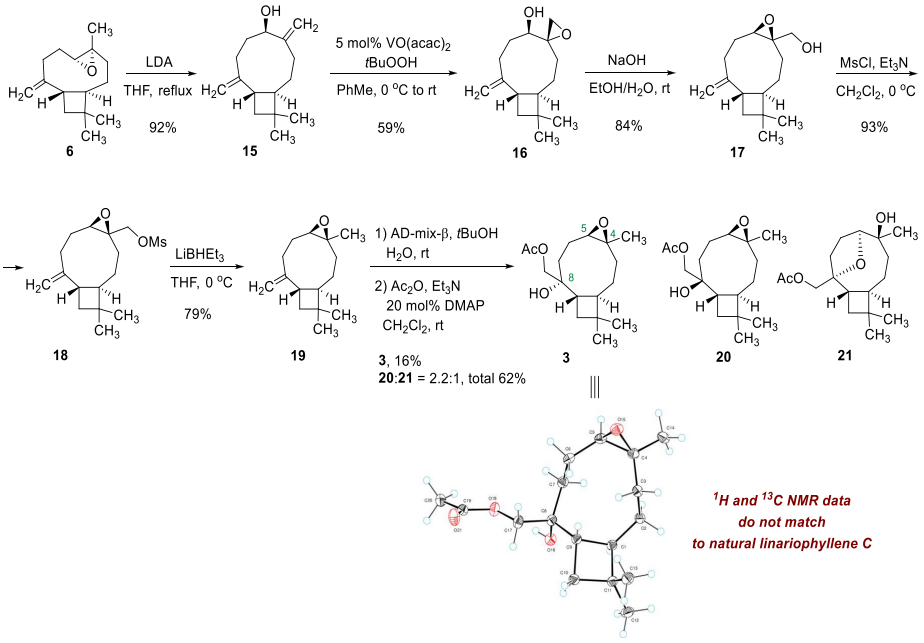
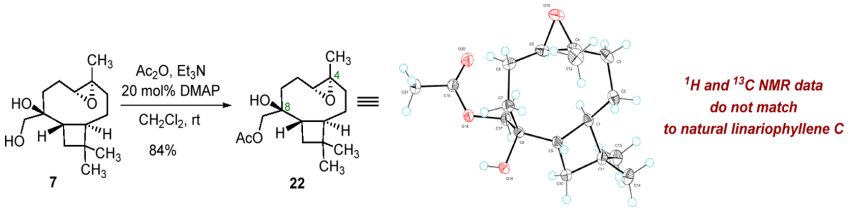
Scheme 2. Synthesis of Linariophyllene C (Disproved Structure 3)



Scheme 3. Synthesis of Acetate 22, a Diastereomer of Disproved Compound 3 as Linariophyllene C



deduced that the C-5 stereocenter of linariophyllene A (Scheme 1) was originally determined erroneously.[1]

The synthesis of linariophyllene C (proposed structure **3**) (Scheme 2) started from β-caryophyllene oxide (**6**) by LDA-mediated isomerization to allylic alcohol **15**.[4,15,16] Compound **15** was subjected to vanadium(IV)-catalyzed epoxidation in the presence of *t*BuOOH to obtain epoxyalcohol **16** as the only detectable diastereomer, reproducing the literature results.[17] The 1,1-disubstituted epoxide **16** is preorganized for the intramolecular alcohol attack on the epoxide in an S_N2 reaction and was converted to cis-trisubstituted epoxide **17** via Payne rearrangement in basic media. Mesylation and a subsequent sulfonate **18** reduction using $LiBHEt_3$ afforded isocaryophyllene-4*S*,5*R*-oxide (**19**). Noteworthy, the reduction of mesylate **18** can also be achieved with $LiAlH_4$; however, the isolated yield of reduction product **19** dropped to 33%. Dihydroxylation with AD-mix-β followed by acetylation provided the proposed structure of linariophyllene C[1] (**3**) together with a chromatographically inseparable mixture of its epimer **20** and tetrahydrofuran-containing acetate **21** (Scheme 2). It should be noted that the use of AD-mix-α did not significantly alter the dihydroxylation diastereoselectivity, indicating the substrate-controlled stereoselectivity for this transformation. The presence of **21** can be explained by intramolecular S_N2-type cleavage of the epoxide by the tertiary alcohol moiety. This transformation happens only to a diastereomer in which the nucleophile (tertiary alcohol) and the electrophile (epoxide) are located on opposite faces of the molecule, thus assuring effective nucleophilic attack in an S_N2 fashion.

Inspecting the NMR spectra of compound **3**, we found significant deviations in its ^1H and ^{13}C NMR chemical shifts and multiplicity patterns of diastereotopic protons compared to those of natural linariophyllene C.[1] In particular, the chemical shift (measured in acetone-d_6) of a H-5 in **3** was found to be 2.68 ppm (vs 3.18 ppm in the natural isolate[1]). Therefore, along with other spectroscopic divergences, we concluded that the structure of linariophyllene C was erroneously determined for the compound isolated from the natural source.[1]

We hypothesized that the correct structure of linariophyllene C could have been attributed to another diastereomer of **3**, as the discrepancies between **3** and the natural isolate were not large enough to suggest a connectivity error in interpretation of the spectra.[1] Therefore, our next efforts were focused on synthesis of other possible stereoisomers of compound **3** in order to establish the true structure of linariophyllene C. First, readily available diol **7** (Scheme 1) was subjected to acetylation conditions using Ac_2O, Et_3N, and catalytic amounts

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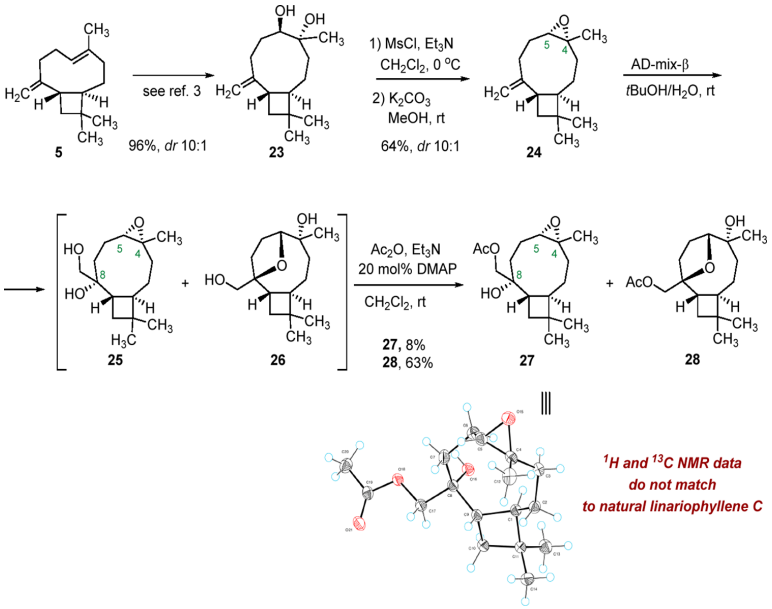
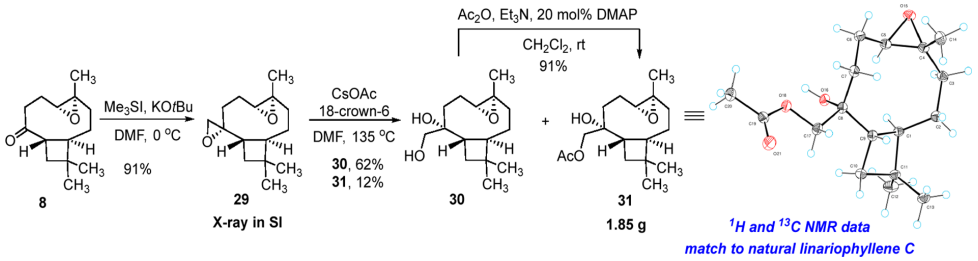
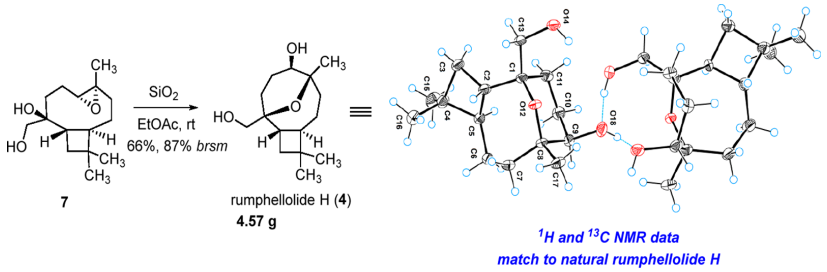
Scheme 4. Synthesis of Acetate 27, a Diastereomer of Disproved Compound 3 as Linariophyllene C



Scheme 5. Synthesis Linariophyllene C (Confirmed Structure 31)



Scheme 6. Synthesis of Rumphellolide H (Confirmed Structure 4)



of DMAP, obtaining acetate **22** with inverted centers at C-4 and C-8 compared to **3** (Scheme 3). However, its NMR data also did not correspond to those of linariophyllene C.

In the pursuit of other diastereomers of structure **3**, an endocyclic double bond in *β*-caryophyllene (**5**) was dihydroxylated to obtain diol **23**[3] (Scheme 4). It was converted to isocaryophyllene-4*R*,5*S*-oxide (**24**) via mesylation of a secondary alcohol with subsequent Williamson epoxide synthesis in basic media. Dihydroxylation of the exocyclic double bond in **24** provided a mixture of diol **25** and cyclic ether **26**, obviously resulting from cyclization of a diastereomer of diol **25**. The crude mixture was subjected to acetylation, giving rise to acetate **27** and tetrahydrofuran derivative **28**. Yet again, the ^{1}H and ^{13}C NMR data of **27** did not corroborate with natural linariophyllene C.[1]

In an attempt to synthesize the diastereomer of structure **3** with an inverted stereocenter at C-4, kobusone (**8**) was subjected to the nucleophilic hydroxymethylation with

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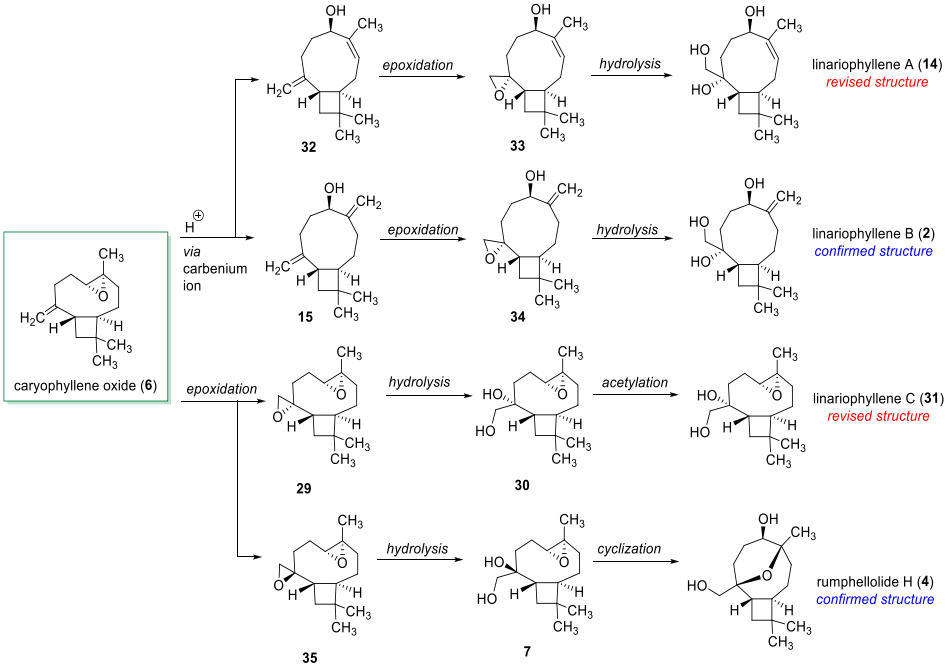

Figure 2. Plausible biosynthetic pathways toward linariophyllenes A, B, and C (**14**, **2**, and **31**) and rumphellolide H (**4**).

$Me_2(iPrO)SiCH_2MgCl$. Unfortunately, the reaction failed to give the expected diol (as in Scheme 1); instead, exclusively *β*-caryophyllene oxide (**6**) was obtained as a result of the Peterson olefination. To install the diol, kobusone (**8**) was converted to diepoxide **29** in excellent yield and stereoselectivity by using the Corey−Chaykovsky epoxidation (Scheme 5). Subsequent cleavage of one of the epoxides in diepoxide **29** with CsOAc in the presence of 18-crown-6 at elevated temperature gave diol **30** as the main product, likely due to the presence of moisture introduced by the reagents. However, the desired acetate **31** was also isolated from the reaction mixture in 12% yield. Fortunately, diol **30** could be converted to acetate **31** using a standard acetylation protocol (Scheme 5).

The NMR spectra of **31** perfectly matched to those of linariophyllene C isolated from *Evolvulus linarioides*.[1] Furthermore, its single-crystal X-ray analysis unambiguously confirmed the structure. The sign of the optical rotation also matched that of natural isolate, thus fully elaborating the absolute configuration of linariophyllene C. Moreover, the synthesis was conducted on a gram scale, thus obtaining 1.85 g of the target compound **31**.

Rumphellolide H (proposed structure **4**) was obtained by exposing diol **7** to SiO_2, which resulted in an intramolecular S_N1-type epoxide cleavage by the tertiary alcohol (Scheme 6).[2] These conditions were more productive (66% on a multigram scale) compared to the literature described cyclization of **7** by using neutral alumina, which gave rumphellolide H (proposed structure **4**) in 16% yield.[18] The structure of rumphellolide H (**4**) was confirmed by single-crystal X-ray analysis.

The obtained NMR data of rumphellolide H structure **4** were in full accordance with the corresponding natural isolate.[2] The sign of its optical rotation matches that isolated from the natural source, thus confirming the absolute configuration.

Having confirmed and corrected structures of linariophyllenes A−C and rumphellolide H, we suggest plausible biosynthetic routes toward these natural products (Figure 2).

Presumably, linariophyllenes A and B (**14** and **2**) stem from naturally occurring allylic alcohols **32** and **15**,[19] which are the products of acid-catalyzed rearrangement of *β*-caryophyllene oxide (**6**).[20] Enzymatic epoxidation[21] of the exocyclic double bond can furnish epoxyalcohols **33** and **34**, which can undergo hydrolytic ring opening to give linariophyllenes A (**14**) and B (**2**). Linariophyllene C (**31**) and rumphellolide H (**4**) may originate from diastereomeric diepoxides **29** and **35**, respectively. The 1,1-disubstituted epoxide of both diastereomers can undergo hydrolytic ring opening, resulting in diols **30** and **7**. Our synthetic routes demonstrated that acetylation of intermediate **30** gives linariophyllene C (**31**), whereas acidic cyclization of compound **7** furnishes rumphellolide H (**4**). The difference in proposed biosynthesis of linariophyllene C (**31**) and rumphellolide H (**4**) is the diastereoselectivity in the epoxidation step of caryophyllene oxide (**6**). This might be due to different enzymes involved in the epoxidation step for terrestrial and marine organisms.

CONCLUSIONS

In conclusion, we have demonstrated new diastereoselective synthetic routes toward the anti-inflammatory natural products linariophyllenes A−C and an improved route to rumphellolide H. The semisynthetic access to these natural products enabled access to X-ray structures of the proposed structures. Based on these studies, the originally proposed structure **1** for linariophyllene A was disproved and corrected to structure **14**. Structure **2** for linariophyllene B was confirmed. Structure **3** for linariophyllene C was disproved. Semisynthetic routes to the diastereomers of compound **3** were established, which

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allowed correction of the structure of linariophyllene C to be compound **31**. The confirmed/corrected structures of linariophyllenes A−C and the improved route to rumphellolide H and synthetic sequences allowed proposal of biosynthetic routes toward these caryophyllane-type sesquiterpenoids **2**, **4**, **14**, and **31**. In addition, semisynthetic access expands the library of readily available sesquiterpenoids and enables an extensive profiling of their biological properties. The obtained compounds can also act as reference standards in the analysis of chemical constituents of other living organisms.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were detected with an OptiMelt MPA100 melting point apparatus, with a heating rate of 2.5 °C/min. Optical rotations were measured at the specified temperature on a Rudolph Research Analytical Autopol VI polarimeter, cell length 100 mm, using the solvent and concentration stated, at 589 nm. Infrared spectra (IR) were obtained using a Shimadzu IR Prestige-21 Fourier-transform IR spectrometer. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a 400 MHz Bruker spectrometer using the residual solvent peak (7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$; 7.16 and 128.06 ppm for ^{1}H and ^{13}C in C_6D_6; 2.05 and 29.84 ppm for ^{1}H and ^{13}C in acetone-d_6) as an internal reference. HRMS were obtained on a Waters Synapt G2-Si hybrid quadrupole time-of-flight (TOF) mass spectrometer equipped with an electron spray ion source (ESI). Gas chromatographic (GC) analysis was performed on an Agilent Technologies gas chromatograph with triple-axis detector, heating range 40−280 °C, column 30 m × 0.25 mm, 0.25 μm, 7 in. cage. Reagents were purchased from commercial sources and used as received. Commercial β-caryophyllene oxide (CAS 1139-30-6, 95%) was obtained from Acros. Commercial β-caryophyllene (CAS 87-44-5, ≥80% from Sigma-Aldrich) was purified by column chromatography using hexanes as the eluent to remove humulene and oxidized material prior to use. Flash chromatography was carried out using Kieselgel (35−70 μm) silica gel. Thin layer chromatography was performed on TLC silica gel 60 F_{254} aluminum sheets (Merck) and was visualized by staining with $KMnO_4$ or cerium ammonium molybdate stain systems.

Crystal Structure Analysis. A suitable crystal was selected, and the X-ray crystal data were acquired on an XtaLAB Synergy-S, Dualflex, HyPix diffractometer (Rigaku) with Cu Kα radiation (λ = 1.54184 Å). The crystal was kept at 110 (for **3**), 130 (for **2**), 140 (for **27** and **29**), 150 (for **4**, **7**, **14**, **22**, and **31**), or 220 K (for **9**) during data collection. The CrysAlis PRO 1.171.40.35a software package was used for intensity data acquisition. Crystal structures were solved and refined by the SHELXT 2014/4 program. Non-hydrogen atoms were refined anisotropically with the full least-squares approximation. Hydrogen-atom positions were calculated geometrically and refined using the riding-model approximation. The absolute configuration of the compounds has been determined both by the anomalous dispersion method and by known stereogenic centers from the parent compound. Single-crystal X-ray crystallography data, ORTEP drawings, and the refinement model description are available in the Supporting Information. Crystallographic data for the structures have been deposited in the Cambridge Crystallographic Data Centre.

Synthesis. *(1R,4R,6R,9S,10S)-9-Hydroxymethyl-4,12,12-trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecane-9-ol (**7**).* (−)-β-Caryophyllene oxide (**6**), 15.4 g; 69.8 mmol) was dissolved in an acetone (630 mL) and H_2O (70 mL) mixture. NMO (4-methylmorpholine-4-oxide, 8.99 g; 76.7 mmol) and $K_2OsO_4{\cdot}2H_2O$ (103 mg; 0.30 mmol) were added to the solution. The reaction mixture was stirred for 24 h at rt and quenched with a 20% $Na_2S_2O_3$ aqueous solution (150 mL). Acetone was evaporated under reduced pressure, and the mixture was extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered; the solvent was evaporated under reduced pressure. The title product (17.7 g, quant.) was obtained as a white crystalline solid (EtOAc, mp 131−133 °C). $[\alpha]_D^{20}$ −85.4 (*c* 1.05, $CHCl_3$). FT-IR (thin film): ν_{max} 3296, 2937, 2861, 1455, 1386, 1366, 1261, 1148, 1074, 1038, 891, 861, 819, 753, 638 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.74 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 1H), 2.84 (dd, *J* = 10.2, 5.1 Hz, 1H), 2.31−2.15 (m, 2H), 2.13−2.04 (m, 2H), 1.97 (dt, *J* = 14.2, 5.0 Hz, 1H), 1.78 (br s, 1H), 1.76−1.65 (m, 4H), 1.60 (t, *J* = 10.7 Hz, 1H), 1.54−1.37 (m, 2H), 1.32 (s, 3H), 1.00−0.91 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 76.0, 65.4, 62.4, 59.9, 50.3, 46.4, 39.8, 35.7, 34.4, 33.0, 30.4, 28.7, 24.1, 22.7, 16.7. HRMS (ESI/TOF-Q) *m*/*z*: 277.1786 [M + Na]$^+$ (calcd for $C_{15}H_{26}O_3Na$, 277.1780). Single-crystal data: 2 ($C_{15}H_{26}O_3{\cdot}H_2O$) (*M* = 544.77 g/mol), monoclinic, space group $P2_1$ (No. 4), *a* = 15.9971(2) Å, *b* = 5.74763(7) Å, *c* = 16.7207(2) Å, β = 91.569(1)°, *V* = 1536.82(3) Å^3, *Z* = 2, *T* = 150.0(1) K, μ(Cu Kα) = 0.672 mm^{-1}, D_{calcd} = 1.1772 g/cm^3, 25 362 reflections measured (2Θ ≤ 160.0°), 6634 unique (R_{int} = 0.0504, R_{sigma} = 0.0518), which were used in all calculations. The final R_1 was 0.0373 ($I > 2\sigma(I)$), and wR_2 was 0.0995 (all data).

*Kobusone (**8**).* Diol **7** (17.7 g; 69.8 mmol) was dissolved in a MeOH (630 mL) and H_2O (70 mL) mixture. $NaIO_4$ (17.9 g; 83.7 mmol) was added to the solution. The reaction mixture was stirred at rt for 16 h followed by evaporation of MeOH under reduced pressure and subsequent extraction with EtOAc (3 × 120 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered; solvent was evaporated under reduced pressure. The title product (15.2 g, 98%) was obtained as a white crystalline solid (EtOAc, mp 60−62 °C). $[\alpha]_D^{20}$ −133 (*c* 1.05, $CHCl_3$). FT-IR (thin film): ν_{max} 2937, 2860, 1695, 1456, 1386, 1370, 1340, 1262, 1164, 1122, 1084, 1067, 996, 918, 854, 810 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.09−3.00 (m, 1H), 2.69 (dd, *J* = 10.0, 4.9 Hz, 1H), 2.60−2.49 (m, 2H), 2.46−2.34 (m, 1H), 2.15 (dt, *J* = 13.1, 3.5 Hz, 1H), 2.09−2.02 (m, 1H), 1.98−1.88 (m, 1H), 1.68−1.59 (m, 2H), 1.59−1.38 (m, 2H), 1.30 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.94 (td, *J* = 13.2, 4.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 214.3, 61.8, 59.1, 52.8, 51.5, 39.2, 37.9, 35.4, 34.7, 29.5, 26.6, 24.9, 22.4, 16.4. HRMS (ESI/TOF-Q) *m*/*z*: 223.1703 [M + H]$^+$ (calcd for $C_{14}H_{23}O_2$ 223.1698). Spectroscopic data correspond to the literature.[7,8]

*Isokobusone (**9**).* Kobusone (**8**, 15.2 g; 68.4 mmol), NaI (13.9 g; 93.0 mmol), and NaOAc (1.23 g; 15.0 mmol) were dissolved in AcOH (42.5 mL). The reaction mixture was stirred at rt for 16 h and then quenched by dropwise addition of a saturated Na_2CO_3 aqueous solution until pH = 8. The reaction mixture was extracted with EtOAc (3 × 150 mL), and the combined organic layers were washed sequentially with a 20% $Na_2S_2O_3$ aqueous solution (500 mL) and brine. The organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The title product was purified by flash column chromatography using an EtOAc−hexane (1:1, v/v) mixture as an eluent with subsequent trituration (150 mL) with EtOAc−hexane (1:20, v/v). The white crystalline (EtOAc, mp 109−110 °C) precipitate was filtered and dried under reduced pressure to obtain the title product (10.8 g, 71%). $[\alpha]_D^{20}$ −42 (*c* 0.93, $CHCl_3$). FT-IR (thin film): ν_{max} 3387, 2960, 2931, 2891, 2864, 1694, 1678, 1457, 1437, 1381, 1366, 1292, 1201, 1151, 1063, 1044, 921, 897, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.01 (d, *J* = 1.2 Hz, 1H), 4.94 (d, *J* = 1.3 Hz, 1H), 4.14 (dd, *J* = 9.7, 4.5 Hz, 1H), 3.05 (td, *J* = 9.5, 7.3 Hz, 1H), 2.58 (dtd, *J* = 13.9, 4.8, 1.3 Hz, 1H), 2.47−2.38 (m, 1H), 2.33−2.15 (m, 2H), 2.11−1.97 (m, 2H), 1.90−1.79 (m, 3H), 1.76−1.67 (m, 2H), 1.42 (dd, *J* = 10.6, 7.3 Hz, 1H), 1.02 (s, 3H), 1.00 (s, 3H)—*ketone tautomer*. ^{13}C NMR (101 MHz, $CDCl_3$, δ): 213.3, 147.5, 117.1, 76.6, 51.4, 46.8, 40.6, 34.3, 33.2, 29.9, 29.8, 29.5, 27.3, 22.3—*ketone tautomer*. ^{13}C NMR (101 MHz, $CDCl_3$, δ): 154.3, 111.8, 108.9, 80.0, 45.2, 45.1, 35.5, 34.5, 32.1, 31.3, 30.0, 28.7, 27.9, 22.6—*hemiacetal tautomer*. HRMS (ESI/TOF-Q) *m*/*z*: 223.1696 [M + H]$^+$ (calcd for $C_{14}H_{23}O_2$ 223.1698). Single-crystal data: $C_{14}H_{20}O_2$, M_r = 220.30, tetragonal, *I*4 (No. 79), *a* = 20.7312(5) Å, *c* = 5.9640(2) Å, *V* = 2563.2(2) Å^3, *T* = 220.0(2) K, *Z* = 8, *Z*′ = 1, μ(Cu Kα) = 0.587, 5121 reflections measured, 2305 unique (R_{int} = 0.0510) which were used in all calculations. The final wR_2 was 0.1643 (all data), and R_1 was 0.0457 ($I > 2\sigma(I)$).

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*(1S,5R,9R)-5-((tert-Butyldimethylsilyl)oxy)-10,10-dimethyl-6-methylenebicyclo[7.2.0]undecane-2-one (**10**).* Isokobusone (**9**, 3.00 g; 13.5 mmol) and imidazole (2.76 g; 40.5 mmol) were dissolved in DMF (*N*,*N*-dimethylformamide, 25 mL), and the solution was cooled to 0 °C. TBSCl (3.05 g; 20.2 mmol) was added to the mixture at 0 °C, and the solution was warmed up to rt. The reaction mixture was stirred for 4 h at rt and then quenched with a saturated $NaHCO_3$ aqueous solution (100 mL). The mixture was extracted with Et_2O (3 × 150 mL), the combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexane (1:8, v/v) elution afforded the title product (4.39 g, 92%) as a white crystalline solid (EtOAc, mp 56−58 °C). $[\alpha]_D^{20}$ −49.1 (*c* 1.12, $CHCl_3$). FT-IR (thin film): ν_{max} 3077, 2952, 2929, 2884, 2854, 1701, 1698, 1694, 1460, 1445, 1409, 1381, 1360, 1281, 1257, 1248, 1194, 1153, 1081, 1006, 907, 864, 837, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 4.90 (t, *J* = 1.2 Hz, 1H), 4.83 (t, *J* = 1.3 Hz, 1H), 4.13−4.04 (m, 1H), 3.07 (td, *J* = 9.6, 7.2 Hz, 1H), 2.63−2.52 (m, 1H), 2.45−2.34 (m, 1H), 2.30−2.15 (m, 2H), 2.07 (t, *J* = 10.2 Hz, 1H), 1.96−1.81 (m, 2H), 1.77 (ddd, *J* = 12.9, 6.4, 2.3 Hz, 1H), 1.72−1.64 (m, 2H), 1.40 (dd, *J* = 10.6, 7.3 Hz, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 213.4, 147.9, 116.2, 77.2 (overlaps with $CDCl_3$ signal), 51.6, 46.5, 40.7, 34.3, 33.0, 31.3, 29.9, 29.5, 26.8, 25.9, 22.4, 18.4, −4.8, −4.9. HRMS (ESI/TOF-Q) *m*/*z*: 359.2377 $[M + Na]^+$ (calcd for $C_{20}H_{36}O_2SiNa$ 359.2382).

*(1S,2R,5R,9R)-5-((tert-Butyldimethylsilyl)oxy)-2-(hydroxymethyl)-10,10-dimethyl-6-methylenebicyclo[7.2.0]undecane-2-ol (**12**).* 1,2-Dibromoethane (0.05 mL) was added to magnesium turnings (921 mg; 35.0 mmol) in anhydrous THF (10 mL). To the reaction mixture a solution of $Me_2Si(OiPr)CH_2Cl$ (5.56 mL, 30.0 mmol) in anhydrous THF (20 mL) was added dropwise with occasional cooling to 0 °C. The reaction mixture was stirred for 6 h at rt and then cooled to −20 °C, and a solution of ketone **10** (3.36 g; 10.0 mmol) in anhydrous THF (45 mL) was added dropwise. After 15 min, the reaction mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexane (1:8, v/v) elution afforded starting material **10** (1.01 g, 30%) and intermediate **11** (2.74 g, 59%) as a colorless oil, which was used immediately in the next step. Intermediate **11** (2.74 g; 5.85 mmol) was dissolved in a THF/MeOH mixture (50 mL, 1:1, v/v). To the solution, $KHCO_3$ (3.51 g; 35.1 mmol), KF (2.04 g; 35.1 mmol), and a 30% H_2O_2 aqueous solution (8.81 mL; 87.8 mmol) were added sequentially. The reaction mixture was stirred at rt for 16 h; then, it was cooled to 0 °C and quenched with a 20% $Na_2S_2O_3$ aqueous solution (75 mL). The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexane (1:4, v/v) elution afforded the title product (1.84 g, 85%) as a white amorphous solid. $[\alpha]_D^{20}$ −3.98 (*c* 1.07, $CHCl_3$). FT-IR (thin film): ν_{max} 3391, 2952, 2929, 2858, 1649, 1473, 1462, 1447, 1383, 1382, 1366, 1361, 1289, 1257, 1250, 1210, 1114, 1047, 1006, 955, 947, 898, 835, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 5.16 (d, *J* = 2.0 Hz, 1H), 5.00 (d, *J* = 1.8 Hz, 1H), 4.16 (d, *J* = 4.7 Hz, 1H), 3.27 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.15 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.44−2.35 (m, 1H), 1.98 (ddd, *J* = 10.7, 8.5, 2.6 Hz, 1H), 1.91−1.77 (m, 3H), 1.77−1.67 (m, 3H), 1.66−1.52 (m, 4H), 1.48 (ddd, *J* = 10.8, 8.8, 0.9 Hz, 1H), 1.40 (dt, *J* = 13.4, 4.4 Hz, 1H), 0.97 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 151.1, 111.2, 75.3, 74.0, 68.2, 44.6, 43.2, 34.1, 34.0, 32.0, 30.4, 29.8, 27.1, 26.0, 25.6, 23.4, 18.4, −4.8, −4.9. HRMS (ESI/TOF-Q) *m*/*z*: 391.2634 $[M + Na]^+$ (calcd for $C_{21}H_{40}O_3SiNa$ 391.2644).

*Linariophyllene B (**2**).* Silyl ether **12** (1.77 g, 4.79 mmol) was dissolved in a $MeCN/H_2O$ (50 mL, 2:1, v/v) mixture. $Bi(OTf)_3$ (943 mg; 1.44 mmol) was added to the solution. The reaction mixture was stirred at rt for 48 h and quenched with a saturated $NaHCO_3$ aqueous solution (100 mL). The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc + 5% MeOH elution afforded the title product **2** (1.16 g, 95%) as a white crystalline solid (EtOAc, mp 183−185 °C). $[\alpha]_D^{25}$ −6 (*c* 0.09, MeOH). FT-IR (KBr): ν_{max} 3557, 3338, 3100, 2962, 2910, 2857, 1740, 1648, 1472, 1456, 1437, 1363, 1290, 1269, 1260, 1232, 1175, 1140, 1119, 1098, 1069, 1037, 987, 952, 924, 896, 852, 820, 785, 717, 653, 633, 584 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ): 5.15 (s, 1H), 5.05 (d, *J* = 1.5 Hz, 1H), 4.18−4.12 (m, 1H), 3.16 (d, *J* = 10.9 Hz, 1H), 3.12 (d, *J* = 10.8 Hz, 1H), 2.46−2.32 (m, 1H), 2.09−1.90 (m, 3H), 1.81−1.73 (m, 2H), 1.72−1.62 (m, 3H), 1.62−1.56 (m, 1H), 1.56−1.50 (m, 1H), 1.47 (dd, *J* = 10.8, 8.4 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD, δ): 152.6, 110.9, 75.7, 75.0, 68.9, 45.1, 43.4, 34.6, 34.4, 32.9, 31.5, 29.8, 28.5, 25.4, 23.9. HRMS (ESI/TOF-Q) *m*/*z*: 237.1861 $[M - OH]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855). Single-crystal data: $C_{15}H_{26}O_3$ (*M* = 254.37 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 8.4042(1) Å, *b* = 10.7765(2) Å, *c* = 15.7796(2) Å, *V* = 1429.12(4) $Å^3$, *Z* = 4, *T* = 130.0(1) K, μ(Cu Kα) = 0.637 mm^{-1}, D_{calcd} = 1.1822 g/cm^3, 13 472 reflections measured ($2\Theta \leq 160.0°$), 3114 unique (R_{int} = 0.0528, R_{sigma} = 0.0495), which were used in all calculations. The final R_1 was 0.0404 ($I > 2\sigma(I)$), and wR_2 was 0.0980 (all data).

*(1S,2R,5R,9R,Z)-5-((tert-Butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6,10,10-trimethylbicyclo[7.2.0]-undec-6-en-2-ol (**13**).* A solution (1 M, 43 mL) of potassium 3-aminopropylamide (prepared in advance by addition of 1,3-diaminopropane (50 mL, freshly distilled from CaH_2) to dry KH (2.00 g; 50.0 mmol)) was added to linariophyllene B (**2**, 182 mg, 0.72 mmol). The reaction mixture was stirred for 72 h at rt, then quenched with a 5% $KHSO_4$ aqueous solution at 0 °C, and extracted with EtOAc (5 × 30 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc + 5% MeOH afforded 120 mg (66%) of an inseparable mixture of isomerized product and starting material (1.5:1). This mixture (120 mg; 0.47 mmol) and imidazole (193 mg; 2.83 mmol) were dissolved in DMF (5 mL) and cooled to 0 °C. After subsequent addition of TBSCl (178 mg; 1.18 mmol), the reaction mixture was left to stir at rt for 4 h. The mixture was quenched with a saturated $NaHCO_3$ aqueous solution and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and solvent was evaporated under reduced pressure. Purification by flash column chromatography with Et_2O−hexane (1:15, v/v) afforded the title product (133 mg, 58%) as a colorless oil. $[\alpha]_D^{20}$ −27 (*c* 0.95, $CHCl_3$). FT-IR (thin film): ν_{max} 3572, 2952, 2929, 2859, 1473, 1464, 1451, 1406, 1389, 1362, 1300, 1289, 1257, 1219, 1117, 1101, 1068, 1005, 989, 951, 856, 836, 774, 671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 5.33 (ddt, *J* = 8.7, 7.4, 1.3 Hz, 1H), 4.44 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.24 (d, *J* = 9.5 Hz, 1H), 3.20 (d, *J* = 9.5 Hz, 1H), 2.34−2.26 (m, 2H), 2.23−2.11 (m, 1H), 2.08−1.98 (m, 1H), 1.93 (q, *J* = 9.3 Hz, 1H), 1.76−1.69 (m, 2H), 1.68 (s, 3H), 1.66−1.59 (m, 1H), 1.54−1.34 (m, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 9H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 139.9, 123.2, 74.1, 73.3, 67.1, 43.8, 38.3, 34.2, 33.6, 32.9, 31.2, 30.0, 26.8, 26.1, 26.0, 24.0, 19.0, 18.5, 18.4, −4.8, −5.3, −5.4. HRMS (ESI/TOF-Q) *m*/*z*: 465.3580 $[M - OH]^+$ (calcd for $C_{27}H_{53}O_2Si_2$ 465.3584).

*Linariophyllene A (**14**).* **14** was prepared analogously to linariophyllene B from silyl ether **13** (96 mg; 0.20 mmol). Purification by flash column chromatography with EtOAc + 5% MeOH afforded the title product **14** (49 mg, 97%) as a white crystalline solid (EtOAc, mp 124−126 °C). $[\alpha]_D^{25}$ −31 (*c* 0.11, MeOH). FT-IR (KBr): ν_{max} 3350, 2962, 2932, 2886, 2862, 2843, 2730, 1607, 1465, 1452, 1430, 1375, 1327, 1262, 1235, 1175, 1113, 1059, 1032, 1004, 988, 864, 850, 637, 594 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ): 5.45−5.38 (m, 1H), 4.40 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.25 (d, *J* = 11.1 Hz, 1H), 3.19

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(d, J = 11.1 Hz, 1H), 2.27−2.16 (m, 2H), 2.13−2.01 (m, 2H), 1.90−1.75 (m, 2H), 1.73 (s, 3H), 1.72−1.67 (m, 1H), 1.59−1.51 (m, 1H), 1.51−1.44 (m, 1H), 1.40 (dd, J = 10.3, 8.5 Hz, 1H), 1.01 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD, δ): 140.3, 125.4, 75.1, 73.9, 67.5, 44.8, 40.1, 35.1, 34.1, 33.5, 30.7, 30.1, 27.5, 24.1, 19.6. HRMS (ESI/TOF-Q) m/z: 237.1852 $[M - OH]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855). Single-crystal data: $C_{15}H_{26}O_3$ (M = 254.37 g/mol), trigonal, space group $P3_2$ (No. 145), a = 14.9954(5) Å, c = 5.6442(2) Å, V = 1099.12(7) Å^3, Z = 3, T = 150.0(6) K, μ(Cu Kα) = 0.622 mm^{-1}, D_{calcd} = 1.1528 g/cm^3, 17 965 reflections measured ($2\Theta \leq 167°$), 2971 unique (R_{int} = 0.0774, R_{sigma} = 0.0652), which were used in all calculations. The final R_1 was 0.0528 ($I > 2\sigma(I)$), and wR_2 was 0.1384 (all data).

(1S,5R,9R)-10,10-Dimethyl-2,6-dimethylenebicyclo[7.2.0]-undecan-5-ol (**15**). Synthesis and characterization data were described in our previous paper.[4] Diisopropylamine (3.85 mL; 27.5 mmol) was dissolved in anhydrous tetrahydrofuran (THF, 70 mL), and the solution was cooled to 0 °C. A solution (2.0 M) of nBuLi in hexanes (13.7 mL, 27.5 mmol) was added dropwise to the mixture. The reaction mixture was stirred for 15 min at 0 °C, and a solution of (−)-β-caryophyllene oxide (**6**, (5.50 g; 25.0 mmol) in anhydrous THF (25 mL) was added dropwise. The reaction mixture was refluxed for 4 h. Then, it was allowed to cool down to rt and quenched with a saturated aqueous NH_4Cl solution (100 mL). THF was evaporated under reduced pressure, and the mixture was extracted with Et_2O (3 × 100 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc−hexane (1:4, v/v) elution to obtain the title product (5.07 g, 92%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.04 (s, 1H), 4.95 (s, 1H), 4.78 (d, J = 1.4 Hz, 1H), 4.76 (d, J = 1.4 Hz, 1H), 4.09 (ddd, J = 8.9, 3.9, 1.0 Hz, 1H), 2.57−2.47 (m, 1H), 2.31 (ddd, J = 18.2, 9.5, 5.7 Hz, 2H), 2.09−1.89 (m, 2H), 1.89−1.68 (m, 4H), 1.68−1.49 (m, 4H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 152.6, 151.4, 113.6, 109.3, 75.3, 54.4, 44.0, 37.1, 33.6, 33.0, 32.7, 32.6, 30.8, 30.2, 22.1. HRMS (ESI/TOF-Q) m/z: 221.1908 $[M + H]^+$ (calcd for $C_{15}H_{25}O$ 221.1905).

(1R,4S,5R,9S)-11,11-Dimethyl-8-methylenespiro[bicyclo[7.2.0]-undecane-4,2′-oxiran]-5-ol (**16**). Allylic alcohol **15** (4.83 g; 21.9 mmol) was dissolved in anhydrous PhMe (220 mL). $VO(acac)_2$ (290 mg; 1.10 mmol) was added to the solution, and the reaction mixture was cooled to 0 °C. A 5 M solution of tBuOOH in decane (13.1 mL; 65.7 mmol) was added to the mixture, which was then warmed up to rt and left to stir for 16 h. The mixture was quenched with a saturated Na_2SO_3 solution and extracted with Et_2O (3 × 75 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexanes (1:4, v/v) elution afforded the title product (3.04 g, 59%) as a white crystalline solid (EtOAc, mp 51−53 °C). $[\alpha]_D^{20}$ −22.5 (c 1.10, $CHCl_3$). FT-IR (thin film): ν_{max} 3485, 3077, 2952, 2930, 1638, 1452, 1369, 1279, 1073, 893 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.93 (s, 2H), 3.83 (td, J = 5.1, 1.9 Hz, 1H), 2.95 (d, J = 4.7 Hz, 1H), 2.64 (d, J = 4.7 Hz, 1H), 2.52−2.37 (m, 2H), 2.16 (s, 1H), 2.12−2.02 (m, 1H), 1.92−1.80 (m, 1H), 1.79−1.71 (m, 3H), 1.71−1.58 (m, 4H), 1.53−1.40 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 151.7, 110.7, 67.9, 62.5, 56.3, 50.5, 43.6, 36.6, 35.5, 34.3, 33.8, 32.7, 30.1, 26.0, 22.1. HRMS (ESI/TOF-Q) m/z: 237.1862 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855).

((1R,4R,6R,10S)-12,12-Dimethyl-9-methylene-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-4-yl)methanol (**17**). Epoxyalcohol **16** (2.86 g; 12.1 mmol) was dissolved in an EtOH/H_2O mixture (120 mL, 1:1, v/v). A 1 M aqueous solution of NaOH (48.3 mL, 48.3 mmol) was added to the mixture, which was left to stir at rt for 16 h. The mixture was then extracted with Et_2O (3 × 75 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexanes (1:3, v/v) elution afforded the title product (2.39 g, 84%) as a white crystalline solid (EtOAc, mp 109 °C). $[\alpha]_D^{20}$ +44.6 (c 1.07, $CHCl_3$). FT-IR (thin film): ν_{max} 3295, 3246, 2972, 2941, 2922, 2863, 1632, 1463, 1367, 1283, 1259, 1074, 1034, 1018, 951, 924, 886, 868, 835, 788, 718, 650 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.87 (dd, J = 1.7, 0.8 Hz, 1H), 4.83 (d, J = 1.5 Hz, 1H), 3.78 (dd, J = 12.2, 4.8 Hz, 1H), 3.51 (dd, J = 12.2, 8.0 Hz, 1H), 2.98 (ddd, J = 11.0, 3.6, 1.1 Hz, 1H), 2.49 (q, J = 8.9 Hz, 1H), 2.39−2.18 (m, 3H), 2.00−1.94 (m, 1H), 1.93−1.80 (m, 2H), 1.76 (dd, J = 8.2, 5.0 Hz, 1H), 1.62−1.48 (m, 3H), 1.47−1.35 (m, 2H), 1.04 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 154.4, 111.3, 63.7, 63.2, 60.7, 48.9, 41.0, 38.3, 33.7, 30.4, 30.2, 27.1, 24.3, 23.6, 22.9. HRMS (ESI/TOF-Q) m/z: 237.1847 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855).

((1R,4R,6R,10S)-12,12-Dimethyl-9-methylene-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-4-yl)methyl methanesulfonate (**18**). Epoxyalcohol **17** (1.38 g; 5.85 mmol) and Et_3N (5.71 mL; 41.0 mmol) were dissolved in CH_2Cl_2 (60 mL). The reaction mixture was cooled to 0 °C, and methanesulfonyl chloride (1.81 mL; 23.4 mmol) was added dropwise to the mixture. The reaction mixture was warmed up to rt and left to stir for 4 h. The mixture was quenched with a saturated NH_4Cl aqueous solution (40 mL), washed with a saturated $NaHCO_3$ aqueous solution (40 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexanes (1:3, v/v) elution afforded the title product (1.70 g, 93%) as a white crystalline solid (EtOAc, mp 79−80 °C). $[\alpha]_D^{20}$ +7.0 (c 0.99, $CHCl_3$). FT-IR (thin film): ν_{max} 3067, 2946, 2863, 1638, 1458, 1358, 1176, 950, 893, 842 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6, δ): 4.82−4.78 (m, 1H), 4.70 (s, 1H), 4.32 (d, J = 11.8 Hz, 1H), 3.66 (dd, J = 11.8, 0.9 Hz, 1H), 2.38−2.36 (m, 1H), 2.35 (s, 3H), 2.13 (q, J = 8.9 Hz, 1H), 2.04−1.94 (m, 2H), 1.93−1.82 (m, 2H), 1.73 (ddd, J = 10.9, 8.8, 0.8 Hz, 1H), 1.70−1.63 (m, 1H), 1.50 (dd, J = 11.0, 8.8 Hz, 1H), 1.51−1.38 (m, 1H), 1.28−1.10 (m, 3H), 0.97 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6, δ): 154.2, 111.4, 73.0, 60.9, 60.6, 49.5, 41.2, 37.4, 37.2, 33.4, 31.1, 30.1, 26.4, 23.5, 23.4, 22.9. HRMS (ESI/TOF-Q) m/z: 315.1627 $[M + H]^+$ (calcd for $C_{16}H_{27}O_4S$ 315.1630).

Isocaryophyllene-4S,5R-oxide (**19**). A solution of methanesulfonate **18** (902 mg; 2.87 mmol) in anhydrous THF (30 mL) was cooled to 0 °C. To the solution, 1 M $LiBHEt_3$ (4.31 mL; 4.31 mmol) in THF was added dropwise. The reaction mixture was then warmed up to rt and stirred for 4 h. The mixture was quenched with a saturated $NaBO_3$ aqueous solution (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc−hexanes (1:8, v/v) elution afforded the title product (499 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ +31 (c 0.94, $CHCl_3$). FT-IR (thin film): ν_{max} 3070, 2952, 2929, 2860, 1631, 1464, 1380, 1368, 1283, 1262, 1120, 1059, 914, 887, 834, 770, 753, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.86−4.84 (m, 1H), 4.82 (t, J = 1.6 Hz, 1H), 2.68 (ddd, J = 10.9, 3.4, 1.1 Hz, 1H), 2.47 (qd, J = 8.9, 0.7 Hz, 1H), 2.38−2.28 (m, 1H), 2.28−2.18 (m, 2H), 1.95−1.87 (m, 1H), 1.84 (ddd, J = 10.9, 8.8, 0.8 Hz, 1H), 1.78 (dddd, J = 13.5, 4.2, 3.2, 1.1 Hz, 1H), 1.60−1.48 (m, 3H), 1.45−1.30 (m, 2H), 1.24 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 154.8, 110.9, 65.0, 60.9, 48.7, 41.0, 38.0, 33.5, 30.8, 30.2, 27.8, 27.7, 24.5, 23.0, 21.9. HRMS (ESI/TOF-Q) m/z: 221.1916 $[M + H]^+$ (calcd for $C_{15}H_{25}O$ 221.1905).

((1R,4S,6R,9R,10S)-9-Hydroxy-4,12,12-trimethyl-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-9-yl)methyl acetate (**3**). Isocaryophyllene-4S,5R-oxide (**19**), 243 mg; 1.10 mmol) was dissolved in a tBuOH/H_2O mixture (10 mL, 1:1, v/v). To the solution 1.55 g of AD-mix-β was added. The reaction mixture was stirred at rt for 16 h. The mixture was then quenched with a 20% $Na_2S_2O_3$ aqueous solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure to yield a crude mixture of diols as an off-white amorphous solid, whose yield was assumed to be quantitative. It was then

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dissolved in CH_2Cl_2 (12 mL), and Et_3N (0.51 mL; 3.64 mmol) and DMAP (30 mg; 0.24 mmol) were sequentially added. To the reaction mixture, Ac_2O (0.17 mL; 1.82 mmol) was added dropwise at rt. The reaction mixture was stirred for 6 h, quenched with a saturated $NaHCO_3$ aqueous solution (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc/hexanes (2:3, v/v) + 1% Et_3N elution afforded the title product **3** (58 mg, 16%) as a white crystalline solid (EtOAc, mp 45−47 °C). $[\alpha]_D^{25}$ +0.16 (*c* 0.12, MeOH). FT-IR (KBr): ν_{max} 3524, 3443, 2936, 2867, 1723, 1472, 1457, 1385, 1363, 1291, 1252, 1197, 1116, 1090, 1065, 1047, 1005, 930, 911, 881, 843, 830, 776, 741, 732, 676, 630, 546, 528 cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2CO$, δ): 3.85 (d, *J* = 11.2 Hz, 1H), 3.79 (dd, *J* = 11.1, 0.9 Hz, 1H), 3.66 (d, *J* = 0.9 Hz, 1H), 2.68 (ddd, *J* = 10.5, 3.8, 0.9 Hz, 1H), 2.12 (dtd, *J* = 9.7, 6.4, 0.9 Hz, 1H), 2.07−2.02 (m, 1H, overlaps with solvent signal), 2.00 (s, 3H), 1.99−1.83 (m, 3H), 1.82−1.75 (m, 1H), 1.74−1.63 (m, 2H), 1.63−1.55 (m, 1H), 1.55−1.44 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 1.12−1.02 (m, 1H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$, δ): 171.1, 73.5, 69.5, 64.8, 60.3, 41.4, 36.9, 34.1, 32.8, 31.2, 29.6, 29.2, 26.1, 24.4, 22.6, 22.3, 20.8. HRMS (ESI/TOF-Q) *m*/*z*: 297.2069 $[M + H]^+$ (calcd for $C_{17}H_{29}O_4$ 297.2066). Single-crystal data: $C_{17}H_{28}O_4$ (*M* = 296.41 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 5.4201(1) Å, *b* = 16.9072(3) Å, *c* = 17.7207(3) Å, *V* = 1623.90(5) $Å^3$, *Z* = 4, *T* = 110.0(1) K, μ(Cu Kα) = 0.680 mm^{-1}, D_{calcd} = 1.2123 g/cm^3, 32 056 reflections measured (2Θ ≤ 160°), 3532 unique (R_{int} = 0.0508, R_{sigma} = 0.0266), which were used in all calculations. The final R_1 was 0.0344 ($I > 2\sigma(I)$), and wR_2 was 0.0796 (all data).

((1R,4S,6R,9S,10S)-9-Hydroxy-4,12,12-trimethyl-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-9-yl)methyl acetate (**20**) *and ((1R,2S,5R,8S,9S)-8-Hydroxy-4,4,8-trimethyl-12-oxatricyclo[7.2.1.0^{2,5}]dodecan-1-yl)-methyl acetate* (**21**). **20** and **21** were isolated after the aforementioned dihydroxylation and acetylation sequence of isocaryophyllene-4*S*,5*R*-oxide (**19**). Purification by flash column chromatography with EtOAc/hexanes (2:3, v/v) + 1% Et_3N elution afforded a 2.2:1 mixture (**20**:**21**) as a white amorphous solid (222 mg, 62%). ^1H NMR of **20** (400 MHz, $(CD_3)_2CO$, δ): 3.78 (d, *J* = 11.0 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.55 (s, 1H), 2.70 (dd, *J* = 10.0, 5.1 Hz, 1H), 2.17−2.07 (m, 1H), 2.00 (s, 3H), 1.96−1.67 (m, 4H), 1.66−1.56 (m, 3H), 1.56−1.34 (m, 3H), 1.33−1.27 (m, 1H), 1.18 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H). ^1H NMR of **21** (400 MHz, $(CD_3)_2CO$, δ): 3.97 (s, 2H), 3.88−3.83 (m, 1H), 3.24 (s, 1H), 2.29−2.16 (m, 2H), 2.06−2.02 (m, 1H, overlaps with solvent signal), 2.00 (s, 3H), 1.97−1.76 (m, 5H), 1.56−1.34 (m, 4H), 1.23 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H). ^{13}C NMR of **20** (101 MHz, $(CD_3)_2CO$, δ): 171.1, 72.9, 71.7, 64.2, 60.8, 47.0, 45.5, 36.7, 34.5, 29.7, 28.4, 26.0, 25.1, 22.4, 21.8, 21.3, 20.8. ^{13}C NMR of **21** (101 MHz, $(CD_3)_2CO$, δ): 170.9, 86.5, 82.5, 73.9, 68.0, 45.4, 42.8, 37.1, 35.5, 35.1, 34.2, 30.6, 28.5, 26.5, 22.8, 22.4, 20.8. HRMS (ESI/TOF-Q) *m*/*z*: 297.2069 $[M + H]^+$ (calcd for $C_{17}H_{29}O_4$ 297.2066).

((1R,4R,6R,9S,10S)-9-Hydroxy-4,12,12-trimethyl-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-9-yl)methyl acetate (**22**). Diol **6** (200 mg; 0.79 mmol), Et_3N (0.33 mL; 2.36 mmol), and DMAP (4-(dimethylamino)pyridine, 19 mg; 0.16 mmol) were dissolved in CH_2Cl_2 (8 mL). To the mixture, Ac_2O (0.13 mL; 1.34 mmol) was added dropwise, and the reaction mixture was stirred at rt for 6 h. The reaction mixture was quenched with a saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc/hexanes (2:3, v/v) + 1% Et_3N elution afforded the title product (196 mg, 84%) as a white crystalline solid (*n*-hexane, mp 134−136 °C). $[\alpha]_D^{20}$ −80.9 (*c* 1.06, $CHCl_3$). FT-IR (thin film): ν_{max} 3517, 2947, 2907, 1721, 1458, 1394, 1368, 1323, 1279, 1250, 1231, 1076, 1041, 986, 927, 819, 785 cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2CO$, δ): 4.26 (d, *J* = 11.4 Hz, 1H), 4.10 (d, *J* = 11.5 Hz, 1H), 2.87 (dd, *J* = 10.3, 4.7 Hz, 1H), 2.28 (dt, *J* = 10.5, 9.2 Hz, 1H), 2.10−2.07 (m, 1H), 2.05 (s, 3H), 2.03−1.97 (m, 2H), 1.91 (tt, *J* = 9.5, 1.1 Hz, 1H), 1.78−1.60 (m, 4H), 1.60−1.47 (m, 1H), 1.45−1.34 (m, 1H), 1.28 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.95−0.89 (m, 1H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$, δ): 171.2, 74.4, 68.8, 62.3, 59.8, 51.3, 47.1, 40.5, 37.1, 35.5, 33.4, 30.3, 29.2, 24.7, 22.7, 20.9, 17.2. HRMS (ESI/TOF-Q) *m*/*z*: 319.1889 $[M + Na]^+$ (calcd for $C_{17}H_{28}O_4Na$ 319.1885). Single-crystal data: $C_{17}H_{28}O_4$ (*M* = 296.41 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 5.75713(6) Å, *b* = 12.1197(2) Å, *c* = 23.0596(3) Å, *V* = 1608.98(4) $Å^3$, *Z* = 4, *T* = 150.0(1) K, μ(Cu Kα) = 0.687 mm^{-1}, D_{calcd} = 1.2235 g/cm^3, 16 334 reflections measured (2Θ ≤ 160°), 3462 unique (R_{int} = 0.0306, R_{sigma} = 0.0245), which were used in all calculations. The final R_1 was 0.0297 ($I > 2\sigma(I)$), and wR_2 was 0.0771 (all data).

(1R,4R,5R,9S)-4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]-undecane-4,5-diol (**23**). Synthesis and full characterization data were described in our previous papers.[3,4] 4-Methylmorpholine 4-oxide (NMO, 852 mg, 7.27 mmol) and $K_2OsO_4{\cdot}2H_2O$ (24 mg, 0.07 mmol) were added to the solution of β-caryophyllene ((**5**), 1.35 g, 6.61 mmol) in Me_2CO/H_2O (100 mL, 9:1 v/v). The reaction mixture was stirred overnight at rt and then quenched with 15% aqueous $Na_2S_2O_3$ (100 mL). Excess Me_2CO was evaporated under reduced pressure, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc−hexanes (1:3 to 1:2, v/v) gradient elution to obtain the title product as a colorless oil (1.51 g, 96%, dr 10:1). ^1H NMR (400 MHz, $CDCl_3$, δ): 4.93 (t, *J* = 1.4 Hz, 1H), 4.91 (t, *J* = 1.4 Hz, 1H), 3.58 (td, *J* = 5.5, 2.7 Hz, 1H), 2.46−2.31 (m, 3H), 2.20−2.16 (m, 1H), 2.11−2.02 (m, 1H), 1.96−1.86 (m, 1H), 1.80−1.49 (m, 7H), 1.36−1.27 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 151.9, 110.6, 75.2, 73.5, 57.1, 42.5, 40.9, 36.2, 34.9, 34.2, 32.7, 30.2, 23.4, 22.2, 21.6. HRMS (ESI/TOF-Q) *m*/*z*: 239.2020 $[M + H]^+$ (calcd for $C_{15}H_{27}O_2$ 239.2011).

Isocaryophyllene-4R,5S-oxide (**24**). Diol **23** (1.11 g; 4.66 mmol) and Et_3N (2.60 mL; 18.6 mmol) were dissolved in CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C, and methanesulfonyl chloride (0.54 mL; 6.99 mmol) was added dropwise. The mixture was quenched with a saturated NH_4Cl aqueous solution (40 mL), washed with a saturated $NaHCO_3$ aqueous solution (40 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. The crude methanesulfonate, whose yield was assumed to be quantitative, was obtained as a yellow oil. It was dissolved in anhydrous MeOH (50 mL) followed by addition of anhydrous K_2CO_3 (6.44 g; 46.6 mmol). The reaction mixture was stirred at rt for 2 h and quenched with saturated NH_4Cl aqueous solution (150 mL). MeOH was removed under reduced pressure, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The residue was purified by column chromatography using EtOAc−hexanes (1:8, v/v) elution to obtain the title product (662 mg, 64%, dr 10:1) as a white crystalline solid (EtOAc, mp 68−70 °C). $[\alpha]_D^{20}$ −5.36 (*c* 1.12, $CHCl_3$). FT-IR (thin film): ν_{max} 3068, 2947, 2929, 2860, 1631, 1455, 1378, 1366, 1282, 1261, 1167, 1123, 1060, 1001, 947, 894, 822, 767, 671, 639 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 4.81 (dd, *J* = 2.3, 0.7 Hz, 1H), 4.70−4.63 (m, 1H), 2.78−2.71 (m, 1H), 2.64 (td, *J* = 9.9, 8.4 Hz, 1H), 2.56 (dddd, *J* = 13.7, 7.8, 2.4, 1.1 Hz, 1H), 2.31 (ddd, *J* = 13.7, 10.4, 8.0 Hz, 1H), 2.12 (ddt, *J* = 13.5, 8.1, 2.6 Hz, 1H), 1.97−1.89 (m, 1H), 1.79 (td, *J* = 10.1, 2.4 Hz, 1H), 1.76−1.68 (m, 1H), 1.64−1.47 (m, 3H), 1.37−1.31 (m, 2H), 1.27 (s, 3H), 1.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 150.7, 112.5, 64.9, 61.6, 50.7, 44.5, 40.7, 34.6, 33.6, 30.0, 29.6, 25.7, 25.1, 22.6, 21.7. HRMS (ESI/TOF-Q) *m*/*z*: 221.1911 $[M + H]^+$ (calcd for $C_{15}H_{25}O$ 221.1905).

((1R,4R,6S,9R,10S)-9-Hydroxy-4,12,12-trimethyl-5-oxatricyclo-[8.2.0.0^{4,6}]dodecan-9-yl)methyl acetate (**27**). **27** was obtained from isocaryophyllene-4*R*,5*S*-oxide (**24**, 607 mg; 2.75 mmol) via a dihydroxylation−acetylation sequence in analogy to that of isocaryophyllene-4*S*,5*R*-oxide (**19**). Purification by flash column chroma-

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tography with EtOAc–hexanes (2:3, v/v) + 1% Et_3N elution afforded the title product (66 mg, 8%) as a white crystalline solid (EtOAc, mp 98–100 °C). $[\alpha]_D^{20}$ −32.1 (*c* 1.09, $CHCl_3$). FT-IR (thin film): 3503, 2957, 2929, 2857, 1717, 1464, 1451, 1397, 1378, 1362, 1266, 1232, 1169, 1085, 1045, 945, 919, 861, 818, 758, 626, 606, 548 cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2CO$, δ): 3.77 (s, 2H), 3.65 (d, J = 1.0 Hz, 1H), 2.63 (ddd, J = 10.8, 2.8, 0.8 Hz, 1H), 2.19–2.11 (m, 1H), 2.11–2.07 (m, 1H), 2.01 (s, 3H), 2.03–1.94 (m, 2H), 1.84–1.72 (m, 2H), 1.71–1.57 (m, 2H), 1.56–1.49 (m, 1H), 1.49–1.40 (m, 2H), 1.34–1.26 (m, 1H), 1.28 (d, J = 0.8 Hz, 3H), 0.97 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$, δ): 171.0, 72.5, 70.7, 65.6, 61.9, 46.6, 44.2, 34.79, 34.76, 34.2, 33.7, 29.7, 26.5, 23.7, 22.9, 21.4, 20.8. HRMS (ESI/TOF-Q) m/z: 319.1883 $[M + Na]^+$ (calcd for $C_{17}H_{28}O_4Na$ 319.1885). Single-crystal data: $C_{17}H_{28}O_4$ (M = 296.41 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), a = 5.46997(6) Å, b = 12.4952(2) Å, c = 24.0538(3) Å, V = 1644.04(4) Å^3, Z = 4, T = 140.0(3) K, μ(Cu Kα) = 0.672 mm^{-1}, D_{calcd} = 1.1974 g/cm^3, 15 054 reflections measured ($2\Theta \leq 160°$), 3553 unique (R_{int} = 0.0363, R_{sigma} = 0.0327), which were used in all calculations. The final R_1 was 0.0349 ($I > 2\sigma(I)$), and wR_2 was 0.0864 (all data).

*((1S,2S,5R,8R,9R)-8-Hydroxy-4,4,8-trimethyl-12-oxatricyclo-[7.2.1.0^{2,5}]dodecan-1-yl)methyl acetate (**28**).* **28** was obtained from isocaryophyllene-4*R*,5*S*-oxide (**24**, 607 mg; 2.75 mmol) via a dihydroxylation–acetylation sequence in analogy to that of isocaryophyllene-4*S*,5*R*-oxide (**19**). Purification by flash column chromatography with EtOAc–hexanes (2:3, v/v) + 1% Et_3N elution afforded the title product (511 mg, 63%) as a colorless oil. $[\alpha]_D^{20}$ +0.654 (*c* 1.04, $CHCl_3$). FT-IR (thin film): 3459, 2933, 2866, 2718, 1745, 1723, 1458, 1387, 1368, 1246, 1126, 1085, 1064, 1042, 932, 877, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 4.04 (ddd, J = 8.2, 7.2, 0.9 Hz, 1H), 3.93 (d, J = 11.6 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 2.25–2.10 (m, 2H), 2.07 (s, 3H), 2.07–1.96 (m, 2H), 1.84–1.74 (m, 1H), 1.73–1.63 (m, 1H), 1.63–1.51 (m, 2H), 1.50–1.40 (m, 2H), 1.34 (d, J = 0.9 Hz, 3H), 1.30–1.21 (m, 1H), 1.17–1.07 (m, 2H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 171.3, 85.8, 85.6, 75.6, 68.2, 48.0, 45.0, 39.3, 36.1, 35.5, 29.9, 27.53, 27.49, 26.2, 25.9, 21.2, 21.0. HRMS (ESI/TOF-Q) m/z: 297.2069 $[M + H]^+$ (calcd for $C_{17}H_{29}O_4$ 297.2066).

*(1′R,2R,4′R,6′R,10′S)-4′,12′,12′-Trimethyl-5′-oxaspiro[oxirane-2,9′-tricyclo[8.2.0.0^{4,6}]dodecane] (**29**).* Kobusone (**8**, 3.78 g; 17.0 mmol) and Me_3SI (11.1 g; 54.3 mmol) were dissolved in anhydrous DMF (85 mL). The mixture was cooled to 0 °C, and KO*t*Bu (8.65 g; 74.7 mmol) was added to the mixture. The reaction mixture was warmed to rt, stirred for 6 h, and then quenched with a saturated NH_4Cl aqueous solution (100 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with EtOAc–hexanes (1:4, v/v) elution afforded the title product (3.83 g, 95%) as a white crystalline solid (EtOAc, mp 72–74 °C). $[\alpha]_D^{20}$ −59.7 (*c* 1.15, $CHCl_3$). FT-IR (thin film): 2988, 2959, 2941, 2923, 2860, 1486, 1457, 1381, 1316, 1285, 1255, 1079, 1068, 990, 948, 911, 901, 868, 842, 805, 765, 685 cm^{-1}. ^1H NMR (400 MHz, C_6D_6, δ): 3.09 (dd, J = 9.9, 4.7 Hz, 1H), 2.33 (dd, J = 5.5, 1.0 Hz, 1H), 2.12 (d, J = 5.4 Hz, 1H), 2.11–2.02 (m, 1H), 1.93 (dt, J = 12.6, 3.1 Hz, 1H), 1.77 (ddd, J = 10.3, 9.4, 7.8 Hz, 1H), 1.73–1.63 (m, 1H), 1.65–1.59 (m, 1H), 1.38–1.29 (m, 2H), 1.28–1.19 (m, 2H), 1.17–1.08 (m, 1H), 1.08 (s, 3H), 1.12–1.06 (m, 1H), 1.05–0.94 (m, 1H), 0.82 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6, δ): 61.9, 58.5, 58.0, 56.0, 47.9, 46.9, 40.1, 35.2, 33.4, 30.5, 29.4, 27.5, 25.6, 21.6, 16.5. HRMS (ESI/TOF-Q) m/z: 237.1862 $[M + H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1855). Single-crystal data: $C_{15}H_{24}O_2$ (M = 236.34 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.6936(2) Å, b = 10.3517(2) Å, c = 13.6631(3) Å, V = 1371.03(5) Å^3, Z = 4, T = 140.0(1) K, μ(Cu Kα) = 0.575 mm^{-1}, D_{calcd} = 1.145 g/cm^3, 11 423 reflections measured ($2\Theta \leq 160°$), 2918 unique (R_{int} = 0.0446, R_{sigma} = 0.0304), which were used in all calculations. The final R_1 was 0.0337 ($I > 2\sigma(I)$), and wR_2 was 0.0888 (all data).

*(1R,4R,6R,9R,10S)-9-Hydroxymethyl-4,12,12-trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecane-9-ol (**30**).* In a pressure tube, diepoxide **29** (3.32 g; 14.0 mmol) and 18-crown-6 (5.56 g; 21.0 mmol) were dissolved in DMF (28 mL) followed by addition of CsOAc (8.07 g; 42.1 mmol). The reaction mixture was heated at 135 °C and stirred for 16 h. Then, it was allowed to cool down to rt, and the contents were poured into H_2O (280 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography with gradient elution from EtOAc–hexanes (2:3, v/v) + 1% Et_3N to EtOAc–hexanes (1:1, v/v) + 1% Et_3N afforded linariophyllene C (**31**, 482 mg, 12%) and the title product (2.22 g; 62%) as a white crystalline solid (EtOAc, mp 123–125 °C). $[\alpha]_D^{20}$ −119 (*c* 1.05, $CHCl_3$). FT-IR (thin film): 3446, 2952, 1456, 1384, 1367, 1280, 1261, 1214, 1167, 1141, 1112, 1090, 1067, 1041, 962, 890, 858, 759, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 3.32 (dd, J = 10.3, 4.2 Hz, 1H), 3.29–3.24 (m, 1H), 3.15 (dd, J = 10.3, 5.6 Hz, 1H), 2.24–2.12 (m, 2H), 2.11 (d, J = 0.7 Hz, 1H), 2.09–2.03 (m, 1H), 2.00–1.89 (m, 2H), 1.89–1.82 (m, 1H), 1.70–1.60 (m, 2H), 1.54 (dd, J = 10.5, 7.6 Hz, 1H), 1.49–1.40 (m, 1H), 1.39–1.32 (m, 1H), 1.31–1.23 (m, 1H), 1.28 (d, J = 0.4 Hz, 3H), 1.06–0.97 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 73.9, 69.0, 61.4, 59.4, 49.3, 46.2, 40.5, 35.4, 33.6, 32.2, 29.5, 28.3, 25.0, 22.4, 16.3. HRMS (ESI/TOF-Q) m/z: 277.1794 $[M + Na]^+$ (calcd for $C_{15}H_{26}O_3Na$ 277.1780).

*Linariophyllene C (**31**).* **31** was obtained from diepoxide **29** (3.32 g; 14.0 mmol) together with diol **30**. Alternatively, the title product can be prepared in a separate step by acetylation of diol **30** (1.74 g; 6.84 mmol) by an analogous procedure to that of the acetylation of diol **6**. Purification by flash column chromatography with EtOAc–hexanes (2:3, v/v) + 1% Et_3N elution afforded the title product (1.85 g, 91%) as a white crystalline solid (*n*-hexane, mp 150 °C). $[\alpha]_D^{25}$ −101 (*c* 0.12, MeOH). FT-IR (KBr): 3536, 3026, 2958, 2929, 2856, 1723, 1457, 1389, 1367, 1305, 1258, 1092, 1045, 967, 934, 916, 892, 855, 838, 743, 704, 625 cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2CO$, δ): 3.84 (s, 1H), 3.79 (dd, J = 10.5, 0.8 Hz, 1H), 3.71 (dd, J = 10.6, 0.9 Hz, 1H), 3.19 (dd, J = 9.4, 5.3 Hz, 1H), 2.21 (td, J = 9.3, 8.7, 4.6 Hz, 1H), 2.15 (dt, J = 10.2, 7.1 Hz, 1H), 2.03–2.00 (m, 1H), 2.01 (s, 3H), 2.00–1.95 (m, 2H), 1.78 (t, J = 10.2 Hz, 1H), 1.66 (dt, J = 15.1, 4.0 Hz, 1H), 1.57–1.46 (m, 3H), 1.24 (s, 3H), 1.22–1.11 (m, 1H), 0.97 (s, 3H), 0.95–0.86 (m, 1H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$, δ): 171.1, 72.8, 71.7, 61.1, 58.8, 49.9, 46.4, 41.5, 35.7, 34.1, 33.6, 29.6, 28.8, 25.3, 22.7, 20.8, 16.5. HRMS (ESI/TOF-Q) m/z: 319.1887 $[M + Na]^+$ (calcd for $C_{17}H_{28}O_4Na$ 319.1885). Single-crystal data: $C_{17}H_{28}O_4$ (M = 296.41 g/mol), orthorhombic, space group $P2_12_12_1$ (No. 19), a = 5.65862(5) Å, b = 15.1190(2) Å, c = 18.9882(2) Å, V = 1624.49(3) Å^3, Z = 4, T = 150.0(1) K, μ(Cu Kα) = 0.680 mm^{-1}, D_{calcd} = 1.2119 g/cm^3, 15 664 reflections measured ($2\Theta \leq 160.0°$), 3509 unique (R_{int} = 0.0481, R_{sigma} = 0.0413), which were used in all calculations. The final R_1 was 0.0342 ($I > 2\sigma(I)$), and wR_2 was 0.0909 (all data).

*Rumphellolide H (**4**).* Diol **7** (6.96 g, 27.3 mmol) was dissolved in EtOAc (280 mL). To the solution, 280 g of SiO_2 (35–70 μm particle size) was added. The reaction mixture was stirred at rt for 3 h and filtered. The solvent was evaporated under reduced pressure, and the mixture was separated using flash column chromatography with gradient elution from EtOAc–hexane (1:1, v/v) to pure EtOAc, affording starting material **7** (1.45 g, 21%) and the title product (4.57 g, 66%) as a white crystalline solid (EtOAc, mp 111–113 °C). $[\alpha]_D^{20}$ −6.90 (*c* 1.10, $CHCl_3$). FT-IR (thin film): ν_{max} 3312, 2942, 2923, 2860, 1475, 1456, 1366, 1252, 1077, 1067, 1046, 1013, 964, 832, 701, 646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 3.56 (dd, J = 6.7, 3.1 Hz, 1H), 3.26 (d, J = 11.0 Hz, 1H), 3.16 (d, J = 11.0 Hz, 1H), 2.17 (s, 2H), 2.13–2.05 (m, 1H), 2.04–1.98 (m, 1H), 1.91 (ddd, J = 12.0, 10.2, 5.1 Hz, 1H), 1.86–1.77 (m, 2H), 1.74–1.64 (m, 2H), 1.59–1.51 (m, 2H), 1.50–1.40 (m, 2H), 1.20 (s, 3H), 1.18–1.14 (m, 1H), 1.02 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 78.2, 75.8, 70.6, 69.6, 47.4, 44.7, 38.9, 37.0, 35.0, 30.5, 28.0, 25.6, 23.7, 20.8, 19.5. HRMS (ESI/TOF-Q) m/z: 277.1786 $[M + Na]^+$ (calcd

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for $C_{15}H_{26}O_3Na$ 277.1780). Single-crystal data: $C_{30}H_{52}O_6$, M_r = 508.71, monoclinic, $P2_1$ (No. 4), a = 6.1708(2) Å, b = 30.377(1) Å, c = 8.0913(2) Å, β = 112.081(3)°, V = 1405.44(7) Å^3, T = 150.0(1) K, Z = 2, Z' = 1, μ(Cu Kα) = 0.648, 12 638 reflections measured, 4700 unique (R_{int} = 0.0758), which were used in all calculations. The final wR_2 was 0.1299 (all data), and R_1 was 0.0423 ($I > 2\sigma(I)$).

■ ASSOCIATED CONTENT

Data Availability Statement

The NMR data for compounds **2**–**4**, **7**–**10**, **12**–**19**, **20**/**21**, **22**–**24**, and **27**–**31** have been deposited in the Natural Products Magnetic Resonance Database (NP-MRD; www.np-mrd.org) and can be found at NP0331809 (compound **7**), NP0137067 (compound **8**), NP0059013 (compound **9**), NP0331812 (compound **10**), NP0331822 (compound **12**), NP0331817 (compound **2**), NP0331830 (compound **13**), NP0331820 (compound **14**), NP0331825 (compound **15**), NP0331826 (compound **16**), NP0331824 (compound **17**), NP0331811 (compound **18**), NP0331814 (compound **19**), NP0331828 (compound **3**), NP0331813 (mixture **20**/**21**), NP0331818 (compound **22**), NP0331821 (compound **23**), NP0331810 (compound **24**), NP0331823 (compound **27**), NP0331829 (compound **28**), NP0331815 (compound **29**), NP0331809 (compound **30**), NP0331827 (compound **31**), and NP0331819 (compound **4**).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.3c00574.

NMR spectroscopic data with assignments of all protons and carbons and their interactions in NOESY and HMBC spectra for **2**–**4**, **9**, **14**, and **31**; comparison of NMR data of isolated and synthesized **2**, **4**, **9**, and **14**; comparison of NMR shifts between the proposed structure of linariophyllene C (**3**), the corresponding natural isolate, and the revised structure of linariophyllene C (**31**); comparison of specific rotation data between synthetic and isolated **2**, **4**, **9**, **14**, and **31**; copies of NMR spectra for **2**–**4**, **7**–**10**, **12**–**19**, **20**/**21**, **22**–**24**, and **27**–**31**; copies of IR spectra of all aforementioned compounds; X-ray crystallography data for compounds **2**–**4**, **7**, **9**, **14**, **22**, **27**, **29**, and **31** (PDF)

X-ray crystallography data for compound **7** (CIF)

X-ray crystallography data for compound **9** (CIF)

X-ray crystallography data for compound **2** (CIF)

X-ray crystallography data for compound **14** (CIF)

X-ray crystallography data for compound **3** (CIF)

X-ray crystallography data for compound **22** (CIF)

X-ray crystallography data for compound **27** (CIF)

X-ray crystallography data for compound **29** (CIF)

X-ray crystallography data for compound **31** (CIF)

X-ray crystallography data for compound **4** (CIF)

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Notes

The authors declare no competing financial interest.

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Bridgehead Epoxide Iso-Euphoranin E from β-Caryophyllene Oxide *via* Sequential Cationic Formation and Scission of [4.3.2]Propellane.

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RESEARCH ARTICLE

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Bridgehead epoxide iso-euphoranin E from β-caryophyllene oxide *via* sequential cationic formation and scission of [4.3.2]propellane†

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The development of Gassman's Lewis-acid-catalyzed [2 + 2] cycloaddition in (–)-β-caryophyllene-oxide-derived naturally occurring enone **8** represent a missing link connecting **8** with the natural [4.3.2]propellane-containing alcohol **9**. Further chemical transformations involving propellane **9** established a route toward bridgehead epoxide iso-euphoranin E (**11**), which was found to be a diastereomer of the natural product euphoranin E (**2**) isolated from *Euphorbia wangii*. DFT calculations were performed to explain the observed stereoselectivities of the solvolysis of key mesylate **15** to form the euphoranin E core and [2 + 2] cycloaddition in enone **8** to form precursor **9** of iso-euphoranin E (**11**). The presented research expands the chemical space around caryophyllane-type sesquiterpenoids containing bridgehead motifs.

Introduction

Bridgehead epoxide-containing terpenoids are an exceptionally rare type of natural products (NPs). So far, these structural motifs are found only in salsolene oxide (**1**) obtained from *Artemisia salsoloides* Willd[1–3] and euphoranin E (**2**) isolated from *Euphorbia wangii* Oudejans[4] (Fig. 1).

Bridgehead olefins **3a,b** (Fig. 1), which are structurally similar to euphoranin E, have served as key intermediates for the synthesis of psiguadial B,[5] as well as substrates for bioorthogonal reactions used for *in vitro* protein labeling.[6] The structure of euphoranin E (**2**) was found to be identical[4] to the minor oxidation product (0.5% yield) of (–)-β-caryophyllene (**4**) with $Pb(OAc)_4$ (Fig. 2).[7]

A biosynthetic precursor of euphoranin E, the bridgehead olefin **7**, is a known natural product,[8] which has been prepared by a biomimetic sequence from caryophyllene oxide (**5**) involving naturally occurring allylic alcohol **6**[9,10] (Fig. 2). Interestingly, ketone **8**, an oxidation product of alcohol **6**, is found in certain plants;[10] however, its role as an intermediate in the biosynthesis of other natural products has not been reported.

The exploration of the construction of bridgehead olefin[11,12] and epoxide motifs from affordable and renewable starting materials, such as (–)-β-caryophyllene (**4**) and its oxide (**5**), would enable access to non-abundant NPs. Recent examples of this approach from our group and other researchers include the semisynthesis of several terpenoids in a concise manner from (–)-β-caryophyllene (**4**) and its oxide (**5**).[13–18] In addition, these studies resulted in the confirmation or revision of known NP structures, as well as the elucidation of the biogenetic pathways of the NPs.[18]

Here, we show that ketone **8** derived from (–)-β-caryophyllene oxide (**5**) can be transformed into naturally occurring propellane derivative **9** (see ESI† for the list of plants) by employing a modification of the intramolecular Gassman cationic [2 + 2] cycloaddition.[19,20] Moreover, propellane **9** can be transformed into the bridgehead olefin **10**, which is a precursor of iso-euphoranin E (**11**).

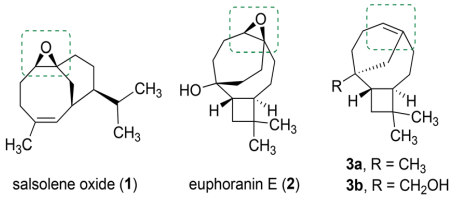

Fig. 1 NPs containing bridgehead epoxide and bridgehead olefins **3**.

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†Electronic supplementary information (ESI) available: General information, synthetic procedures and characterization; NMR spectroscopic data; comparison of NMR data between natural and synthetic compounds; X-ray crystallography data of compounds **2**, **7**, **10**, **11**, and **13**; procedure for DFT calculations and optimized geometries. CCDC 2346928–2346932. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4qo00940a

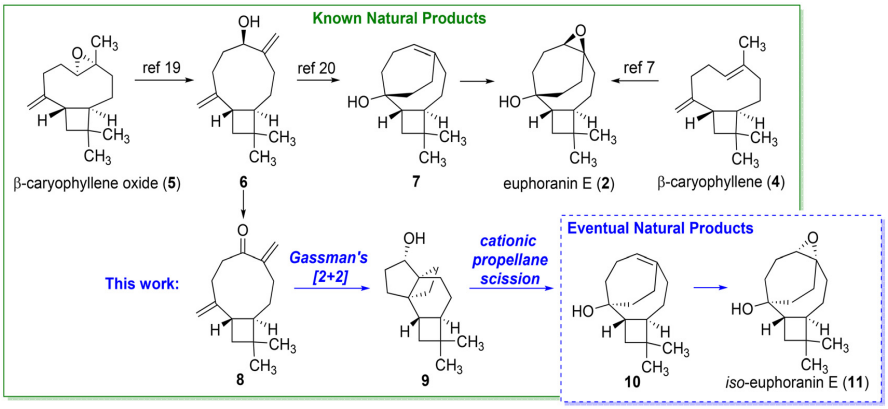


Fig. 2 Biosynthetic path to euphoranin E (**2**) and synthetic path to iso-euphoranin E (**11**).

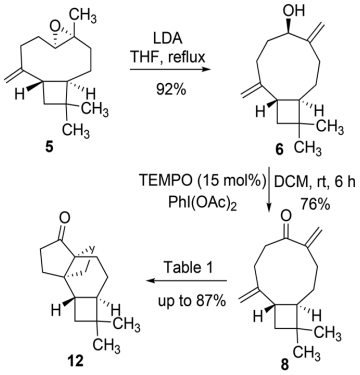
Results and discussion

Enone **8** was readily obtained from (−)-β-caryophyllene oxide (**5**) by LDA-mediated epoxide isomerization[21,22] and subsequent oxidation[23] of the resulting allylic alcohol **6** (Scheme 1).

In contrast to allylic alcohol **6**, whose acid-catalyzed skeletal rearrangement has been reported,[15,17,24,25] rearrangements involving enone **8** are not known.

Examination of the reactivity of enone **8** revealed that exposure to acids gives rise to ketone **12** with a [4.3.2]propellane structure (Scheme 1, Table 1).

Screening of the conditions was performed to find the most productive conversion of enone **8** to propellane **12** (Table 1). Zinc and copper triflates were ineffective catalysts for this transformation (Table 1, entry 1). Cyclization with $BF_3{\cdot}OEt_2$ did not proceed in ethereal solvents (Table 1, entry 2); however, changing the solvent to DCM or MeCN gave the propellane **12** in moderate and good yields, respectively (Table 1, entries 3 and 4). Lewis acid catalysts such as $TiCl_4$, Me_3SiOTf, and $AlCl_3$ were also explored using MeCN as the solvent



Scheme 1 Synthesis of propellane **12** by cyclization of enone **8**.

Table 1 Optimization studies of the cyclization of enone **8**

Entry	Catalyst, 15 mol%	Conditions[a]	Yield[b] (%)
1	$Zn(OTf)_2$ or $Cu(OTf)_2$	MeCN, reflux, 24 h	n.r.[c]
2	$BF_3{\cdot}OEt_2$	Et_2O or THF, rt, 24 h	n.r.[c]
3	$BF_3{\cdot}OEt_2$	DCM, 0 °C, 1 h	57[d]
4	$BF_3{\cdot}OEt_2$	MeCN, 0 °C, 1 h	71[d]
5	$TiCl_4$	MeCN, 0 °C, 1 h	40[d]
6	Me_3SiOTf	MeCN, 0 °C, 1 h	59[d]
7	$AlCl_3$	MeCN, 0 °C, 1 h	90[d] (87[e])
8	*S*-CSA or $TsOH{\cdot}H_2O$	PhMe, rt, 24 h	n.r.[c]
9	CF_3CO_2H	DCM, rt, 24 h	n.r.[c]
10	TfOH	DCM, 0 °C, 1 h	43[d]

[a] 0.1 M concentration of enone **8**. [b] Isolated yield. [c] No reaction. [d] 1 mmol scale. [e] 12.4 mmol scale. Ts – tosyl; Tf – triflyl; CSA – 10-camphorsulfonic acid.

(Table 1, entries 5–7); among them, $AlCl_3$ provided the highest yield of propellane **12** (Table 1, entry 7). Out of the Brønsted acids investigated (Table 1, entries 8–10), only TfOH produced the desired propellane **12**, albeit in moderate yield.

The proposed mechanism of the cyclization of enone **8** to propellane **12** involves Lewis acid (LA) coordination to the carbonyl group, leading to complex **A** (Fig. 3). In this complex, concerted or stepwise mechanisms to form the [4.3.2]propellane could be envisioned. In the stepwise mechanism, the 1,1-disubstituted double bond attacks the electron-deficient carbon, resulting in tertiary carbocation **B**. Intramolecular attack of the enolate forms the propellane skeleton of ketone **12**. In turn, the concerted mechanism does not involve the formation of a tertiary carbocation, instead immediately giving propellane **12** *via* transition state **C** and the decomplexation of Lewis acid from oxygen of the carbonyl.

To distinguish between the concerted and stepwise pathways as well as to explain the observed stereoselectivity, DFT calculations were performed using Gaussian 09 software. The results (see Fig. 4 and ESI†) were in accordance with the concerted pathway, which is also supported by the absence of the possible products arising from Ritter reaction between cation

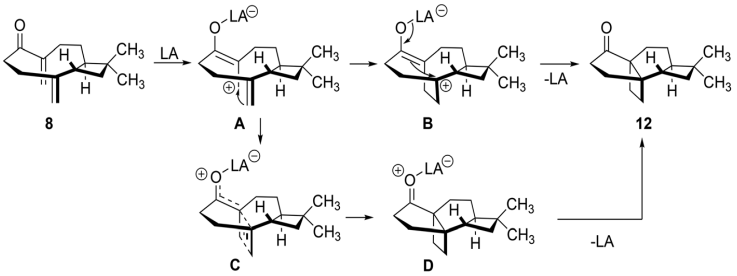


Fig. 3 Proposed stepwise (upper) and concerted (lower) mechanisms for the cyclization leading to ketone **12**.

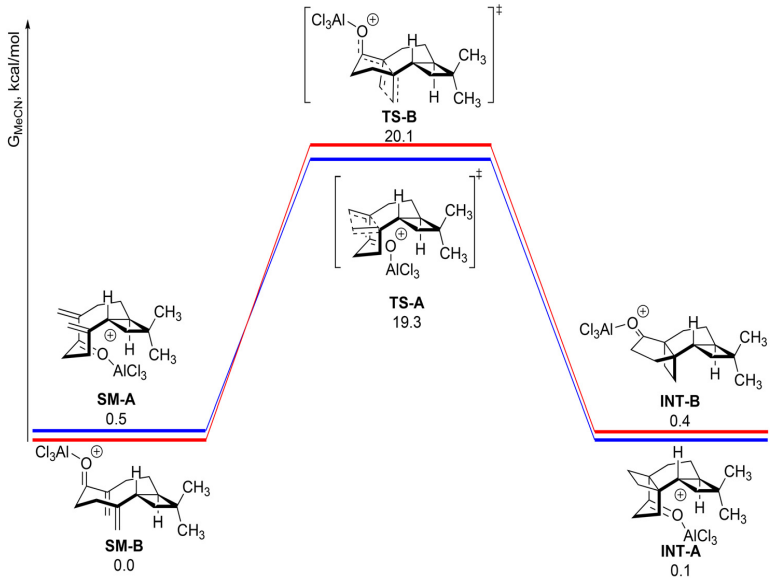
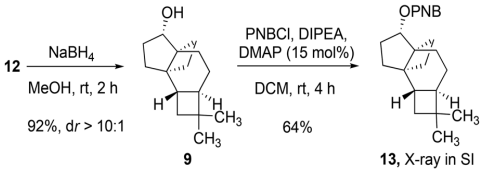


Fig. 4 Calculated energy profile of [2 + 2] cycloaddition of enone **8**.

B and MeCN as the reaction solvent. However, the reason for the diastereoselectivity remains unknown, since the energy difference between the two conformations of the enone–$AlCl_3$ complex **A** was found to be only 0.5 kcal mol^{-1}.

Overall, this reaction can be regarded as a Lewis-acid-catalyzed [2 + 2] intramolecular cycloaddition. Similar inter- and intramolecular reactions were pioneered by Gassman.[19,20] This reaction was subsequently employed in the formal total synthesis of raikovenal and its epimer.[26] Later, temporary hydrazine and hydroxyamide tethers were designed to yield unfused cyclobutanes.[27] However, to the best of our knowledge, this is the first example of such an intramolecular reaction between an alkene and unprotected enone fragments. It is also the first synthesis of a cyclobutane moiety of [4.3.2]propellane using Gassman's approach and without application of photochemical conditions.[28–32]

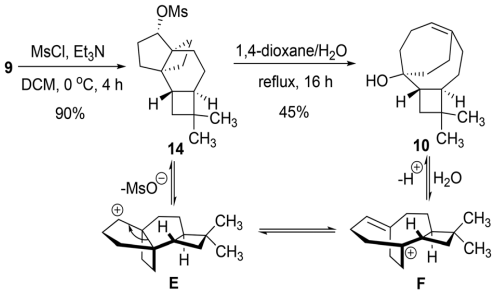
Ketone **12** was reduced to a secondary alcohol **9** with excellent substrate-controlled diastereoselectivity (Scheme 2). The



Scheme 2 Synthesis of propellane derivatives **9** and **13** (PNB – 4-nitrobenzoyl).

propellane structure of alcohol **9** was confirmed by X-ray crystallography of its derivative 4-nitrobenzoate **13**.‡ Alcohol **9** has been detected in numerous plant extracts under the name 4,4-dimethyltetracyclo[6.3.0^{2,5}.0^{1,8}]tridecan-9-ol (see ESI,

‡CCDC deposition number of **13**: 2346928.

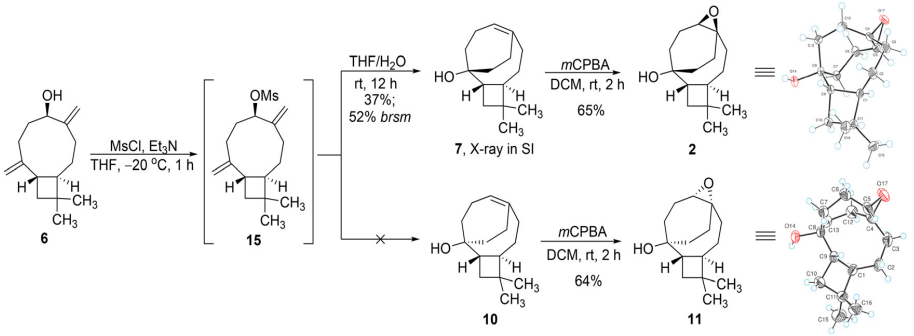


Scheme 3 Synthesis of mesylate **14** and proposed mechanism of its rearrangement to bridgehead olefin **10**.

Table S1†);[33] however, neither its relative nor absolute configuration has been reported. The available mass spectrum of natural isolate[34] is in good accordance to our data (see ESI†), thus confirming the occurrence of compound **9** in natural sources.

Mesylation of alcohol **9** (Scheme 3) was performed to give intermediate **14**, which was subjected to the skeletal rearrangement. Mesylate **14** underwent solvolysis in aqueous media to give bridgehead olefin **10**.

The proposed mechanism for the formation of bridgehead olefin **10** starts with the solvolysis of mesylate **14** to give a secondary carbocation **E** (Scheme 3). This undergoes fragmentation, leading to a bridgehead tertiary carbocation **F**, which furnishes alcohol **10** upon reaction with water.



Scheme 4 Synthesis of euphoranin E (**2**) and iso-euphoranin E (**11**), and their ORTEP images with 50% contour probability.

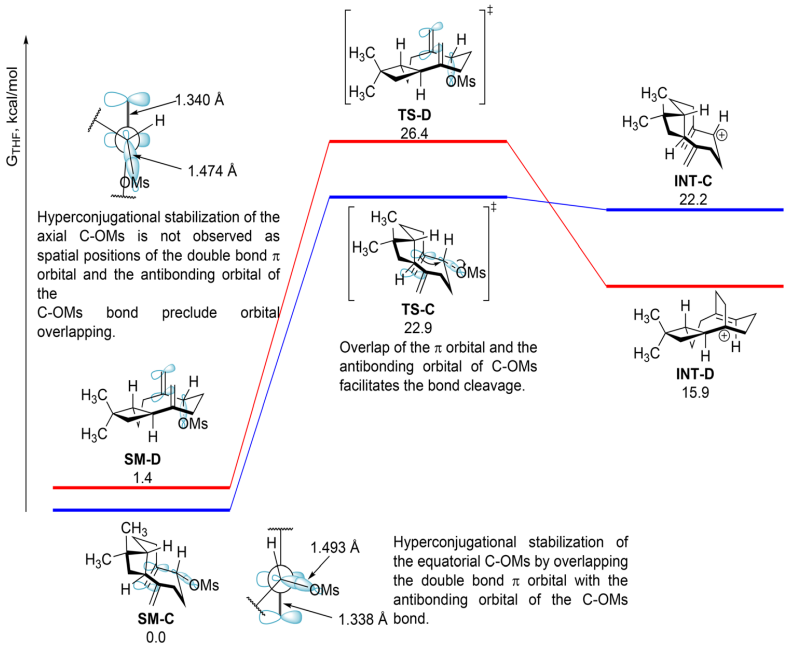


Fig. 5 Calculated energy profile of solvolysis of mesylate **15**.

The bridgehead olefin **10** is a diastereomer of olefin **7**, which is synthesized from allylic alcohol **6**-derived mesylate **15** (Scheme 4).[21,22] Diastereomers **7** and **10** were epoxidized in a diastereoselective fashion to give euphoranin E (**2**) and isoeuphoranin E (**11**), respectively (Scheme 4). It was revealed that the stereoselectivity of the bridgehead olefin epoxidation is dependent on the configuration of the tertiary alcohol stereocenter, since its inversion furnished the epoxide with opposite configuration (Scheme 4).

The DFT calculations were performed to gain insight into the diastereoselectivity of the solvolysis of mesylate **15**. From analyzing the most energetically favorable transition states, the conformation **SM-C** of mesylate **15** leading to alcohol **7** was found to be significantly lower in energy (Fig. 5) compared to the opposite conformation **SM-D**, which can potentially furnish alcohol **10**, thus fully corroborating the experimental results. The selectivity can be explained by the hyperconjugational stabilization[35] between the π-orbitals of the double bond and σ*-orbital of the equatorial C–OMs bond; thus, the difference between **TS-D** (no stabilization) and **TS-C** (with stabilization) was calculated to be 3.5 kcal mol^{-1}, assuring a >99 : 1 diastereomeric ratio. It is also noteworthy that **TS-C** and **INT-C** have nearly the same energy, indicating that **TS-C** is a late transition state, whereas cation **INT-D** has lower energy than **INT-C** due to the immediate formation of the C–C bond and migration of the positive charge.

It is worth mentioning that compounds **10** and **7**, when crystallized, give crystal structures§ that are pseudoenantiomorphic.

In both crystal structures, there are strong intermolecular hydrogen bonds of the OH···O type. By means of these bonds, spiral molecular chains are formed in the crystal structures along the threefold symmetry axis. The difference between these molecular chains is that in **10**, the molecular chain (along crystallographic screw axis 3_1) forms a right-handed helix, while in **7**, the molecular chain (along crystallographic screw axis 3_2) is a left-handed helix (see ESI, Fig. S4†).

In contrast to **10** and **7**, the epoxidized diastereomers **2** and **11** crystallized¶ quite differently. The crystal structure of **2** closely resembles the structure of **7** (see ESI, Fig. S6†), whereas the compound **11** belongs to monoclinic space group $P2_1$. It should be noted that, unlike in **2**, in **11** the formation of the hydrogen bonds involves epoxide oxygen atoms (see ESI, Fig. S7 and S8†).

Bridgehead olefin **7** is a natural product, which has been isolated from *Euphorbia wangii*,[8] and its spectral data perfectly correspond to those of the natural isolate (see ESI, Table S8†). In contrast, initial inspection of the NMR data of euphoranin E (**2**) revealed deviations between the ^{13}C NMR chemical shifts of product **2** prepared by us and those reported in the literature[4] (see ESI, Table S9†). Additionally, the discrepancies (see ESI, Table S10†) between the characteristic ^{1}H NMR chemical shifts (*gem*-dimethyl and CH of epoxide moiety) were very large in the reported solvent.[4] Fortunately, this initial divergence of the spectral data in ^{1}H NMR was ameliorated by recording the NMR spectra of **2** in C_6D_6, which resulted in a perfect match between the aforementioned characteristic chemical shifts and those reported for euphoranin E (**2**). This can be explained by an erroneous report of the deuterated solvent used for the acquisition of the ^{1}H NMR data of **2** by authors, who performed the isolation of epoxide **2** from a natural source.[4] The partial match of the ^{13}C NMR signals of compound **2** in can be explained by the presence of impurities in the natural isolate, which might have complicated the interpretation of the spectra. Nevertheless, the majority of the carbon signals correspond to those of the natural product, giving assurance to the confirmation of the euphoranin E structure as **2**.

§CCDC deposition number of **10** and **7**: 2346929 and 2346931, respectively.
¶CCDC deposition number of **2** and **11**: 2346932 and 2346930, respectively.

Conclusions

In conclusion, we have reported a concerted Lewis-acid-catalyzed [2 + 2] intramolecular cycloaddition in naturally occurring enone **8** to form naturally occurring [4.3.2]propellane **9**. This indicates the possible biosynthetic pathway linking both compounds. Further transformations involving the cationic rearrangement of mesylate **14** derived from propellane **9** provided diastereomeric bridgehead olefin **10**, which is a diastereomer of naturally occurring olefin **7**. Diastereoselective epoxidation of olefins **7** and **10** provided euphoranin E (**2**) and isoeuphoranin E (**11**), respectively. Additionally, DFT calculations provided a conclusive explanation for the diastereoselective solvolysis of allylic mesylate **15**. Despite the fact that bridgehead olefin **10** and bridgehead epoxide **11** have not been yet reported as natural products, the possibility of their occurrence in natural sources is high, since both compounds can be derived from naturally abundant propellane **9**.

Author contributions

G. S. – synthesis, conceptualization, writing (original draft); D. R. and A. J. – conceptualization, supervision, writing (review & editing); S. B. – data curation (X-ray crystallography), A. K. – data curation (DFT calculations).

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for compounds **2**, **7**, **10**, **11**, and **13** has been deposited at the Cambridge Crystallography Data Center (CCDC) under accession numbers 2346932, 2346931, 2346929, 2346930, and 2346928, respectively and can be obtained from **https://www.ccdc.cam.ac.uk/structures/**.

Conflicts of interest

There are no conflicts to declare.

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Bioinspired Semisynthesis and Structure Revisions of Chlorinated Norsesquiterpenoids Rumphellatins A–C

Georgijs Stakanovs,* Anastasija Blazevica, Dace Rasina, Sergey Belyakov, and Aigars Jirgensons*

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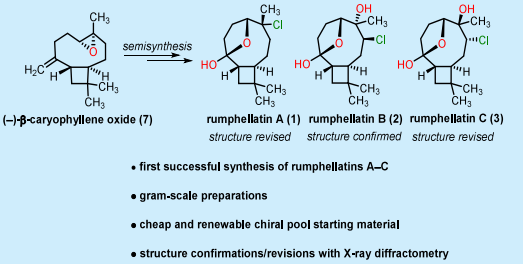
ABSTRACT: The first synthesis of chlorine-containing hemiketals, rumphellatins A–C (**1**–**3**), previously inaccessible by means of total synthesis, was achieved starting from commercially available (−)-β-caryophyllene oxide (**7**). Structures of rumphellatins A (**1**) and C (**3**) were revised, while structures of rumphellatin B (**2**) and intermediate rumphellolide C (**19**) were confirmed. The study expands availability of exotic norsesquiterpenoids for profiling their biological activity as well as facilitates the elucidation of biosynthetic pathways of their formation.



Rumphellatins A–C (**1**–**3**; Figure 1) are chlorinated norsesquiterpenoids isolated from gorgonian corals

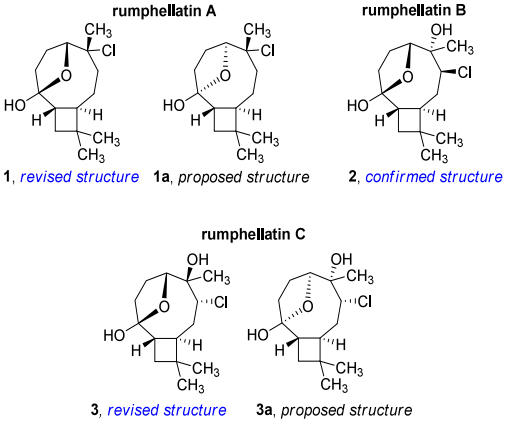


Figure 1. Rumphellatins A–C with their proposed and revised structures.

Rumphella antipathies.[1,2] These natural products contain a distinctive 12-oxatricyclo[7.2.1.$0^{2,5}$]dodecane hemiketal framework, which is not found in other known terpenoids. Antibacterial assays revealed that rumphellatin A (**1**) is active against Gram-negative bacteria (*Escherichia coli* and *Vibrio parahemolyticus*),[1] whereas rumphellatin B (**2**) displays activity against Gram-positive *Staphilococcus aureus*.[2]

Owing to biological activity and unique structural features, these natural products were the target of total synthesis.[3] An attempt has been made to construct the 12-oxatricyclo-[7.2.1.$0^{2,5}$]dodecane core of rumphellatins A–C starting from cyclic allene **4** (Scheme 1). Triene **4** was successfully transformed to epoxide **5**; however, its successive cleavage/cyclization sequence to obtain key intermediate **6** failed.

Due to the structural similarity between rumphellatins A–C and commercially available (−)-β-caryophyllene and its oxide, we envisioned their synthesis from these starting materials, which have predisposition for chemical transformations, leading to increased structural complexity.[4−10] With their high abundance and their role as nodes for biosynthesis of a plethora of terpenoids taken into account, (−)-β-caryophyllene and its oxide (**7**) have been used as chiral pool starting materials for semisynthesis of several exotic natural products by our group and others.[10−16] Notable examples include syntheses of psiguadial B,[4] rumphellaones A–C,[11,15] and presilphiperfolan-1β-ol.[10]

Herein, we report the use of caryophyllene oxide (**7**) for the semisynthesis of rumphellatins A–C as well as revision of their relative configuration (**1**–**3**; Figure 1). The synthetic strategy toward rumphellatin A (**1**) involved our previously established scalable route to isokobusone (**8**)[14] bearing an exocyclic double bond, whereas the pathway leading to rumphellatins B and C (**2** and **3**) involved regioselective isomerization of the *trans*-epoxide moiety of (−)-β-caryophyllene oxide (**7**) to allylic alcohol **9** possessing an endocyclic double bond (Scheme 1).

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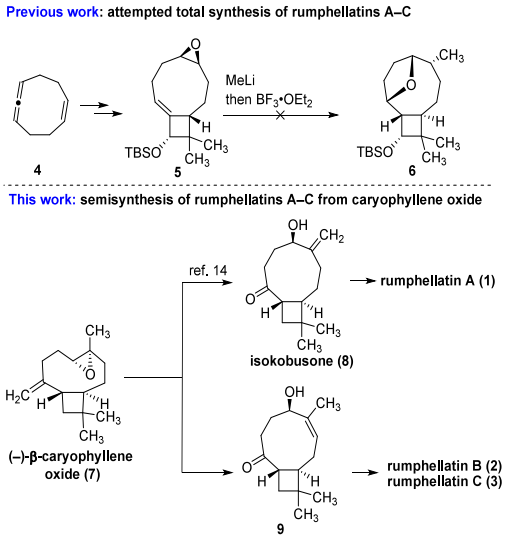
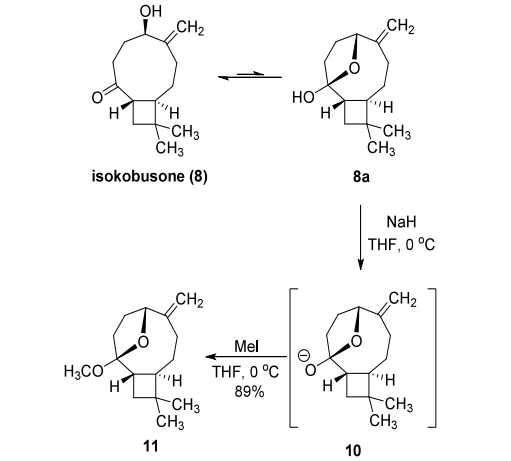
Scheme 1. Attempted Total Synthesis Route and Semisynthetic Routes Toward Rumphellatins A−C



Our previous studies revealed that isokobusone exists as a mixture of major ketone **8** and minor (∼13%) hemiketal tautomer **8a** in $CDCl_3$ (Scheme 2). Hence, we hypothesized

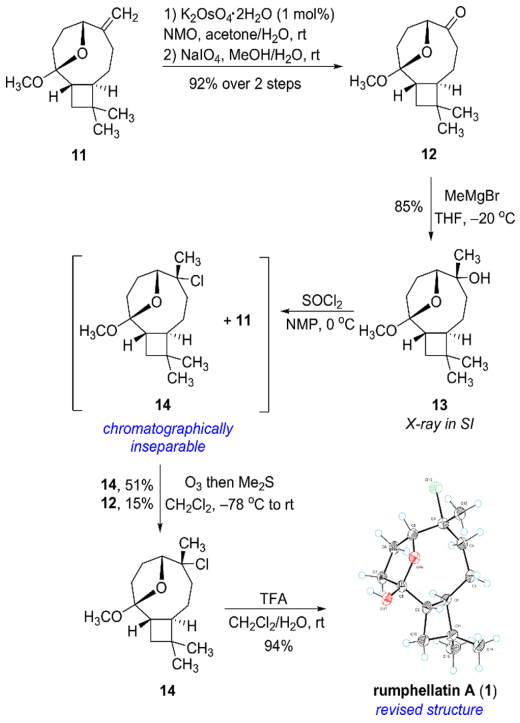
Scheme 2. Isokobusone Ketone−Hemiketal Tautomeric Forms (8 and 8a) and Synthesis of Ketal 11



that deprotonation of isokobusone would form hemiketal anion **10**, which can be captured by the outer electrophile. This worked out successfully using alkylation with MeI, which led to the isolation of ketal **11** bearing a 12-oxatricyclo-[7.2.1.$0^{2,5}$]dodecane scaffold (Scheme 2).

Ketal **11** was then used as a key intermediate for the semisynthesis of rumphellatin A (**1**). Initial synthetic attempts involved hydroboration/oxidation of the exocyclic methylene group to aldehyde followed by α-chlorination and subsequent reduction of aldehyde to the methyl group (see Scheme S1 of the Supporting Information). Albeit successfully delivering the final product, this approach was abandoned due to the high number of steps and poor yields. Improved synthesis of rumphellatin A (**1**) involved installation of ketone functionality via a dihydroxylation/diol cleavage sequence to provide compound **12**, which underwent diastereoselective Grignard addition of MeMgBr furnishing tertiary alcohol **13** (Scheme 3). Diastereoselective Grignard addition to ketone **12** can be

Scheme 3. Synthesis of Rumphellatin A (1) and Its Oak Ridge Thermal Ellipsoid Plot (ORTEP) Image with 50% Contour Probability



explained by steric factors in face selection induced by the preferred conformation of a nine-membered cycle resulting from the dipole−diplole interaction between carbonyl and bridging oxygen in compound **12** (see Scheme S3 of the Supporting Information). Chlorination of resultant alcohol **13** with $SOCl_2$ gave a chromatographically inseparable mixture of chloride **14** and alkene **11** as an elimination byproduct. Fortunately, ozonolysis of this mixture selectively converted compound **11** into ketone **12**, thus facilitating the separation. Conversion from ketal **14** into rumphellatin A (**1**) was readily achieved by treating it with aqueous trifluoroacetic acid (TFA) (Scheme 3). The nuclear magnetic resonance (NMR) data of rumphellatin A (**1**) obtained from β-caryophyllene oxide (**7**) matched to that of the product isolated from natural sources (see Table S6 of the Supporting Information).[1] This fact implies that the correct structure of rumphellatin A (**1**) possesses inverted stereocenters at the tetrahydrofuran fragment in comparison to its proposed structure **1a** (Figure 1).[1]

The synthesis of rumphellatins B and C started from epoxydiol **15** (Scheme 4), which was prepared by dihydroxylation of (−)-β-caryophyllene oxide (**7**) according to a

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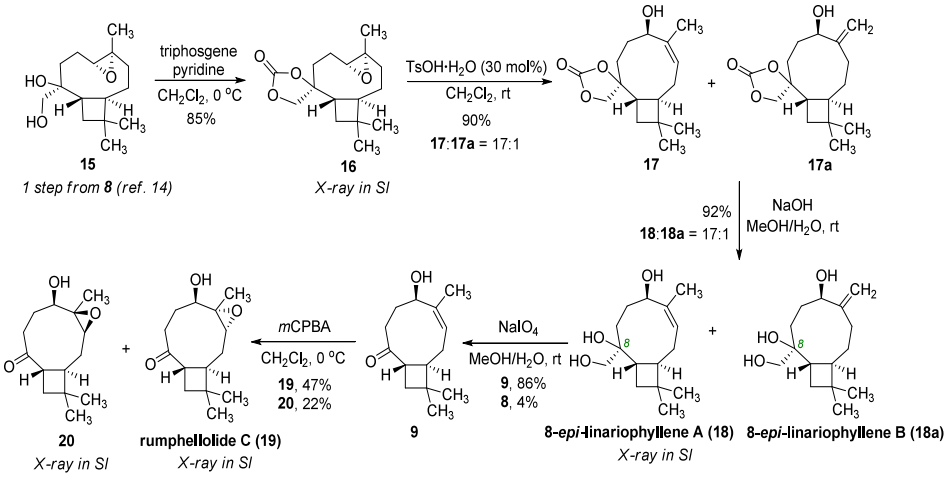
Scheme 4. Synthesis of Keto Alcohol 9, Its Epoxidation to Rumphellolide C (19), and Its Diastereomer 20

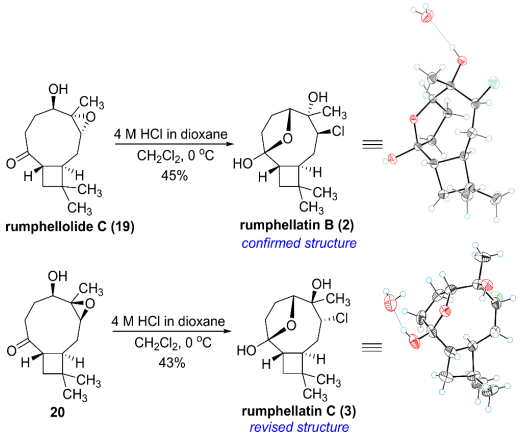


published protocol.[14] Diol **15** was subjected to the reaction with triphosgene in the presence of pyridine to afford epoxycarbonate **16**. Acid-catalyzed isomerization of epoxide **16** to allylic alcohol **17** smoothly provided the desired endocyclic double bond with exocyclic double bond isomer **17a** as an inseparable minor contaminant (~6%). The hydrolysis of carbonate furnished 8-*epi*-linariophyllene A (**18**),[14,17] which gave keto alcohol **9** upon treatment with $NaIO_4$. Minor inseparable exocyclic 8-*epi*-linariophyllene B (**18a**)[14,17] yielded isokobusone (**8**), which was successfully separated from major alcohol **9**. Epoxidation of allylic alcohol **9** yielded two diastereomeric epoxyalcohols **19** and **20**, with the former matching the structure of known natural product rumphellolide C (**19**),[18] as confirmed by X-ray crystallography.

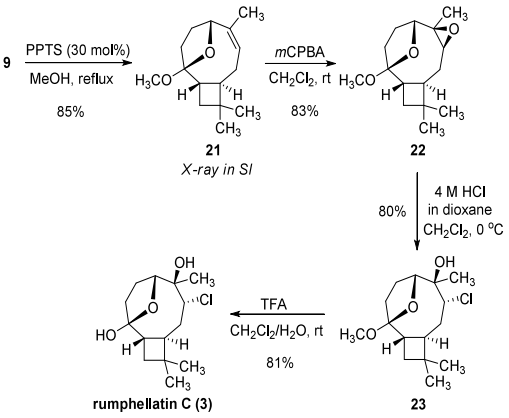
The cleavage of epoxide **19** with HCl gave rumphellatin B (**2**) (Scheme 5). NMR data of rumphellatin B (**2**) matched the compound isolated from natural sources, thus confirming the proposed structure (see Table S8 of the Supporting Information).[2] This transformation of rumphellolide C to rumphellatin B by the action of HCl implies that a similar reaction may occur in *R. antipathies* species (see Scheme S5 of the Supporting Information). Minor epoxide diastereomer **20** was converted to rumphellatin C (**3**) with HCl under analogous conditions (Scheme 5). In both reactions, epoxide opening with chloride proceeded with a stereoinversion at secondary carbon, indicating the S_N2 mechanism as the major pathway. Minor byproducts were observed, which could have originated from competitive regioselectivity in epoxide opening at tertiary carbon; however, their purification and structure elucidation were fruitless. The observed regioselectivity leading to the formation of products **2** and **3** can be explained by the destabilizing effect of oxygen in the β position of tertiary carbocation as a competing intermediate in epoxide cleavage.

An alternative diastereoselective synthesis of rumphellatin C (**3**) was developed by the transformation of keto alcohol **9** into ketal **21** (Scheme 6). Interestingly, the previously applied conditions for ketalization of isokobusone **8** (NaH and MeI) led to only a moderate yield of target ketal **21**, whereas

Scheme 5. Synthesis of Rumphellatins B (2) and C (3) with Their Corresponding ORTEP Images as Monohydrates with 50% Contour Probability



Scheme 6. Diastereoselective Synthesis of Rumphellatin C (3)



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pyridinium *p*-toluenesulfonate (PPTS)-catalyzed ketalization provided the desired compound **21** in 85% yield. Subsequent diastereoselective epoxidation gave epoxide **22**. We propose that diastereoselective epoxidation of olefin **21** to epoxide **22** is due to the hydrogen bond formation between bridging oxygen and *meta*-chloroperoxybenzoic acid (*m*CPBA), which directs the epoxidation from the side of the cyclic ether (see Scheme S4 of the Supporting Information). Treatment of epoxide **22** with HCl yielded chlorohydrin **23**, which in comparison to epoxyalcohols **19** and **20** displayed a considerably better reaction profile, producing desired product **23** in a much higher yield. The cleavage of ketal using aqueous TFA furnished rumphellatin C (**3**), whose spectral data fully corresponded to the natural analogue (Scheme 6).

The synthesis and X-ray structure of rumphellatin C (**3**) enabled revision of the proposed structure[2] of this natural product (**3a**; Figure 1), not only proving an inverted configuration of the tetrahydrofuran fragment but also a tertiary alcohol moiety. Noteworthy that the sign of specific optical rotation of all synthesized norsesquiterpenoids **1**−**3** and **19** is the same compared to the corresponding natural isolates (see Table S1 of the Supporting Information), thus confirming their absolute configuration.

The semisyntheses and structure revisions of rumphellatins A−C (**1**−**3**) allow for the proposal of a unified biosynthetic pathway toward these natural products starting from kobusone (see Scheme S5 of the Supporting Information), whose occurrence was proven in *R. antipathies*.[19] It is possible that incorporation of chlorine, furnishing all target compounds **1**−**3**, is mediated by halohydrin dehydrogenases, which can facilitate transformation from epoxides to corresponding halohydrins.[20]

In conclusion, we report the first semisynthetic route toward chlorinated norsesquiterpenoids rumphellatins A−C from (−)-*β*-caryophyllene oxide. This approach successfully enabled the formation of the 12-oxatricyclo[7.2.1.$0^{2,5}$]dodecane scaffold, which was unattainable during a previous attempt using a total synthesis approach. Moreover, multiple stereocenters of rumphellatins A and C were proven to be inverted, whereas the structures of rumphellatin B and rumphellolide C were fully confirmed. This revision revealed a biogenetic linkage between natural products kobusone, rumphellolide C (**19**), and rumphellatins A−C (**1**−**3**). The access to rumphellatin A−C (**1**−**3**) provides material for further biological activity studies of these exotic norsesquiterpenoids as well as provides tools for chemical profiling of marine organisms.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02942.

Description of initial synthetic strategies toward rumphellatin A, proposed explanations for observed stereoselectivities, proposed biosynthetic route toward rumphellatins A−C, synthetic procedures and characterization of isolated compounds, NMR spectroscopic assignments of all protons and carbons with their nuclear Overhauser effect spectroscopy (NOESY) and heteronuclear multiple bond correlation (HMBC) interactions for compounds **1**−**3** and **19**, comparison of NMR shifts and specific optical rotations between isolated and synthetic compounds **1**−**3** and **19**, copies of infrared (IR) and NMR spectra of isolated compounds, X-ray crystallography data for compounds **1s**, **6s**, **1**−**3**, **13**, **16**, and **18**−**21** (PDF)

Accession Codes

CCDC 2374589−2374590, 2374593−2374596, 2374618−2374620, 2374855, and 2374857 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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