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First asymmetric synthesis of achaetolide

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ABSTRACT

The first asymmetric synthesis of the 10-membered macrolide achaetolide is reported in this article. The main highlight of the synthetic strategy is the ring-closing metathesis (RCM) of intermediate **19**, which in turn can be accessed from coupling between alcohol **11** and acid **18**. The synthesis of **11** involves enzymatic kinetic resolution (EKR) coupled with a Mitsunobu inversion strategy, while **18** can be prepared by adopting a metal-enzyme combined dynamic kinetic resolution (DKR) reaction followed by functional group manipulation.

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1. Introduction

Naturally occurring 10-membered ring lactones from fungal metabolites present a wide variety of bioactive substances. Examples of 10-membered ring-containing macrolides that display potent biological activity include aspinolide B,[1] pinolidoxin,[2] decarestrictines A–D,[3–6] herbarumins I–II,[7] and stagonolides A–I.[8,9] Since some of these exhibit potent biological activities (cholesterol biosynthesis inhibition activity, antimicrofilament activity and phytotoxicity, etc), this class of lactone has received special attention from the synthetic organic chemist in recent years. Achaetolide, a hydroxylated small ring macrolide, as reported by Bodo et al.[10] in 1983, was isolated from a fermentation broth of *Ophiobolus* sp. The absolute configuration (3*S*,6*R*,7*S*,9*R*) of achaetolide was further established by Cabellero et al.[11] in 2009 by a combination of extensive NMR analysis and GC methods. All the noneolides mentioned above possess interesting structural features, as they are compact and contain a properly placed olefinic moiety with well-defined geometry; the presence of stereochemically pure hydroxy appendages make them a very good synthetic target. Recently we have focused our attention on the asymmetric total synthesis of such small ring macrolides by adopting a chemoenzymatic strategy.[12,13] Herein we report the total synthesis of such a noneolide achaetolide. Retrosynthetic analysis of the target molecule achaetolide is shown in Scheme 1. The internal double bond between C_4–C_5 was thought to be a crucial disconnection as it can be reconnected through an RCM reaction. The crucial ester linkage between C_1–C_9 was planned to be constructed by an esterification reaction of an appropriately substituted acid and alcohol. The required acid and the alcohol are constructed from the more easily available starting materials. Two of the stereocenters in the parent molecule for example, C_3 and C_9 are thought to be constructed by applying a metal-enzyme combined DKR strategy and EKR/Mitsunobu inversion reaction, while the two hydroxy stereocenters C_6 and C_7 are assembled through an asymmetric dihydroxylation reaction.

2. Results and discussion

2.1. Synthesis of (*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-nonan-2-ol 11

The synthesis starts from *n*-octanal, which upon addition with a Grignard reagent generated from allyl bromide and Mg metal afforded alcohol **2** in 86% yield. Enzymatic kinetic resolution of **2** was attempted by using CAL-B (novozyme-435) and vinyl acetate as the acyl donor which yielded alcohol **3** (ee = 96%, slow reacting enantiomer) and acetate **4** (ee = 98%, with c = 49.4% and E = 422) according to Kazlauskas empirical rule.[14] Acetate **4** was hydrolyzed with K_2CO_3 in methanol and the alcohol was inverted by applying a Mitsunobu inversion strategy to give alcohol **3** (overall yield 82% after three steps). The free hydroxy group in alcohol **3** was protected as its TBDPS (*tert*-butyldiphenyl silyl) ether by treatment with imidazole and TBDPS-Cl to afford compound **5** in 89% yield. Dihydroxylation of the terminal olefinic double bond in **5** with OsO_4 afforded the diol; oxidative cleavage of the diol with $NaIO_4$ produced the aldehyde **6** in 80% yield. The *cis*-selective HWE olefination of aldehyde **6** using an Ando method[15] yielded *Z*-ester **7** in 88% yield (*Z*:*E* = 15:1). Dihydroxylation of ester **7** with AD Mix-α[16] produced the required diol **8** in 78% yield. Diol **8** was protected as its acetonide by treatment with 2,2-DMP[17] (2,2-dimethoxy propane) in the presence of a catalytic amount of CSA (camphore sulfonic acid) to afford **9** in 92% yield. Selective reduction of the ester functionality with DIBAL-H followed by Wittig olefination with methyltriphenylphosphonium iodide in the presence of LHMDS produced olefin **10** in 82% overall yield over two steps. Deprotection of the TBDPS group in **10** was achieved by treatment

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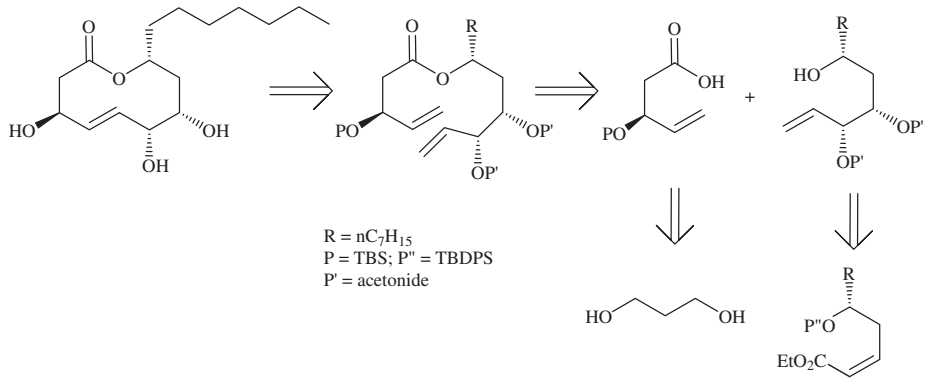


Scheme 1. Retrosynthetic analysis of achaetolide.

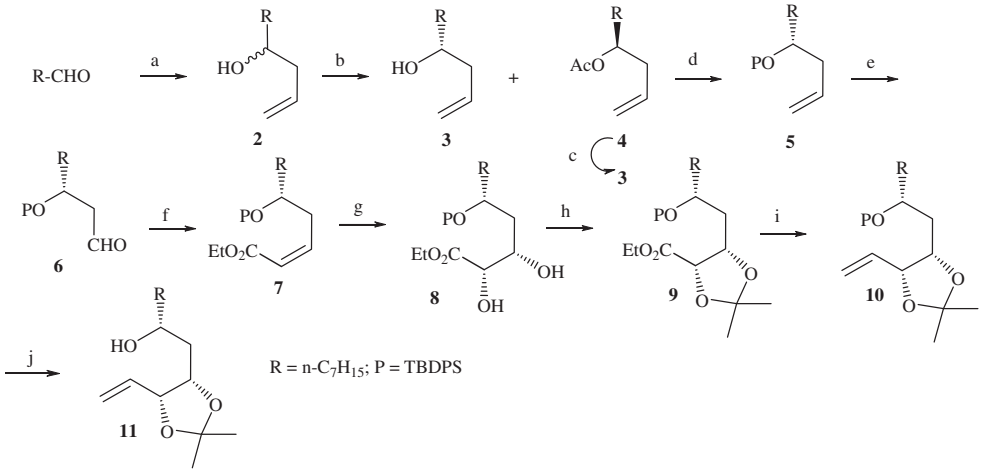
with TBAF in tetrahydrofuran (THF) to afford compound **11** in 88% yield (Scheme 2).[18]

2.2. The synthesis of (*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-enoic acid 18

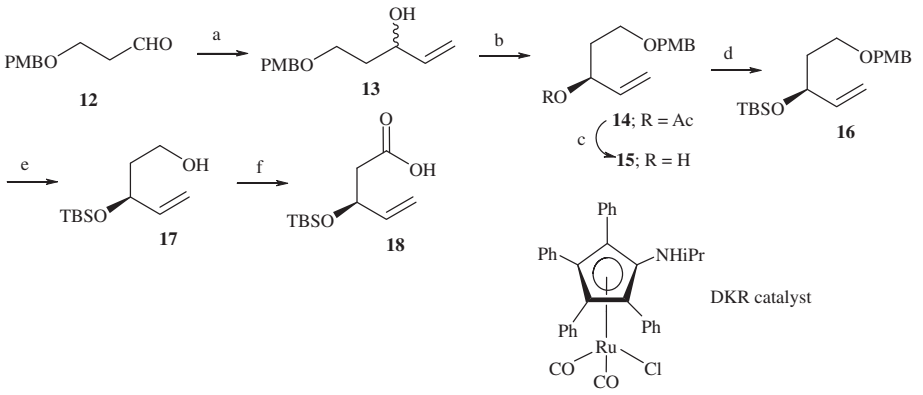
For the synthesis of the required acid fragment, we started from the known aldehyde 3-(4-methoxy-benzyloxy)-propionaldehyde. Upon addition of vinylmagnesium bromide at −78 °C, racemic alcohol **13** was produced in 86% yield. The DKR of the secondary alcohol functionality in compound **13** was achieved by coupling the enzyme-catalyzed transesterification reaction with a metal-catalyzed (ruthenium based catalyst shown in Scheme 3) racemization method, as reported by Kim et al.[19] Isopropenyl acetate was used as the acyl donor in the DKR reaction. The DKR reaction is highly efficient for compound **13** as it yields the corresponding acetate **14** in 92% yield with excellent enantioselection (ee = 98%).[20] The acetate functionality was removed by treatment with K_2CO_3 in MeOH to yield enantiomerically pure **15** in 94% yield. The free secondary hydroxy group in compound **15** was protected as its TBS (*tert*-butyldimethyl silyl) ether by treatment with TBS-Cl and imidazole to produce compound **16** in 88% yield. Removal of the PMB group was achieved with DDQ[21] to afford compound **17** in 82% yield. The primary hydroxy group in **17** was transformed to its corresponding carboxylic acid by treatment with PDC in DMF to afford **18** in 78% yield. At first, compound **17** was oxidized to the corresponding aldehyde by Swern oxidation,[22] followed by oxidation under Pinnic condition[23] to give acid **18** in 78% yield (overall in two steps, Scheme 3).

2.3. Coupling of fragments 11 and 18 for the total synthesis of achaetolide

After the successful construction of both the required fragments **11** and **18**, the remaining step was to couple the two fragments followed by RCM strategy. The coupling of the two fragments was successfully achieved by treating acid **18** with EDCI·HCl/DMAP followed by the addition of alcohol **11** to afford the coupled ester **19** in 85% yield. The final RCM reaction seems to be crucial and problematic. After numerous conditions were attempted with Grubbs-I and Grubbs-II[22] catalyst in different solvents such as DCM, benzene and toluene, the final outcome was same in all the cases; either inseparable mixtures of various compounds were obtained or the starting material had decomposed during the course of the reaction. We envisioned that this may be due to the presence of a TBS group at one end and an acetonide functionality at another end in **19**, which causes some steric crowding, hence the two terminal vinyl groups cannot be in proximity to have an efficient complexation with the metal catalyst, which is a prerequisite in the RCM reaction; similar precedences have been reported before.[23] Finally deprotection of the TBS and acetonide functionality was achieved by treating compound **19** with pyridinum *para* toluene sulfonate (PPTS)[24] in methanol to afford triol **24** in 85% yield. Compound **24**, upon treatment with Grubbs second generation catalyst



Scheme 2. Reagents and conditions: (a) CH_2=$CHCH_2MgBr$, THF, rt, 86%; (b) CAL-B, CH_2=CHOAc, DIPE (iPr_2O), MS 4 Å; (c) K_2CO_3/MeOH, DIAD, TPP, $PhCO_2H$, NaOH, 82%; (d) imidazole, TBDPS-Cl, 89%; (e) OsO_4, NMO, THF/H_2O (1:1), $NaIO_4$, THF/H_2O (1:1), 80%; (f) $(PhO)_2POCH_2CO_2Et$, NaH, 0 °C, 88%; (g) AD Mix-α, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 78%; (h) 2,2-DMP, CSA, 92%; (i) DIBAL-H (1 equiv), DCM, −78 °C, $Ph_3P^+MeI^-$, LHMDS, THF, 0 °C, 82%; (j) TBAF, THF, 88%.



Scheme 3. Reagents and conditions: (a) CH_2=CHMgBr, THF, −78 °C, 86%; (b) CAL-B, isopropenylacetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II), K_2CO_3, KO*t*Bu 92%; (c) K_2CO_3, MeOH, 94%; (d) imidazole, TBS-Cl, 88%; (e) DDQ, DCM/H_2O (19:1), 82%; (f) PDC, DMF, 78%.

afforded the target molecule achaetolide (Scheme 4; overall yield = 11% from *n*-octanal).

3. Conclusion

In conclusion we have described an efficient asymmetric synthesis of the polyhydroxylated small ring macrolide achaetolide for the first time. Two of the stereocenters (C_3 and C_9) in the target molecule have been fixed by a metal-enzyme combined DKR and EKR strategy, whereas the other two hydroxy stereocenters (C_6 and C_7) have been created by asymmetric dihydroxylation reaction. The RCM reaction has been successfully applied to create the 10-membered macrolide ring in an efficient way.

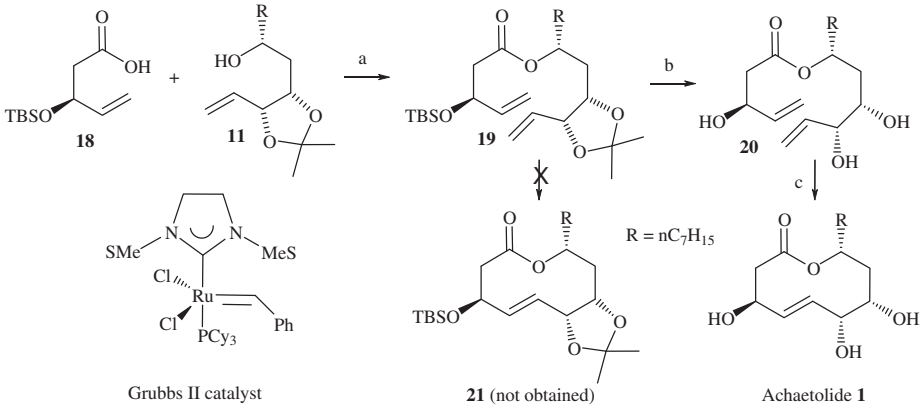
4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodiumbenzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Diisopropylether (DIPE) was refluxed over P_2O_5 and distilled prior to use. Vinyl acetate and isopropenyl acetate were freshly distilled prior to use. CAL-B (*Candida antartica* lipase-B, Novozym-435, immobilized on acrylic resin) was obtained from Sigma and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 400 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as an internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Elemental analysis was performed by using Perkin Elmer model: 2400, series II CHN analyzer. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Chiral HPLC was performed using Chiral OD-H column (0.46 × 25 cm, Daicel industries) with Shimadzu Prominence LC-20AT chromatograph coupled with a UV–vis detector (254 nm). The eluting solvent used involved different ratios of hexane and 2-propanol.

4.2. Undec-1-en-4-ol 2

Magnesium turnings (3.3 g) were charged with iodine and anhydrous ethyl ether (30 mL) placed under argon in a dry, three-necked flask equipped with a mechanical stirrer. Then allyl bromide (4 mL, 46.2 mmol) in 10 mL of anhydrous ether was added and stirred for few minutes until the effervescence ceased. Then *n*-octanal (4 g, 31 mmol) was added and stirred for 1.5 h after which the reaction mixture was cooled in a water-ice bath, and a saturated aqueous ammonium chloride solution was added. The combined organic layer was extracted with ethyl acetate and brine and dried over $MgSO_4$. Purification by silica gel chromatography



Scheme 4. Reagents and conditions: (a) EDCI·HCl, DMAP, 85%; (b) PPTS, MeOH, 85%; (c) Grubbs-II (10 mol %), DCM, 62%.

(3:1, hexane/EtOAc) afforded alcohol **2** in 86% yield. δ_H: 5.88–5.67 (m, 1H), 5.11–5.03 (m, 2H), 3.56 (m, 1H), 2.28–2.11 (m, 2H), 1.39–1.13 (m, 12H), 0.82 (t, J = 6.8 Hz, 3H). δ_C: 134.9, 117.9, 70.6, 41.9, 36.7, 31.8, 29.6, 29.2, 25.6, 22.6, 14.0. Elemental Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.56; H, 13.09.

4.3. (*R*)-Undec-1-en-4-ol 3 and acetic acid (*S*)-1-allyl-octyl ester 4

In a typical resolution experiment, a solution of compound **2** (4.2 g, 24.8 mmol) in anhydrous diisopropyl ether (75 ml) was stirred with vinyl acetate (1 equiv, 1.7 mL) and powdered molecular sieves (25 mg, 4 Å) followed by the addition of CAL-B (1 g). The reaction mixture was stirred in an orbit shaker (250 rpm) at room temperature for 1 h. After 50% conversion (by TLC analysis), the reaction mixture was filtered through a pad of Celite and evaporated to dryness. The alcohol and the acetate were isolated by column chromatography. Acetate **4** was deprotected and converted to the desired alcohol **3** by Mitsunobu inversion. Compound **4**; δ_H: 5.71–5.63 (m, 1H), 5.03–4.97 (m, 2H), 4.86 (m, 1H), 2.25 (t, J = 6.6 Hz, 2H), 1.98 (s, 3H), 1.49 (m, 2H), 1.21 (m, 10H), 0.83 (t, J = 6.6 Hz, 3H). Compound **4**; δ_C: 170.6, 133.8, 117.4, 73.2, 38.6, 33.3, 31.7, 29.4, 29.1, 25.3, 22.6, 21.1, 14.0.

4.4. ((*R*)-1-Allyl-octyloxy)-*tert*-butyl-diphenyl-silane 5

The desired alcohol **3** (3.8 g, 22.3 mmol) was taken in anhydrous DCM (50 mL) and cooled to 0 °C. Imidazole (3 g) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBDPS-Cl (7 mL, 26.76 mmol). The reaction mixture was allowed to warm at room temperature for 6 h, after which water was added to it and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation and purification yielded the mono TBDPS-protected alcohol in 89% yield. δ_H: 7.78 (m, 4H), 7.46 (m, 6H), 5.90–5.73 (m, 1H), 5.05–4.96 (m, 2H), 3.82 (m, 1H), 2.29 (m, 2H), 1.50 (m, 2H), 1.25 (m, 10H), 1.15 (m, 9H), 0.95 (t, J = 7.2 Hz, 3H). δ_C: 136.0, 135.1, 134.7, 129.5, 127.5, 116.7, 72.9, 41.1, 36.1, 31.9, 29.6, 29.3, 27.2, 24.9, 22.7, 19.5, 14.2. $[\alpha]_D^{29} = -0.9$ (c 1.5 MeOH).

4.5. (*R*)-3-(*tert*-Butyl-diphenyl-silanyloxy)-decanal 6

The TBDPS-protected alcohol **5** (7.2 g, 17.84 mmol) was taken in THF/H_2O (3:1) and OsO_4 (0.05 M, 7 mL) and NMO (3.1 g) was added at room temperature and stirred for 12 h, after which a saturated solution of $NaHSO_3$ was added and the solution stirred for a further 1 h. The organic layer was extracted with ethyl acetate and evaporated to dryness to afford the diol. The crude diol was taken in 30 mL of tetrahydrofuran and 20 mL of water, followed by the addition of sodium periodate (4.8 g, 22.5 mmol). The mixture was stirred for 1 h and followed by TLC to ascertain cleavage of the glycol. Ether (50 mL) and water (25 mL) were added, and the customary workup afforded aldehyde **6** (4.3 g). δ_H: 9.72 (t, J = 2.4 Hz, 1H), 7.68 (m, 4H), 7.41 (m, 6H), 4.20 (m, 2H), 2.49 (m, 2H), 1.48 (m, 2H), 1.26–1.12 (m, 10H), 1.05 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H). δ_C: 202.5, 136.0, 134.1, 129.9, 127.8, 69.5, 50.4, 37.5, 31.8, 29.4, 29.2, 27.1, 25.0, 22.7, 19.4, 14.2. $[\alpha]_D^{29} = -12.5$ (c 1.2 MeOH).

4.6. (*Z*)-(*R*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-dodec-2-enoicacid ethyl ester 7

To a solution of ethyl (diphenylphosphono)acetate (3.4 g, 10.7 mmol) in THF (40 mL) was added NaH (60%, 513 mg, 12.84 mmol) at 0 °C; after 15 min, aldehyde **5** (4.3 g, 10.7 mmol) in THF (10 mL) was added, and the resulting mixture was gradually warmed to the room temperature over 1.2 h after which water was added, extracted with ethyl acetate and brine, dried over $MgSO_4$ to yield *Z*:*E* isomer (15:1), which was further purified by flash chromatography to afford pure **7** in 88% yield. δ_H: 7.67 (m, 4H), 7.38 (m, 6H), 6.35 (m, 1H), 5.78 (d, J = 11.6 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.84 (m, 2H), 2.89–2.75 (m, 2H), 1.557–1.38 (m, 2H), 1.29 (t, J = 7.0 hz, 3H), 1.22 (m, 10H), 1.10 (s, 9H), 0.87 (t, J = 6.2 Hz, 3H). δ_C: 166.4, 146.7, 135.9, 134.4, 129.6, 127.5, 120.9, 72.5, 59.7, 36.8, 35.7, 31.8, 29.5, 29.2, 27.1, 25.0, 22.7, 19.4, 14.3, 14.1. $[\alpha]_D^{29} = +7.7$ (c 1.0 MeOH).

4.7. (2*S*,3*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-2,3-dihydroxy-dodecanoic acid ethyl ester 8

At first, *t*-BuOH (29 mL), H_2O (29 mL) and AD-mix-α (11.6 g) were mixed and the mixture was stirred for 15 min. Methanesulfonamide (1.1 g) was then added and stirring was continued for a further 15 min. Compound **7** (3.58 g, 8.02 mmol) was then added in one portion. The slurry was stirred vigorously at 20 °C for 24 h. After that time, sodium sulfite (15 g) was added and stirring was continued for a further 1 h. The reaction mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The diol was purified by flash chromatography (3:1; hexane–EtOAc) to afford diol **8** in 78% yield. δ_H: 7.70 (m, 4H), 7.41 (m, 6H), 4.30–3.99 (m, 5H), 1.96–1.25 (m, 17H), 1.06 (s, 9H), 0.87 (t, J = 6.2 Hz, 3H). δ_C: 172.5, 135.9, 133.9, 129.8, 127.7, 74.3, 72.6, 70.1, 61.7, 36.0, 35.7, 31.7, 29.2, 29.0, 27.0, 25.1, 22.6, 19.3, 14.2, 14.1. $[\alpha]_D^{29} = -5.5$ (c 1.75 MeOH).

4.8. (4*S*,5*S*)-5-[(*R*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-nonyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester 9

Compound **8** (4 mmol) was taken in 20 mL of dry DCM. 2,2-Dimethoxypropane (DMP, 1.5 mL, 12 mmol) was then added followed by the addition of a catalytic amount of CSA (0.45 mmol, 122 mg). The reaction mixture was stirred at rt overnight. The product was purified by column chromatography (10:1; hexane–EtOAc) to afford compound **9** in 92% yield. δ_H: 7.67 (m, 4H), 7.36 (m, 6H), 4.62–3.89 (m, 5H), 1.84–1.18 (m, 17H), 1.7 (s, 3H), 1.5 (s, 3H), 1.05 (s, 9H), 0.87 (t, J = 6.4 Hz, 3H). δ_C: 170.6, 135.9, 134.5, 129.5, 127.4, 110.5, 76.4, 74.5, 70.8, 60.9, 37.7, 37.2, 36.6, 31.7, 29.1, 27.1, 26.8, 25.6, 24.6, 22.6, 19.5, 14.3, 14.1. $[\alpha]_D^{29} = -6.1$ (c 0.33 MeOH).

4.9. *tert*-Butyl-[(*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-ylmethyl)-octyloxy]-diphenyl-silane 10

Compound **8** (1.2 g, 2.8 mmol) was taken in dry toluene (10 mL) and cooled to −78 °C. A solution of DIBAL-H (1 M in toluene, 2.8 mL) was added over 30 min. The reaction was stirred for a further 2 h at the same temperature then warmed to −20 °C and quenched with dry methanol and stirred for a further 1.5 h, then extracted with ethyl acetate, brine and dried over $MgSO_4$. The organic extract was evaporated to dryness to afford the crude aldehyde. With this crude aldehyde, a one carbon extension via a Wittig reaction was performed using LHMDS as a base. To a suspension of methyltriphenylphosphonium iodide (1.7 g, 4.2 mmol) in dry ether was added LHMDS (5 mmol) in two portions. The bright yellow mixture was heated at reflux for 1 h. The yellow mixture was allowed to cool to room temperature. A solution of **9** (1.0 g, 2.8 mmol) in 5 mL of Et_2O was added to the reaction mixture. The yellow suspension was stirred at room temperature for a further 1 h. After completion of the reaction, as indicated by TLC, the reaction was quenched with water and the layers were separated and extracted with 20 mL of ether, dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography to afford the compound **10** (1:40 EtOAc/hexane) in 82% yield. δ_H: 7.68 (m, 4H), 7.35 (m, 6H), 5.78–5.62 (m, 1H), 5.26–4.95 (m, 2H),

4.38 (m, 2H), 3.99 (m, 1H), 1.58 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.29 (m, 12H), 1.1 (s, 9H), 0.85 (t, J = 6.4 Hz, 3H). δ_C: 135.9, 134.9, 134.5, 129.4, 127.9, 117.9, 108.0, 79.8, 74.8, 71.0, 37.7, 31.9, 29.7, 29.5, 29.1, 28.2, 27.1, 25.5, 24.4, 22.6, 19.5, 14.1. $[\alpha]_D^{29} = -7.8$ (c 0.5 MeOH).

4.10. (*R*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-nonan-2-ol 11

Compound **10** (768 mg, 1.96 mmol) was taken in dry THF (10 mL). Next, TBAF (1 M in THF, 2 mL) was added, and the reaction mixture was stirred for 3 h at room temperature. After that time, the THF was evaporated, and water (4 ml) was added to it; the reaction mixture was extracted with EtOAc (50 mL), and the organic layer was washed with $NaHCO_3$ and brine, and dried (Na_2SO_4), after which it was purified by flash chromatography (5:1; hexane–EtOAc) to afford compound **10** in 88% yield. δ_H: 5.88–5.70 (m, 1H), 5.34–5.20 (m, 2H), 4.58–4.41 (m, 2H), 3.83 (m, 1H), 1.57 (s, 3H), 1.47 (s, 3H), 1.45–1.14 (m, 14H), 0.92 (t, J = 6.4 Hz, 3H). δ_C: 134.2, 118.9, 109.1, 80.1, 78.7, 71.6, 37.8, 37.5, 32.1, 29.9, 29.5, 28.3, 26.1, 25.8, 25.7, 22.9, 14.3. $[\alpha]_D^{29} = -3.6$ (c 1.0 MeOH). Elemental Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.12; H, 11.19.

4.11. 5-(4-Methoxy-benzyloxy)-pent-1-en-3-ol 13

Aldehyde **12** (2.4 g, 11.6 mmol) was taken in 40 mL of anhydrous THF. A solution of vinylmagnesium bromide (1 M, 17.4 mL, 17.4 mmol) was then added at −78 °C. The reaction mixture was kept at the same temperature for 1 h, after which time saturated NH_4Cl solution was added. The solution was extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane/EtOAc) afforded alcohol **13** in 86% yield. δ_H: 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.96–5.79 (m, 1H), 5.31–5.08 (m, 2H), 4.45 (s, 2H), 4.30 (m, 1H), 3.77 (s, 3H), 3.64 (m, 2H), 1.87 (m, 2H). δ_C: 159.4, 140.7, 130.1, 129.5, 114.5, 114.0, 73.1, 72.1, 68.2, 55.4, 36.4. Elemental Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.26; H, 8.23.

4.12. Acetic acid (*S*)-1-[2-(4-methoxy-benzyloxy)-ethyl]-allyl ester 14

In a 50 mL round-bottomed flask attached with a grease free high vacuum stopcock, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II) [DKR catalyst, 84 mg, 0.136 mmol] was added. The flask was successively charged with alcohol **13** (0.86 g, 3.4 mmol) in 10 mL dry toluene, Na_2CO_3 (3.4 mmol), CAL-B (25 mg) and KO*t*Bu (0.17 mmol) followed by isopropenyl acetate (5 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere. After that time the reaction mixture was filtered off and the solution was evaporated to afford the crude acetate **14**, which was subsequently purified by silica gel chromatography (10:1, hexane/EtOAc) to give the pure acetate **14** in 92% yield. δ_H: 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.83–5.66 (m, 1H), 5.39 (m, 1H), 5.32–5.09 (m, 2H), 4.38 (s, 2H), 3.76 (s, 3H), 3.43 (t, J = 6.4 Hz, 2H), 2.0 (s, 3H), 1.85 (m, 2H). δ_C: 170.2, 159.1, 136.3, 130.3, 129.3, 116.6, 113.7, 72.6, 72.1, 65.8, 55.2, 34.3, 21.1. $[\alpha]_D^{29} = +8.65$ (c 1.0 MeOH). Elemental Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.22; H, 7.69.

4.13. *tert*-Butyl-{(*S*)-1-[2-(4-methoxy-benzyloxy)-ethyl]-allyloxy}-dimethyl-silane 16

The desired alcohol **15** (1.5 g, 6 mmol) was taken in anhydrous DCM (30 mL) and cooled to 0 °C. Imidazole (820 mg) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBDMS-Cl (1.4 g, 9 mmol). The reaction mixture was allowed to warm at room temperature for 6 h, after which water was added and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation and purification yielded the TBDMS-protected alcohol **16** in 88% yield. δ_H: 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.90–5.73 (m, 1H), 5.29–5.0 (m, 2H), 4.41 (m, 2), 4.28 (m, 1H), 3.80 (s, 3H), 3.54 (m, 2H), 1.79 (m, 2H), 0.9 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). δ_C: 159.1, 141.6, 130.7, 129.3, 113.7, 72.7, 70.8, 66.4, 55.3, 38.2, 25.3, 18.2, −4.3, −4.9. $[\alpha]_D^{29} = -3.5$ (c 0.75 MeOH).

4.14. (*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-en-1-ol 17

Compound **16** (1.7 g, 4.8 mmol) was taken in 30 mL of DCM/H_2O (19:1). Next, DDQ (1.6 g, 7.2 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane/EtOAc) afforded the pure compound **17** in 82% yield. δ_H: 5.91–5.74 (m, 1H), 5.24–5.01 (m, 2H), 4.40 (s, 1H), 3.78 (m, 2H), 1.81 (m, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). δ_C: 140.6, 114.3, 73.0, 39.2, 25.8, 18.1, -4.4, -5.0. $[\alpha]_D^{29} = -5.65$ (c 0.5 MeOH).

4.15. (*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-enoic acid 18

Compound **17** (588 mg, 2.4 mmol) was taken in anhydrous DMF (8 mL). Next, pyridinium dichromate (PDC, 3.2 g, 8.5 mmol) was added to the reaction mixture and the reaction mixture was stirred at room temperature until all the starting material had been consumed as indicated by TLC. Water was added to the reaction mixture, and the water layer was extracted three times with EtOAc followed by washing with an aq $KHSO_4$ solution. The organic solvent was dried ($MgSO_4$) and evaporated. The crude acid was purified by silica gel chromatography (1:1, hexane/EtOAc) to afford pure **18** in 78% yield. δ_H: 5.93–5.77 (m, 1H), 5.30–5.10 (m, 2H), 4.59 (m, 1H), 2.56 (d, J = 6.2 Hz, 2H), 0.88 (s, 9H), 0.08 (s, 6H). δ_C: 174.7, 139.3, 115.4, 70.6, 42.8, 25.7, 18.0, −4.4, −5.1. $[\alpha]_D^{29} = -4.95$ (c 2.0 MeOH).

4.16. (*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-enoic acid (*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-ylmethyl)-octyl ester 19

Carboxylic acid **18** (90 mg, 0.42 mmol) was taken in dry DCM (4 mL). Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (EDCI·HCl, 81 mg, 0.42 mmol), DMAP (cat amount) and (*R*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-nonan-2-ol **11** (75 mg, 0.28 mmol) was sequentially added to the reaction mixture. The reaction mixture was kept at room temperature for 3 h. The ester was purified by flash chromatography to afford **19** in 85% yield. δ_H: 5.97–5.77 (m, 2H), 5.38–5.21 (m, 3H), 5.09 (m, 2H), 4.63 (m, 2H), 4.25 (m, 1H), 2.53 (m, 2H), 1.77–11.63 (m, 4H), 1.58 (s, 3H), 1.49 (s, 3H), 1.37 (m, 10H), 0.91 (br, 12H), 0.1 (s, 3H), 0.08 (s, 3H). δ_C: 170.4, 140.3, 134.2, 118.4, 114.6, 108.3, 79.5, 74.9, 72.3, 70.6, 43.7, 35.2, 34.8, 31.8, 29.6, 29.4, 29.1, 28.2, 25.8, 25.7, 25.0, 22.6, 18.1, 14.1, -4.4, -4.9. $[\alpha]_D^{29} = -6.1$ (c 0.33 MeOH).

4.17. (*S*)-3-Hydroxy-pent-4-enoic acid (*R*)-1-((2*S*,3*R*)-2,3-dihydroxy-pent-4-enyl)-octyl ester 20

Coupled ester **19** (70 mg, 0.15 mmol) was taken in methanol (4 mL) after which pyridinium *para*-toluenesulfonate (PPTS, 9 mg, 0.045 mmol) was added. The solution was kept stirring overnight at the same temperature, after which it was purified through silica

gel chromatography to afford the triol **20** in 85% yield. δ_H: 5.95–5.77 (m, 2H), 5.34–5.06 (m, 5H), 4.56 (m, 1H), 4.05 (m, 1H), 3.65 (m, 1H), 3.17 (br, 3H, –OH), 2.52 (m, 2H), 1.63–1.52 (m, 4H), 1.23 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H). δ_C: 172.9, 138.9, 136.0, 117.3, 115.4, 75.8, 72.3, 69.9, 69.2, 41.8, 36.5, 34.8, 31.7, 29.3, 29.1, 25.4, 22.6, 14.1. $[\alpha]_D^{29} = -16.3$ (c 0.5, MeOH). Elemental Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.92; H, 9.86.

4.18. (*E*)-(4*S*,7*R*,8*S*,10*R*)-10-Heptyl-4,7,8-trihydroxy-3,4,7,8,9,10-hexahydro-oxecin-2-one (achaetolide)

Compound **20** (25 mg, 0.077 mmol) was taken in anhydrous degassed DCM (80 mL). Grubbs second generation metathesis catalyst (7 mg, 0.008 mmol) was then added and the solution was refluxed for 8 h. The solution was evaporated and the content of the flask was directly loaded onto a silica gel column. Flash chromatography with hexane: EtOAc (1:3) afforded the pure achaetolide in 62% yield. IR (film) ν_{max} = 3452 (O–H), 3256 (O–H), 1710 (O–C=O) cm^{-1}. δ_H: 5.92 (dd, J = 15.2, 8.4 Hz, 1H), 5.39 (d, J = 15.2 Hz, 1H), 4.73 (m, 1H), 4.53 (m, 2H), 3.72 (m, 1H), 2.75 (m, 1H), 2.42 (m, 1H), 2.35 (m, 1H), 1.53–1.25 (m, 13H), 0.87 (t, J = 6.4 Hz, 3H). δ_C: 171.0, 130.8, 135.2, 75.4, 73.3, 73.3, 67.2, 43.8, 36.9, 36.8, 31.7, 29.4, 29.1, 25.0, 22.6, 14.0. $[\alpha]_D^{29} = -27.8$ (c 0.5 MeOH); Literature value, $[\alpha]_D^{23} = -27$ (c 0.52 MeOH).[11] Elemental Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 63.92; H. 9.36.

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