Stereoselective Concise Total Synthesis of Leodomycin C and D

B. Chinnababu, S. Purushotham Reddy, D. Kumar Reddy, D. Chandra Rao, Y. Venkateswarlu*

Organic Chemistry Division-I, Natural Products Laboratory, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
Fax +91(40)27160512; E-mail: luchem@iict.res.in

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Abstract: Stereoselective concise total synthesis of leodomycin C and D from commercially available propylene oxide using Jacobsen's hydrolytic kinetic resolution (HKR), base-promoted alkyne zipper reaction, TPP-promoted enyne ester (ynoate) to diene ester (dienoate) isomerization, and (*R*)-(+)-2-methyl-CBS-oxazaborolidine reduction as key steps is reported.

Key words: *Bacillus sp*, leodomycin C and D, antimicrobial activity, hydrolytic kinetic resolution, HKR, alkyne zipper reaction, (*R*)-(+)-2-methyl-CBS-oxazaborolidine

Marine fungi are attractive sources for anticancer, antifungal, and antibacterial secondary metabolites.[1] Marine *Bacillus* species, ubiquitous and diverse in marine ecosystems, are well known for producing antimicrobial and anticancer compounds, bio-surfactants, and so on.[2] Marine bacteria isolated from the sediments and the surface of marine algae and invertebrates have been shown to produce secondary metabolites that display antibacterial properties.[3] Recently, four antimicrobial compounds **1**–**4** (Figure 1) were isolated from marine bacterial strain *Bacillus sp*.[4] These compounds exhibited interesting antimicrobial activity against *Bacillus subtilis* and *Escherichia coli* with minimum inhibitory concentrations (MICs) of 32–64 μg/mL.[4a] Recently, the stereoselective synthesis of pharmaceutically active natural products have become significant[4b,c] and to the best of our knowledge, there is no report in the literature on the synthesis of these compounds. Our continued interest towards the total synthesis of biologically active natural products prompted us to undertake the synthesis of demanding targets compounds **1** and **2** from commercially available propylene oxide using Jacobsen's hydrolytic kinetic resolution (HKR), base-promoted alkyne zipper reaction, TPP-promoted enyne ester (ynoate) to diene ester (dienoate) isomerization, and (*R*)-(+)-2-methyl-CBS-oxazaborolidine reduction.[5]

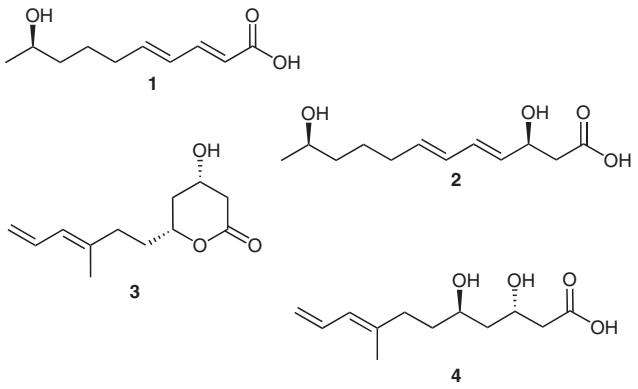
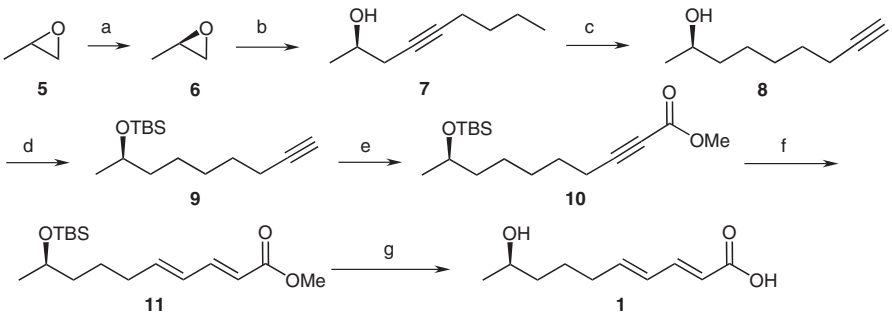


Figure 1 Leodomycin C (**1**), leodomycin D (**2**), leodomycin B (**3**), leodomycin A (**4**)

The synthesis commenced with propylene oxide (**5**) (Scheme 1), which was subjected to Jacobsen's hydrolytic kinetic resolution (HKR) using (*R*,*R*)-salen-Co-(OAc) catalyst to afford (*R*)-propylene oxide (**6**).[6] Compound **6** was reacted with the lithiated hex-1-yne to afford alkynol **7** in 89% yield. The alkynol **7** was subjected to base-mediated alkyne zipper reaction[7] using sodium 3-aminopropylamide in which alkyne functionality moves from the center to the terminus of a chain to give the alkyne **8** in 80% yield. The secondary hydroxy group in compound **8** was protected as *tert*-butyldimethylsilyl ether **9** using



Scheme 1 *Reagents and conditions*: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), 0 °C, 14 h, 46%; (b) hex-1-yne, *n*-BuLi, HMPA, –40 to 0 to –20 °C, 16 h; (c) NaH, 1,3-diaminopropane, 60 °C to r.t., 8 h; (d) TBDMSCl, imidazole, CH_2Cl_2, r.t., 3 h; (e) methyl chloroformate, *n*-BuLi, THF, –78 °C, 1 h; (f) TPP, phenol, benzene, 50 °C, 6 h; (g) KOH, EtOH–H_2O (4:1), 60 °C, 6 h, 6 M HCl.

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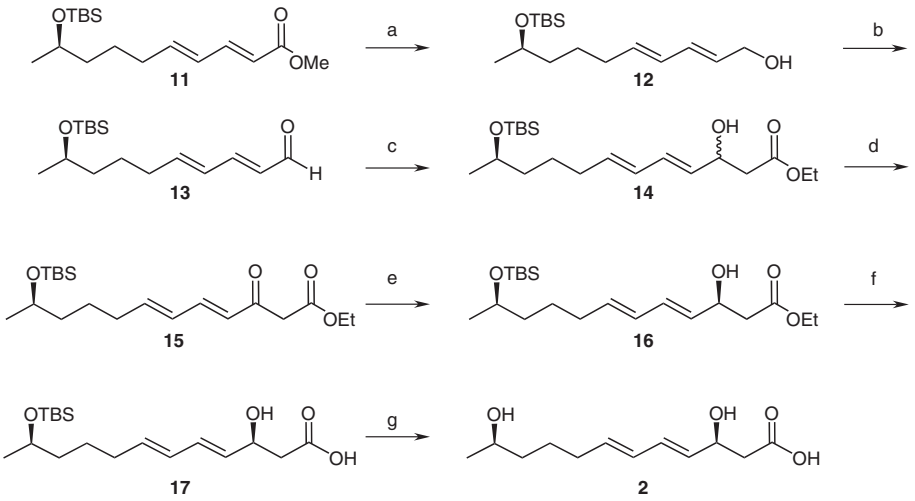

Scheme 2 *Reagents and conditions*: a) DIBAL-H, –78 °C, CH_2Cl_2, 2 h; b) DMP, $NaHCO_3$, CH_2Cl_2, 1.5 h; c) LiHMDS, EtOAc, THF, –78 °C to r.t., 4 h; d) DMP, $NaHCO_3$, CH_2Cl_2, 1 h; e) (*R*)-CBS catalyst, DMS·BH_3, THF, –40 °C, 1.5 h; f) LiOH, THF–H_2O (1:1), r.t., 2.5 h; g) HF·Pyridine, THF, 0 °C to r.t., 6 h.

TBDMSCl and imidazole in dichloromethane in 96% yield. The terminal alkyne group in **9** was carboxylated by reacting with methyl chloroformate in the presence of *n*-butyllithium to afford alkyne ester **10** in 92% yield. The alkyne ester **10** was converted to the diene ester **11** under Rychnovsky's modified conditions for the Trost isomerization.[8] Thus, the ynoate **10**, exposed to Ph_3P/PhOH in benzene at 50 °C for six hours led to the clean formation of diene ester **11** in 93% yield.

Finally the ester **11** was hydrolyzed using KOH/EtOH–THF (1:4) under reflux conditions for 6 hours and during acidic workup the TBS ether was deprotected to give final compound **1** in 80% yield. The physical and spectral data of synthetically prepared compound **1** (^{1}H NMR and ^{13}C NMR) are found to be in agreement with the natural product[4]{$[\alpha]_D^{25}$ +15 (*c* 0.8, $CHCl_3$) Lit.[4] $[\alpha]_D^{25}$ +14.9 (*c* 1, $CHCl_3$)}.

To synthesize leodomycin D (**2**), in a separate experiment the ester **11** was reduced with DIBAL-H in CH_2Cl_2 at –78 °C to the allylic alcohol **12** in 90% yield (Scheme 2). The allyl alcohol **12** on oxidation with Dess–Martin periodinane (DMP) afforded aldehyde **13** in 81% yield. The aldehyde **13** was subjected to C–H insertion reaction using LiHMDS and ethyl acetate to form the racemic alcohol **14** in 80% yield.[9] Dess–Martin oxidation of the secondary hydroxy group in **14** afforded the corresponding ketone **15** in 89% yield.

Selective reduction of the carbonyl group in **15** employing Corey–Bakshi–Shibata (CBS) reagent [(*R*)-(+)-2-methyl CBS-oxazaborolidine] afforded the β-chiral allylic alcohol **16** in 80% yield[10] with an excellent enantioselectivity of 87.18%de. The ester **16** was hydrolyzed with LiOH in H_2O–THF (1:1) to form acid **17** in 86% yield. Finally, the TBS ether in **17** is removed by using HF·Pyridine, to form final compound **2** in 72% yield. The physical and spectral data of synthetically prepared compound **2** (^{1}H NMR and ^{13}C NMR) were found to be in agreement with the natural product[4]{$[\alpha]_D^{25}$ +18 (*c* 0.1, $CHCl_3$), Lit.[4] $[\alpha]_D^{25}$ +17.9 (*c* 0.35, MeOH)}.

In conclusion, an efficient and straightforward total synthesis of leodomycin **C** and **D** has been achieved by using Jacobsen's hydrolytic kinetic resolution (HKR), base-promoted alkyne zipper reaction, TPP-promoted enyne ester (ynoate) to diene ester (dienoate) isomerization, and (*R*)-(+)-2-methyl-CBS-oxazaborolidine reduction reactions. The synthesis of leodomycin A and B is in progress.

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel (60–120 mesh). FTIR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer. Optical rotations were measured on Horiba high sensitive polarimeter in 10 mm cell. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini 500 and Bruker Avance 300 spectrometers. Chemical shifts were reported in parts per million (δ) with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were acquired on a Micro mass Quattro micro™ API (Waters) and high-resolution mass spectra were acquired on QSTARXL Hybrid MS/MS system (applied Biosystems US) mass spectrometers.

(*R*)-Non-4-yn-2-ol (7)

To a cooled (–40 °C) solution of hex-1-yne (7.10 mL, 62.05 mmol) in anhyd THF (40 mL) was added dropwise *n*-BuLi in hexane (1.6 M, 32.22 mL, 51.56 mmol). The reaction mixture was warmed to 0 °C over 30 min and then cooled to –20 °C. To this solution, after the addition of anhyd HMPA (15 mL), was added (*R*)-(+)-propylene oxide (2.0 g, 34.48 mmol) in HMPA (10 mL) over 15 min. The mixture was stirred at –20 °C for 30 min, warmed to 20 °C over 4 h, and stirred for 12 h. The mixture was then poured into ice water (100 mL) and extracted with Et_2O (4 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc–hexane, 1:9) to provide 4.29 g (89%) of **7** as a yellow liquid; $[\alpha]_D^{25}$ –15.7 (*c* 0.35, $CHCl_3$).

IR (neat): 3445, 2924, 2855, 1461, 771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94–3.82 (m, 1 H), 2.40–2.31 (m, 1 H), 2.30–2.21 (m, 1 H), 2.21–2.11 (m, 2 H), 1.92 (br s, 1 H), 1.53–1.33 (m, 4 H), 1.23(d, *J* = 6.2 Hz, 3 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.6, 77.2, 66.2, 39.8, 37.1, 22.2, 21.8, 18.3, 13.5.

ESI-MS: *m*/*z* = 141.7 $[M + H]^+$.

(*R*)-Non-8-yn-2-ol (8)

To anhyd 1, 3-diaminopropane (15 mL) was added NaH (60 wt%, 3.42 g, 142.85 mmol). The heterogeneous mixture was stirred at r.t. for 10 min during which, the solution changed to orange to brown in appearance. The mixture was refluxed at 60 °C for 5 h during which period ammonia gas was released. Then, the solution was allowed to reach 0 °C, and treated with (*R*)-non-4-yn-2-ol (**7**; 4.0 g, 28.57 mmol) in one portion and stirred at 20 °C for 3 h. After completion of the reaction, the mixture was quenched cautiously by the addition of crushed ice in portions and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc–hexane, 1:9) to yield 3.2 g (80%) of **8** as a colorless liquid; $[\alpha]_D^{25}$ –14.1 (*c* 0.35, $CHCl_3$).

IR (neat): 3306, 2934, 2860, 2116, 1460, 1374, 1262, 847, 771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86–3.71 (m, 1 H), 2.22–2.14 (m, 2 H), 1.88 (t, *J* = 3 Hz, 1 H), 1.60–1.35 (m, 8 H), 1.2 (d, *J* = 6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.4, 68.4, 67.6, 39.0, 28.7, 28.3, 25.2, 23.4, 18.3.

ESI-MS: *m*/*z* = 141.6 $[M + H]^+$.

(*R*)-*tert*-Butyldimethyl(non-8-yn-2-yloxy)silane (9)

To a cooled solution (0 °C) of secondary alcohol **8** (3.1 g, 22.14 mmol) and imidazole (3.16 g, 46.49 mmol) in anhyd CH_2Cl_2 (20 mL) was added TBDMSCl (3.67 g, 24.35 mmol) slowly and stirred for 3 h. After completion of the reaction, the mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (EtOAc–hexane, 0.2:9.8) to afford pure TBS ether **9** (5.39 g, 96%) as a colorless liquid; $[\alpha]_D^{25}$ –10 (*c* 1.5, $CHCl_3$).

IR (neat): 2934, 2860, 2238, 1467, 1437, 1376, 1254, 1136, 1101, 1054, 835, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86–3.71 (m, 1 H), 2.23–2.13 (m, 2 H), 1.93 (t, *J* = 2.4 Hz, 1 H), 1.58–1.24 (m, 8 H), 1.11 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.5, 68.0, 39.5, 28.8, 28.5, 25.9, 25.2, 23.8, 18.3, –4.4, –4.7.

ESI-MS: *m*/*z* = 277 $[M + Na]^+$.

Methyl (*R*)-9-(*tert*-Butyldimethylsilyloxy)dec-2-ynoate (10)

To a cooled (–78 °C) solution of **9** (3.0 g, 11.81 mmol) in anhyd THF (10 mL) was added *n*-BuLi (11.03 mL, 17.65 mmol) dropwise and stirred for 0.5 h. To this mixture was added methyl chloroformate (1.18 mL, 15.35 mmol) at –78 °C and stirred for another 1 h. The reaction mixture was then warmed to 0 °C and stirred for 15 min. After completion of the reaction, the mixture was quenched with sat. aq NH_4Cl (10 mL), extracted with Et_2O (3 × 15 mL), the combined organic layers were washed with brine (10 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc–hexane, 0.1:9.9) to give ester **10** (3.39 g, 92%) as a colorless liquid; $[\alpha]_D^{25}$ –10.9 (*c* 1.1, $CHCl_3$).

IR (neat): 2935, 2860, 2238, 1719, 1467, 1437, 1376, 1254, 1136, 1101, 1054, 835, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77–3.73 (m, 1 H), 3.74 (s, 3 H), 2.33 (t, *J* = 6.9 Hz, 2 H), 1.68–1.54 (m, 2 H), 1.47–1.24 (m, 6 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 89.3, 73.1, 68.3, 52.3, 39.4, 39.0, 28.9, 27.5, 25.9, 25.1, 23.9, 18.6, –4.3, –4.7.

ESI-MS: *m*/*z* = 335.1 $[M + Na]^+$.

Methyl (*R*,2*E*,4*E*)-9-(*tert*-Butyldimethylsilyloxy)deca-2,4-dienoate (11)

To a solution of **10** (3.5 g, 11.21 mmol) in benzene (30 mL) was added phenol (1.05 g, 11.21 mmol) and Ph_3P (2.93 g, 11.21 mmol) and stirred at 50 °C for 6 h. After completion of the reaction, the mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with aq 1 M NaOH (2 × 10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc–hexane, 0.1:9.9) to give pure **11** (3.25 g, 93%) as a colorless liquid; $[\alpha]_D^{25}$ –11.6 (*c* 0.6, $CHCl_3$).

IR (neat): 2933, 2859, 1727, 1657, 1439, 1376, 1261, 1198, 1174, 983, 836, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.16 (m, 1 H), 6.14–6.01 (m, 2 H), 5.72 (d, *J* = 16.0 Hz, 1 H), 3.75–3.68 (m, 1 H), 3.67 (s, 3 H), 2.13–2.06 (m, 2 H), 1.40–1.17 (m, 4 H), 1.05 (d, *J* = 6.00, 3 H), 0.81 (s, 9 H), 0.02 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 145.3, 144.7, 128.4, 118.7, 68.3, 51.5, 39.1, 33.0, 29.7, 25.9, 24.8, 23.8, –4.4, –4.7.

MS-EIMS: *m*/*z* = 335 $[M + Na]^+$.

(*R*,2*E*,4*E*)-9-Hydroxydeca-2,4-dienoic Acid (1)

Dienoate **11** (100 mg, 0.32 mmol) was refluxed in a solution of EtOH–H_2O (8:2) containing KOH (300 mg) for 6 h. After completion of the reaction, the mixture was neutralized with aq 6 M HCl to liberate the free acid, which was extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc–hexane, 9:1) to afford pure **1** as a colorless solid (47 mg, 80%); $[\alpha]_D^{25}$ +14.8 (*c* 1, $CHCl_3$).

IR (neat): 3368, 2924, 2853, 1685, 1032, 772 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.24 (dd, *J* = 9.8, 14.7 Hz, 1 H), 6.22 (dd, *J* = 9.8, 14.7 Hz, 1 H), 6.17–6.11 (m, 1 H),5.78 (d, *J* = 15.7 Hz, 1 H), 3.86–3.74 (m, 1 H), 2.29–2.16 (m, 2 H), 1.67–1.54 (m, 1 H), 1.53–1.41 (m, 3 H), 1.16 (d, *J* = 5.8 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 171.1, 146.5, 145.1, 128.9, 120.8, 67.9, 39.6, 33.3, 26.2, 23.4.

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{15}O_3$ $[M - H]^-$: 183.1026; found: 183.1033.

(*R*,2*E*,4*E*)-9-(*tert*-Butyldimethylsilyloxy)deca-2,4-dien-1-ol (12)

To a cooled (–78 °C) solution of **11** (2.0 g, 6.41 mmol) in anhyd CH_2Cl_2 (40 mL) was added DIBAL-H (13.51 mL, 13.51 mmol, 20% solution in toluene) and the reaction mixture was allowed to stir at –78 °C for 2 h. After completion of the reaction, the mixture was quenched with sodium potassium tartarate solution (5 mL). The organic layer was separated and washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc–hexane, 2:8) to afford pure **12** (1.63 g, 90%) as a colorless liquid; $[\alpha]_D^{25}$ –0.8 (*c* 1, $CHCl_3$).

IR (neat): 3393, 2932, 2860, 1717, 1459, 1375, 1254, 1184, 1129, 1048, 978, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.27–6.12 (m, 1 H), 6.09–5.95 (m, 1 H), 5.80–5.59 (m, 2 H), 4.15 (d, *J* = 6 Hz, 2 H), 3.84–3.69 (m, 1 H), 2.14–2.02 (m, 2 H), 1.57–1.21 (m, 4 H), 1.11 (d, *J* = 6 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.4, 132.0, 129.4, 68.5, 63.5, 39.2, 32.6, 29.7, 25.9, 25.4, 23.8, –4.3, –4.7.

MS-ESI: *m*/*z* = 302.6 $[M + NH_4]^+$.

Ethyl (*R*,4*E*,6*E*)-11-(*tert*-Butyldimethylsilyloxy)-3-hydroxydodeca-4,6-dienoate (14)

To solution of compound **12** (1.0 g, 3.52 mmol) and $NaHCO_3$ (529 mg, 6.30 mmol) in CH_2Cl_2 (8 mL) was added DMP (3.31 g, 7.39 mmol) and stirred for 1.5 h. After completion of the reaction, the mixture was diluted with cold H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to yield crude aldehyde **13** (0.80 g, 81%), which was directly used for the next reaction.

To a cooled (–78 °C) solution of anhyd EtOAc (2.74 mL, 27.95 mmol) in anhyd THF (5 mL) was added a 1 M solution of LiHMDS in THF (14.16 mL, 14.16 mmol) and the solution was stirred for 0.5 h. Then, the previously prepared aldehyde **13** (0.8 g, 2.83 mmol) in anhyd THF was added slowly by cannula and the resulting mixture was stirred for 2 h at –78 °C and 2 h at r.t. After completion of the reaction, the mixture was quenched with sat. aq NH_4Cl (5 mL), stirred for an additional 30 min, and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc–hexane, 2:8) to afford an inseparable diastereomeric mixture of aldol product **14** (0.83 g, 80%) as a clear liquid; $[\alpha]_D^{25}$ –6.36 (*c* 1.1, $CHCl_3$).

IR (neat): 3441, 2954, 2931, 2858, 1733, 1466, 1374, 1253, 1220, 1136, 1094, 1038, 835, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (dd, *J* = 10,1 Hz, 1 H), 5.99 (dd, *J* = 11, 15 Hz, 1 H), 5.73–5.65 (m, 1 H), 5.57 (dd, *J* = 6, 15 Hz, 1 H), 4.60–4.51 (m, 1 H), 4.15 (q, *J* = 7 Hz, 2 H), 3.80–3.71 (m, 1 H), 2.87 (br s, 1 H), 2.58–2.47 (m, 2 H), 2.10–2.01 (m, 2 H), 1.51–1.29 (m, 4 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 136.3, 131.7, 131.2, 129.6, 69.0, 68.8, 61.1, 41.9, 39.5, 33.0, 26.3, 25.7, 24.2, 18.5, 14.6, –4.0, –4.3.

MS-ESI: *m*/*z* = 393.1 $[M + Na]^+$.

Ethyl (*R*,4*E*,6*E*)-11-(*tert*-Butyldimethylsilyloxy)-3-oxododeca-4,6-dienoate (15)

To solution of **14** (500 mg, 1.35 mmol) and $NaHCO_3$ (327 mg, 3.90 mmol) in CH_2Cl_2 (8 mL) was added DMP (1.0 g, 2.43 mmol) and stirred for 1 h. After completion of the reaction, the mixture was diluted with cold H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to yield crude β-keto ester **15**. The crude compound was purified by column chromatography on silica gel (EtOAc–hexane, 0.5:9.5) to afford pure **15** (442 mg, 89%) as a viscous liquid; $[\alpha]_D^{25}$ –12.8 (*c* 0.35, $CHCl_3$).

IR (neat): 2928, 2856, 1735, 1664, 1598, 1465, 1374, 1235, 1146, 1038, 835, 806, 776 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.85 (s, 1 H), 7.02 (dd, *J* = 10.9, 15.5 Hz, 1 H), 6.24–6.08 (m, 1 H), 6.05–5.95 (m, 1 H), 5.78 (d, *J* = 14.8 Hz, 1 H), 4.99 (s, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 3.80–3.73 (m, 1 H), 3.55 (s, 1 H), 2.25–2.15 (m, 2 H), 1.57–1.36 (m, 8 H), 1.35–1.23 (m, 5 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 191.9, 169.6, 167.3, 146.9, 145.0, 141.7, 137.5, 129.3, 128.7, 126.9, 123.2, 90.9, 68.3, 61.3, 60.0, 47.3, 39.1, 33.2, 33.0, 29.7, 25.9, 25.1, 24.8, 23.9, 14.3, 14.1, –4.4, –4.7.

MS-ESI: *m*/*z* = 391 $[M + Na]^+$.

Ethyl (3*S*,4*E*,6*E*,11*R*)-11-(*tert*-Butyldimethylsilyloxy)-3-hydroxydodeca-4,6-dienoate (16)

The reagent (*R*)-Me-CBS (1 M in toluene, 0.07 mL, 0.24 mmol) and $DMS{\cdot}BH_3$ (1 M in THF, 0.074 mL, 0.86 mmol) were mixed under N_2 and at r.t. and stirred for 15 min. The mixture was cooled at –40 °C and treated with a solution of **15** (300 mg, 0.81 mmol) in anhyd THF (5 mL). The reaction mixture was stirred for 1.5 h. After completion of the reaction, MeOH (10 mL) was added and the solution was stirred further for additional 1 h and allowed to warm up to r.t. The solvents were then removed under vacuum and the crude was purified by column chromatography on silica gel (EtOAc–hexane, 2:8) to afford pure product **16** with excellent enantioselectivity of 87.18% de [determined by Chiral HPLC: column: Chiral pack-OJ-H (250 × 4.6 mm particle size 5 μ); mobile phase: hexane–*i*-PrOH (95:5); flow rate: 1.0 mL/min; detection: UV/visible detector] (241 mg, 80%) as a clear liquid; $[\alpha]_D^{25}$ –26.0 (*c* 0.25, $CHCl_3$).

IR (neat): 3441, 2954, 2933, 2858, 1733, 1469, 1374, 1253, 1218, 1136, 1094, 1019, 835, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.22 (dd, *J* = 10, 15 Hz, 1 H), 5.98 (dd, *J* = 11, 15 Hz, 1 H), 5.72–5.63 (m, 1 H), 5.55 (dd, *J* = 6, 15 Hz, 1 H), 4.58–4.47 (m, 1 H), 4.16 (q, *J* = 7.0 Hz, 2 H) 3.80–3.69 (m, 1 H), 2.83 (br s, 1 H), 2.57–2.46 (m, 2 H), 2.11–2 (m, 2 H), 1.48–1.30 (m, 4 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 1.10 (d, *J* = 6.0 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 136.0, 131.4, 130.8, 129.3, 68.7, 68.5, 60.8, 41.5, 39.1, 32.6, 25.9, 25.3, 23.9, 18.1, 14.2, –4.4, –4.7.

MS-ESI: *m*/*z* = 393.0 $[M + Na]^+$.

Ethyl (3*S*,4*E*,6*E*,11*R*)-11-(*tert*-Butyldimethylsilyloxy)-3-hydroxydodeca-4,6-dienoic Acid (17)

To solution of **16** (150 mg, 0.40 mmol) in THF–H_2O (1:1) was added LiOH (14 mg, 0.60 mmol) and stirred for 2.5 h. After completion of the reaction, the mixture was diluted with cold H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to yield crude acid **17**. The crude compound was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 8:2) to afford pure **17** (119 mg, 86%) as a clear liquid; $[a]_D^{25}$ –20.6 (*c* 1, $CHCl_3$).

IR (neat): 3445, 2933, 2859, 1727, 1657, 1439, 1376, 1261, 1198, 1174, 1042, 836, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.14 (dd, *J* = 10.4, 15.6 Hz, 1 H), 5.93 (dd, *J* = 10.4, 15.6 Hz, 1 H), 5.72–5.34 (m, 2 H), 4.60–4.26 (m, 2 H), 3.85–3.66 (m, 1 H), 2.51–2.18 (m, 2 H), 2.13–1.92 (m, 2 H), 1.52–1.17 (m, 4 H), 1.10 (d, *J* = 6 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4, 135.2, 131.9, 130.7, 129.6, 69.9, 68.4, 39.4, 32.9, 29.7, 25.9, 25.5, 23.9, 18.1, –4.4, –4.6.

MS-ESI: *m*/*z* = 365.0 $[M + Na]^+$.

(3*S*,4*E*,6*E*,11*R*)-3,11-Dihydroxydodeca-4,6-dienoic Acid (2)

To an ice-cold flask containing acid **17** (60 mg, 0.175 mmol) in THF (10 mL) was added a solution of HF·Pyridine (0.2 mL) and stirred at 0 °C for 6 h. After completion of the reaction, the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to leave a colorless amorphous solid, which was purified by column

chromatography on silica gel (CH_2Cl_2–MeOH, 1:1) to furnish pure **2** (28.8 mg, 72%); $[\alpha]_D^{25}$ +17.9 (*c* 0.35, MeOH).

IR (neat): 3449, 2933, 2869, 1727, 1439, 1350, 1261, 1134, 836, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.18 (dd, *J* = 9.8, 14.9 Hz 1 H), 6.01 (dd, *J* = 9.8, 14.9 Hz, 1 H), 5.65 (dt, *J* = 14.8, 7.05 Hz, 2 H), 4.61–4.28 (m, 1 H), 3.86–3.66 (m, 1 H), 2.41(d, *J* = 6 Hz, 2 H), 2.12–1.96 (m, 2 H), 1.53–1.18 (m, 4 H), 1.11 (d, *J* = 6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4, 136.2, 133.5, 131.9, 130.9, 70.1, 68.4, 43.7, 39.8, 33.7, 26.2, 23.9.

HRMS-ESI: *m/z* calcd for $C_{12}H_{19}O_4$ $[M - H]^-$: 227.1286; found: 227.1293.

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