A Concise Synthesis of (–)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic Acid Using a Cross-Metathesis Approach

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Abstract: A new synthesis of (–)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid, a β-hydroxy carboxylic acid, has been accomplished using a cross-metathesis reaction between two terminal olefin intermediates as the key step.

Key words: β-hydroxy acid, cross-metathesis, Jacobsen's kinetic resolution, TMSI

Two β-hydroxy carboxylic acids, (–)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid (**1**) and a trimeric diester derivative **2** (Figure 1) were isolated by Barrero and co-workers from the aerial parts of *Lafuentea rotundifolia* Lag.[1] This plant belongs to the genus *Lafuentea* (Scrophulariaceae) and grows in lowlands of the Southeast Iberian Peninsula. The structure of **1** was established on the basis of spectral analysis and absolute configuration of chiral centers by Mosher's method. Its limited isolation coupled with the presence of β-hydroxy acid core connected with unique 1,4-dihydroxyl, which remains a difficult task, prompted us to take up its synthesis. So far, three syntheses[2] of **1** starting from isopentyl bromide, epichlorohydrin, and 1-bromo-3-methylbutane, respectively, were reported. These syntheses employed asymmetric allylations and Jacobsen's hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation, cyclic sulfate, and asymmetric allylboration reactions as the key steps. Cross-metathesis (CM)[3] reaction has attracted great attention for C–C bond formation and its utility in the natural product synthesis. In continuation of our interest on the synthesis of natural compounds using CM reaction,[4] we herein report a new concise approach for the synthesis of **1** based on CM reaction as the key step.

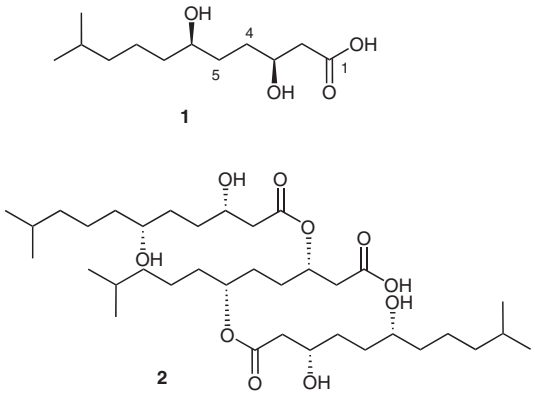
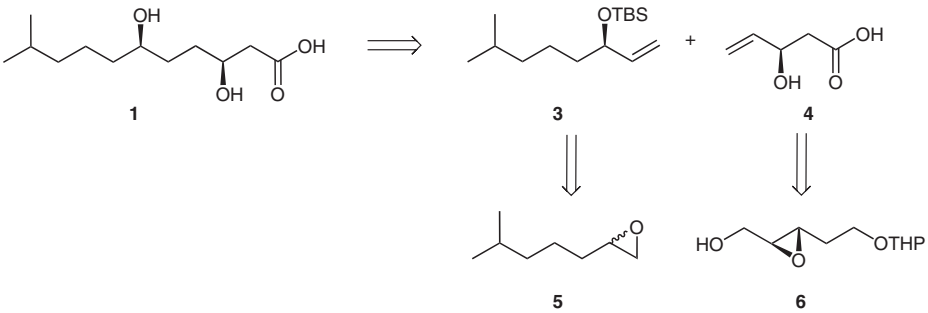


Figure 1 (–)-(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic acid (**1**) and its trimer **2**

Our retrosynthetic analysis of **1** is shown in Scheme 1. We planned to construct the C4–C5 bond of **1** by the cross-metathesis reaction between oxygen-containing terminal olefins **3** and **4**. Compound **3** would be obtainable by Jacobsen's resolution of racemic epoxide **5** and its opening by TMSI, while the other component **4** of the cross-metathesis reaction should readily be prepared by a known epoxide **6** opening.

The synthesis of fragment **3** began with the readily available 5-methylhexan-1-ol (**7**) (Scheme 2). Oxidation of alcohol **7** using Swern oxidation yielded the corresponding aldehyde **8** and subsequent treatment with NaH in DMSO and trimethylsulfonium iodide[5] in THF afforded the racemic epoxide **5** in 65% yield. This epoxide was subjected to Jacobsen's HKR[6] by using (*S*,*S*)-Salen-Co-OAc catalyst to give the chiral epoxide **9** (43%) in highly enantio-



Scheme 1 Retrosynthetic analysis of **1**.

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enriched form (95% ee). Opening of epoxide **9** using trimethylsulfonium iodide[7] in the presence of *n*-BuLi in anhydrous THF at –10 °C provided the secondary allylic alcohol **10** in 76% yield, which was protected as its TBS ether **3**.

Synthesis of the acid component **4** began with the epoxy alcohol **6** (prepared from homopropargylic alcohol).[8] The epoxy alcohol **6** was converted into the corresponding iodide,[9] which on reductive elimination with activated Zn dust[10] in refluxing ethanol for two hours afforded the chiral allylic alcohol **11** (80%) (Scheme 3). The allylic alcohol **11** was converted into the corresponding MOM-protected ether **12** in 92% yield and selective deprotection of the THP group (PPTS, MeOH) produced the alcohol **13** in 85% yield. The free alcohol was then oxidized by using IBX in DMSO–CH_2Cl_2 to afford the corresponding aldehyde, which was oxidized to the acid **14** with $NaClO_2$ in the presence of $NaH_2PO_4 \cdot 2H_2O$ and 2-methylbut-2-ene in 78% yield over two steps. Removal of MOM group using PTSA in MeOH accomplished the synthesis of the required acid fragment **4** (81%) (Scheme 3).

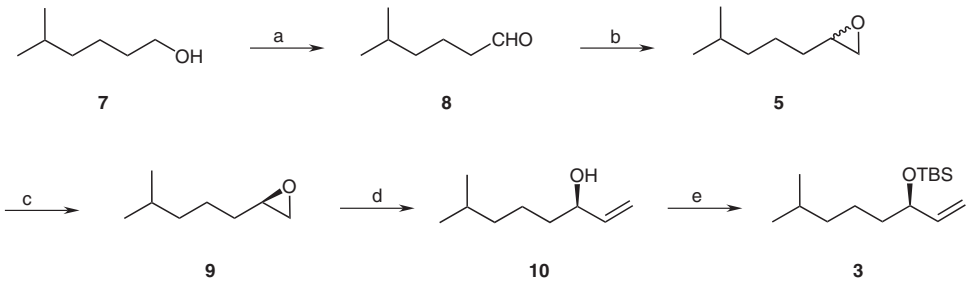
Biographical Sketches

Gowravaram Sabitha was born in India in 1959. She did her M. Sc. (Organic Chemistry) in 1980 at Osmania University where she also obtained her doctorate in 1987 (Prof. A. V. Subba Rao). After a year and a half postdoctoral work with Prof. Edward C. Taylor (Princeton University, USA), she joined Indian Institute of Chemical Technology, Hyderabad (India) as a scientist in 1993. She was awarded the STA postdoctoral fellowship to work for 3 months at RIKEN (The Institute of Physical and Chemical Research), with Prof. Tadashi Nakata (Japan) in 2000. She has published more than 130 research papers. Her research focus lies in the development of novel synthetic methodologies, total synthesis of bioactive natural products and development of new chemical entities.

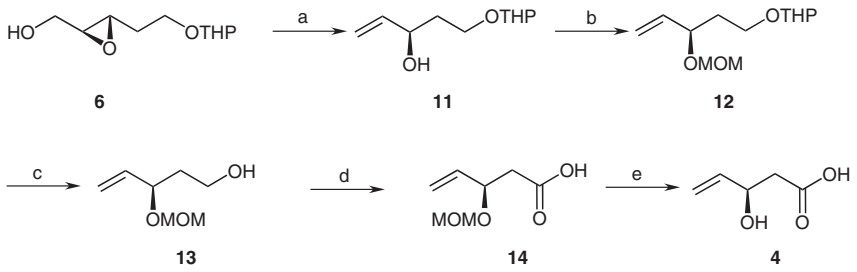
S. Siva Sankara Reddy was born in India in 1982. He received his M.Sc degree in chemistry at Sri Krishnadevaraya University, Anantapur, India in 2005. After that, he joined Dr. G. Sabitha's group at the Indian Institute of Chemical Technology, Hyderabad, India in March 2007 for his doctoral thesis, presently he is working on the total synthesis of bio-active natural products.

Vangala Bhaskar was born in India in 1980. He obtained his M.Sc (Chemistry) in 2003 from Osmania University, Hyderabad, India. After that, he gained industrial experience for two years with Dr. Reddy's pharmaceutical company, India. Then he joined Dr. G. Sabitha's group at the Indian Institute of Chemical Technology in 2005, Hyderabad, India for doctoral thesis. He is currently working as a postdoctoral fellow in the Department of Chemistry at the University of Saskatchewan, Canada with Dr. M.S.C. Pedras.

Dr. J. S. Yadav was born in 1950 in Azamgarh, Uttar Pradesh, India. He has obtained his masters degree in 1972 and doctorate in 1976 from India. He was a postdoctoral fellow at Rice University, Houston and University of Wisconsin, Madison (USA) for 3½ years. He joined in CSIR service in 1981 at National Chemical Laboratory (NCL), Pune. Subsequently he moved to Indian Institute of Chemical Technology (IICT), Hyderabad in 1986. In 2003, Dr. Yadav was appointed as director of the Indian Institute of Chemical Technology, Hyderabad. He occupies number one position among the top 21 scientists from India, shortlisted for their highest productivity in terms of publication during the last 10 years. He is a specialist in asymmetric synthesis to create new chiral centers in complex organic molecules and utilize them effectively in the synthesis of many bioactive molecules. His research findings have been published in more than 800 research papers. He also has 132 Indian and International Patents to his credit. His outstanding efforts and achievements in this field have enabled him to achieve a number of prestigious national and international awards.

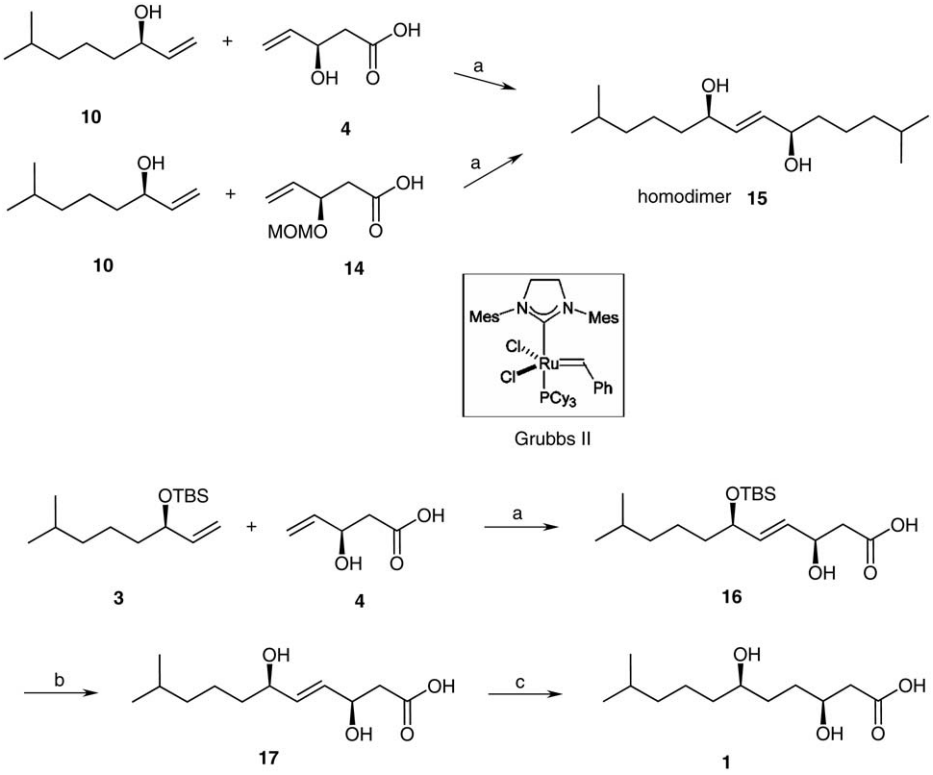


Scheme 2 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2 h; (b) Me_3SI, DMSO, NaH, THF, 0 °C to r.t. 6 h, 65%; (c) (*S*,*S*)-Jacobsen catalyst, AcOH, H_2O, 12 h, 43%; (d) Me_3SI, THF, *n*-BuLi, –10 °C, 2 h, 76%; (e) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 90%.



Scheme 3 *Reagents and conditions*: (a) i. TPP, I_2, imidazole, Et_2O–MeCN (3:1), 0 °C to r.t., 20 min, ii. activated Zn, EtOH, reflux, 1 to 2 h, 80%; (b) MOMCl, Hünig's base, CH_2Cl_2, 0 °C to r.t., 30 min, 92%; (c) PPTS, MeOH, r.t., 4 h, 85%; (d) i. IBX, DMSO,CH_2Cl_2, 0 °C to r.t. 3 h, ii. $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methylbut-2-ene, *t*-BuOH, 6 h, 78%; (e) PTSA, MeOH, r.t., 3 h, 81%.

Having the desired fragments **10**, **3**, **14**, and **4** in hand, we turned our attention towards cross-metathesis reaction (Scheme 4). Olefin cross-metathesis reactions using the second-generation Grubbs catalyst[11] (5 mol% Grubbs II) between **10** and **4** and between **10** and **14** as well, gave the undesired self-metathesis (homodimerization) product **15** exclusively. To our delight, exposure of olefin **3** (bearing the TBS protecting group) to **4** under the above-mentioned metathesis conditions furnished the desired cross-metathesis product **16** (ca. 72% yield) (Scheme 4). The ^1H



Scheme 4 *Reagents and conditions*. (a) Grubbs II catalyst, CH_2Cl_2, reflux, 1 h, **15** (71%), **16** (72%); (b) TBAF, THF, 0 °C, 2 h, 87%; (c) 5% Pd/C, EtOAc, r.t. 6 h, 90%.

and ^{13}C NMR spectra of **16** indicated that the compound was produced with complete *E*-geometrical selectivity.

Removal of TBS group followed by hydrogenation of double bond in **17** with 5% Pd/C afforded the target molecule **1** in 90% yield, the ^{1}H and ^{13}C NMR spectral data of which were identical with those previously reported.[2] The specific rotation ($[\alpha]_D^{25}$ –8.7 (*c* 0.9, $CHCl_3$) showed good agreement with those reported in the literature.

In summary, a concise and stereoselective synthesis of (–)-(3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid (**1**) has been achieved using a cross-metathesis reaction between two terminal olefin intermediates as the key step starting from 5-methylhexan-1-ol and homopropargylic alcohol.

Reactions were conducted under N_2 in anhyd solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Petroleum ether (PE) having a boiling range of 60–80 °C was used. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C NMR) homogeneous material. Air sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Büchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200MHz (Gemini) and Bruker UXNMR FT-300MHz (Avance) spectrometers. Chemical shifts δ are reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high-resolution spectra were recorded on QSTAR XL hybrid MS/MS system (Applied Biosystems/MDS Sciex, Foster City, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 Polarimeter at 20 °C.

(2*R*)-2-(4-Methylpentyl)oxirane (9)

*Aldehyde **8***: To a stirred solution of oxalyl chloride (5.47 g, 43.10 mmol) in anhyd CH_2Cl_2 (40 mL) at –78 °C was added anhyd DMSO (6.72 g, 86.15 mmol) dropwise. After 30 min, alcohol **7** (2.5 g, 21.55 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at –78 °C, Et_3N (13.0 g, 128.71 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to r.t. The mixture was then diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the aldehyde **8**, which was directly used for further reaction.

*2-(4-Methylpentyl)oxirane **5***: A solution of NaH (1.29 g, 53.75 mmol) in DMSO (25 mL) was stirred at 70–75 °C for 30 min and cooled to r.t. THF (50 mL) followed by a suspension of Me_3SI (17.15 g, 84.03 mmol) in DMSO (8 mL) were added at –5 °C and stirred for 5 min. Then, a solution of the above aldehyde in THF (8 mL) was added to the reaction mixture and stirred for 4 h at –5 °C. The reaction mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was evaporated and purified the residue by column chromatography on silica gel (eluent: PE–EtOAc, 9:1) to afford **5** (racemic) as a gummy liquid; yield 1.78 g (65%); R_f = 0.7 (PE–EtOAc, 9:1).

9: A mixture of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (40 mg, 0.06 mmol) in toluene (0.14 mL, 1.30 mmol) and AcOH (0.015 mL, 0.26 mmol) was stirred while open to the air for 1 h at r.t. The reaction mixture was concentrated under reduced pressure and the brown residue was dried under vacuum. The above obtained racemic epoxide (1.70 g, 13.28 mmol) was added in one portion at 0 °C and H_2O (0.13 mL, 7.22 mmol) was added. The reaction mixture was allowed to warm to r.t. and stirred for 12 h. The residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 9:1). (*R*)-Oxirane **9** was eluted first as a colorless liquid; yield: 730 mg (43%); R_f = 0.7 (PE–EtOAc, 9:1); $[\alpha]_D^{25}$ +6.1 (*c* 1.0, $CHCl_3$).

IR (neat): 3018, 2860, 1737, 1462, 1371, 1191 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 6 H), 1.19–1.60 (m, 7 H), 2.40 (dd, *J* = 4.8, 2.9 Hz, 1 H), 2.68 (t, *J* = 4.8 Hz, 1 H), 2.81–2.86 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 23.8, 27.9, 32.7, 38.7, 47.1, 52.3.

ESIMS: *m*/*z* = 129 $[M + H]^{+\cdot}$

(3*R*)-7-Methyloct-1-en-3-ol (10)

To a suspension of Me_3SI (4.0 g, 19.6 mmol) in anhyd THF (30 mL) at –10 °C under N_2 was added *n*-BuLi (2.5 M in hexane, 6.09 mL). After 40 min, compound **9** (0.65 g, 5.07 mmol) in THF (5 mL) was introduced, producing a milky suspension. The reaction was allowed to warm to 0 °C over about 30 min and then to r.t., and stirred for 2 h. The reaction was quenched with H_2O (5 mL) at 0 °C and the mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (eluent: PE–EtOAc, 7:3) to give **10** as a clear liquid; yield: 540 mg (76%); R_f = 0.3 (PE–EtOAc, 7:3); $[\alpha]_D^{25}$ –1.2 (*c* 0.25, $CHCl_3$).

IR (neat): 3451, 2925, 2856, 1727, 1630, 1459 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.7 Hz, 6 H), 1.11–1.60 (m, 7 H), 3.57–3.67 (br s, 1 H, OH), 4.01–4.11 (m, 1 H), 5.07 (dt, *J* = 10.4, 1.1 Hz, 1 H), 5.19 (dt, *J* = 17.1, 1.3 Hz, 1 H), 5.78–5.90 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5 (2 C), 23.1, 27.8, 37.2, 38.8, 73.2, 114.4, 141.3.

ESIMS: *m*/*z* = 165 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_9H_{18}O$ + Na $[M + Na]^+$: 165.2122; found: 165.2128.

***tert*-Butyl(dimethyl)[(1*R*)-1-(4-methylpentyl)prop-2-enyl]oxysilane (3)**

TBSCl (0.23 g, 1.53 mmol) was added to a stirred solution of alcohol **10** (0.2 g, 1.40 mmol) and imidazole (0.19 g, 2.79 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at r.t. for about 1 h and then quenched with H_2O (0.5 mL). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (2 × 2 mL), brine (2 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 9.5:0.5) to afford the product **3** as a colorless syrup; yield: 320 mg (90%); R_f = 0.8 (PE–EtOAc, 9.5:0.5); $[\alpha]_D^{25}$ –6.7 (*c* 1.0, $CHCl_3$).

IR (neat): 2924, 2854, 1738, 1463, 1376, 1254, 1081 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.86–0.91 (m, 15 H), 1.11–1.59 (m, 7 H), 4.01–4.10 (m, 1 H), 4.99 (dt, *J* = 10.3, 1.1 Hz, 1 H), 5.11 (dt, *J* = 17.1, 1.3 Hz, 1 H), 5.70–5.83 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.4, 18.3, 22.6, 23.0, 25.9 (3 C), 27.9, 38.4, 38.9, 73.9, 113.3, 141.9.

ESIMS: *m*/*z* = 279 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{32}OSi$ + Na [M + Na]$^+$: 279.2120; found: 279.2127.

(3*R*)-5-(Tetrahydro-2*H*-2-pyranyloxy)pent-1-en-3-ol (11)

To a stirred solution of **6** (1.5 g, 7.41 mmol) in Et_2O–MeCN (3:1, 20 mL) were added TPP (2.92 g, 11.12 mmol) and imidazole (1.26 g, 18.50 mmol) at 0 °C and the mixture stirred for 5 min. I_2 (2.82 g, 22.20 mmol) was added at 0 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was evaporated in vacuo to afford the crude iodo compound. This was used for the next step without further purification. To a stirred solution of the above iodo compound in EtOH (20 mL) was added activated Zn dust (0.98 g, 14.98 mmol) and the mixture stirred at reflux for 1–2 h. The mixture was passed through a short pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 1:1) to afford **11** (1.09 g, 80%) as a colorless liquid; yield: 1.09 g (80%); R_f = 0.2 (PE–EtOAc, 1:1); $[\alpha]_D^{25}$ –9.6 (*c* 3.75, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39–1.91 (m, 8 H), 2.26 (br s, 1 H, OH), 3.69–3.88 (m, 2 H), 4.06–4.17 (m, 1 H), 4.58 (t, *J* = 3.02 Hz, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 5.22 (d, *J* = 17.4 Hz, 1 H), 5.78–5.91 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.40, 25.3, 30.5, 36.2, 62.2, 65.6, 72.0, 98.9, 114.3, 140.5.

ESIMS: *m*/*z* = 209.0 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}O_3$ + Na [M + Na]$^+$: 209.1153; found: 209.1154.

2-[(3*R*)-3-(Methoxymethoxy)pent-4-enyl]oxytetrahydro-2*H*-pyran (12)

To a cooled (0 °C) solution of the above compound **11** (1.0 g, 5.37 mmol) in CH_2Cl_2 (10 mL) were added sequentially DIPEA (1.75 mL, 10.77 mmol) and MOMCl (0.45 mL, 5.87 mmol) and the mixture stirred at r.t. for 2 h. The mixture was evaporated and the residue purified by column chromatography on silica gel (eluent: PE–EtOAc, 8:2) to afford **12** as a colorless liquid; yield: 1.13 g (92%); R_f = 0.65 (PE–EtOAc, 8:2); $[\alpha]_D^{25}$ +35.8 (*c* 1.4, $CHCl_3$).

IR (neat): 3078, 2939, 2881, 1636, 1441, 1353, 1030, 987, 920, 869 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.69 (m, 6 H), 1.70–1.90 (m, 2 H), 3.34 (s, 3 H), 3.37–3.52 (m, 2 H), 3.72–3.88 (m, 2 H), 4.14 (app pent, *J* = 6.8 Hz, 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.55 (q, *J* = 4.5 Hz, 1 H), 4.66 (d, *J* = 6.0 Hz, 1 H), 5.15–5.27 (m, 2 H), 5.61–5.75 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 25.4, 30.7, 35.5, 62.2, 63.8, 74.3, 74.7, 93.8, 98.9, 117.1, 138.1.

ESIMS: *m*/*z* = 253.0 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{22}O_4$ + Na [M + Na]$^+$: 253.1415; found: 253.1426.

(3*R*)-3-(Methoxymethoxy)pent-4-en-1-ol (13)

To a stirred solution of compound **12** (1.0 g, 4.34 mmol) in MeOH (8 mL) was added PPTS (10 mol%, cat.) and the mixture was stirred at r.t. for 4 h. The MeOH was removed under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: PE–EtOAc, 8:2) to afford **13** as a viscous liquid; yield: 530 mg (85%); R_f = 0.55 (PE–EtOAc, 8:2); $[\alpha]_D^{25}$ +100.6 (*c* 0.9, $CHCl_3$).

IR (neat): 3424, 2945, 1643, 1423, 1151, 1096, 1030, 922 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (t, *J* = 6.0 Hz, 2 H), 2.40 (br s, 1 H, OH), 3.36 (s, 3 H), 3.63–3.80 (m, 2 H), 4.21 (q, *J* = 7.5 Hz, 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.65 (d, *J* = 6.8 Hz, 1 H), 5.15–5.26 (m, 2 H), 5.62–5.75 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7, 55.5, 59.6, 75.9, 93.8, 117.3, 137.6.

ESIMS: *m*/*z* = 169.0 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_7H_{14}O_3$ + Na [M + Na]$^+$: 169.0840; found: 169.0846.

(3*R*)-3-(Methoxymethoxy)pent-4-enoic acid (14)

To an ice-cooled solution of 2-iodoxybenzoic acid (1.53 g, 5.46 mmol) in DMSO (4 mL) was added a solution of **13** (0.4 g 2.73 mmol) in anhyd CH_2Cl_2 (5 mL). The mixture was stirred at r.t. for 5 h and then filtered through a Celite pad (1 g) and washed with CH_2Cl_2 (4 × 50 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine (2 × 4 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the crude aldehyde. This was used for the next step without further purification. To a stirred solution of the above aldehyde in *t*-BuOH–2-methylbut-2-ene (2:1, 3 mL) were added $NaClO_2$ (0.208 g, 2.73 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (0.43 g, 2.75 mmol) [dissolved in H_2O (0.5 mL)] and stirred for 6 h at r.t. The solvent was removed under reduced pressure and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (2 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 7:3) to afford the acid **14** as a colorless liquid; yield: 340 mg (78%); R_f = 0.2 (PE–EtOAc, 7:3); $[\alpha]_D^{25}$ +57.4 (*c* 1.0, $CHCl_3$).

IR (neat): 2933, 1717, 1414, 1217, 1151, 1031 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46–2.68 (m, 2 H), 3.33 (s, 3 H), 4.44–4.53 (m, 2 H), 4.64–4.68 (m, 1 H), 5.24 (d, *J* = 10.4 Hz, 1 H), 5.32 (d, *J* = 16.6 Hz, 1 H), 5.68–5.76 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.7, 55.5, 73.5, 93.8, 118.5, 136.2, 176.3.

ESIMS: *m*/*z* = 183 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}O_4$ + Na [M + Na]$^+$: 183.0633; found: 183.0630.

(3*R*)-3-Hydroxypent-4-enoic Acid (4)

To a stirred solution of compound **14** (0.25 g, 0.70 mmol) in MeOH (5 mL) was added PTSA (10 mol%) and the reaction mixture was stirred at r.t. for 4 h. The MeOH was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: PE–EtOAc, 6:4) to afford the acid **4** as a viscous liquid; yield: 140 mg (81%); R_f = 0.35 (PE–EtOAc, 6:4); $[\alpha]_D^{25}$ +4.1 (*c* 0.75, $CHCl_3$).

IR (neat): 3417, 1719, 1403, 1288, 1136, 1038, 939 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56–2.62 (m, 2 H), 4.50–4.58 (m, 1 H), 5.17 (dt, *J* = 10.5, 1.5 Hz, 1 H), 5.33 (dt, *J* = 17.3, 1.5 Hz, 1 H), 5.81–5.94 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.9, 68.9, 115.8, 138.3, 176.3.

ESIMS: *m*/*z* = 139 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_5H_8O_3$ + Na [M + Na]$^+$: 139.0371; found: 139.0367.

(3*R*,4*E*,6*R*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-3-hydroxy-10-methylundec-4-enoic Acid (16)

Grubbs II catalyst (0.025 g, 0.03 mmol, 5 mol%) was dissolved in CH_2Cl_2 (1 mL) and added dropwise to a solution of the compound **4** (0.07 g, 0.60 mmol) and compound **3** (0.18 g, 0.70 mmol) in CH_2Cl_2 (1 mL) at r.t. After completion of addition, the reaction mixture was allowed to reflux for 1 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel

column chromatography (eluent: PE–EtOAc, 7:3) to afford the pure product **16** as a colorless liquid; yield: 140 mg (72%); R_f = 0.6 (PE–EtOAc, 7:3); $[\alpha]_D^{25}$ +2.4 (*c* 0.65, $CHCl_3$).

IR (neat): 3404, 2926, 2855, 1718, 1460, 1299, 1140, 934 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.84–0.92 (m, 15 H), 1.09–1.58 (m, 7 H), 2.55–2.65 (m, 2 H), 4.05–4.15 (m, 1 H), 4.52–4.61 (m, 1 H), 5.60 (dd, *J* = 15.4,5.7 Hz, 1 H), 5.71 (dd, *J* = 15.4, 5.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.3, 18.2, 22.6, 23.0, 25.9 (3 C), 27.9, 29.7, 38.3, 38.8, 41.2, 68.2, 72.5, 129.3, 135.5, 176.4.

ESIMS: *m*/*z* = 367 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{36}O_4Si$ + Na $[M + Na]^+$: 367.2280; found: 367.2273.

(3*R*,4*E*,6*R*)-3,6-Dihydroxy-10-methylundec-4-enoic Acid (17)

A 1 M solution of TBAF in THF (0.52 mL) was added to a solution of compound **16** (0.09 g, 0.26 mmol) in anhyd THF (5 mL) at 0 °C. The mixture was stirred at r.t., for 1 h. After completion of the reaction, the mixture was diluted with EtOAc (5 mL) and the mixture was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (2 × 2 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure, followed by column chromatography on silica gel (eluent: PE–EtOAc, 2:8) afforded the pure compound **17** as a clear liquid; yield: 50 mg (87%); R_f = 0.3 (PE–EtOAc, 2:8); $[\alpha]_D^{25}$ –3.4 (*c* 0.8, $CHCl_3$).

IR (neat): 3416, 2925, 2855, 1719, 1378, 1219, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.6 Hz, 6 H), 1.11–1.60 (m, 7 H), 2.50–2.65 (m, 2 H), 4.03–4.16 (m, 1 H), 4.32–4.61 (m, 1 H), 5.62–5.82 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (2 C), 23.2, 27.9, 37.1, 38.7, 42.6, 68.3, 72.2, 131.1, 134.5, 175.0.

ESIMS: *m*/*z* = 253 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{22}O_4$ + Na $[M + Na]^+$: 253.1415; found: 253.1424.

(3*S*,6*R*)-3,6-Dihydroxy-10-methylundecanoic Acid (1)

To a solution of compound **17** (0.02 g, 0.086 mmol) in EtOH (2 mL) was added Pd/C (5%, cat.) and the reaction mixture was stirred at r.t. under H_2 atmosphere for 6 h. Then the mixture was filtered off, washed with EtOAc (2 × 1 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: PE–EtOAc, 2:8) to afford compound **1** as a white powder; yield: 18 mg (90%); mp 149–150 °C; R_f = 0.25 (PE–EtOAc, 2:8); $[\alpha]_D^{25}$ –8.7 (*c* 0.9, $CHCl_3$).

IR (neat): 3413, 2926, 2860, 1713, 1654, 1382 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.7 Hz, 6 H), 1.11–1.70 (m, 11 H), 2.42–2.54 (m, 2 H), 3.57–3.69 (m, 1 H), 4.01–4.12 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.3 (2 C), 28.1, 29.8, 33.9, 37.1, 37.5, 39.1, 68.7, 72.5, 182.0.

ESIMS: *m*/*z* = 255 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{24}O_4$ + Na $[M + Na]^+$: 255.1572; found: 255.1584.

(6*R*,7*E*,9*R*)-2,13-Dimethyltetradec-7-ene-6,9-diol (15)

Compound **15** was prepared from **10** and **4** as well as **10** and **14** in 71% yield employing the same procedure as described for compound **16**.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 12 H), 1.11–1.67 (m, 14 H), 4.03–4.14 (m, 2 H), 5.62–5.67 (m, 2 H).

ESIMS: *m*/*z* = 279 $[M + Na]^+$.

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