# Stereoselective Synthesis of (4*S*,6*S*)-6-Hydroxy-4-undecanolide: A Pheromone of the Giant White Butterfly *Idea leuconoe*

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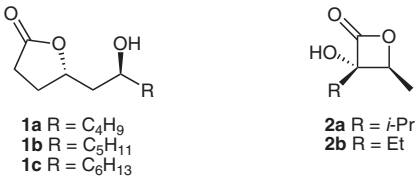
*Received 11 October 2011; revised 6 December 2011*

**Abstract:** The stereoselective synthesis of (4*S*,6*S*)-6-hydroxy-4-undecanolide, a major pheromone component in the secretion of *Idea leuconoe* has been accomplished employing Prins cyclization to produce *anti*-1,3-diols and hydroboration/oxidation of terminal olefin to introduce primary alcohol as the key steps.

**Key words:** pheromones, Prins cyclization, Mitsunobu inversion, *anti*-1,3-diol, chemoselective oxidation of 1,4-diols

The males of the giant white butterfly *Idea leuconoe* possess hairpencils on the end of their abdomen, which release a mixture of compounds, namely, alkaloids, aromatics, terpenoids, hydrocarbons, and lactones, to act as courtship pheromones.[1] The lactones, which are isolated from the hairpencil extract, are hydroxyalkanolides with two chiral centers. The lactone ring size differs from four- to six-membered and the chain lengths vary from $C_{10}$ to $C_{13}$.[2] Of these lactones, the major components of the hairpencil secretion are the g-lactones, 6-hydroxy-4-alkanolides **1a–c**, which are accompanied by trace amounts of the respective β-lactones **2a** (Figure 1). The first synthesis of a 6-hydroxy-4-alkanolide has been reported by Schulz et al. involving enantioselective hydrogenation of 4,6-diketo esters using a ruthenium–BINAP catalyst.[3]



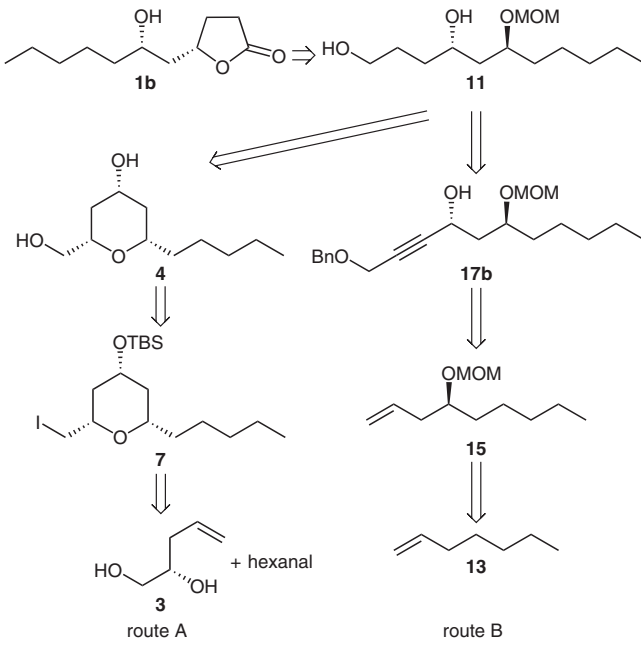

**1a** R = $C_4H_9$
**1b** R = $C_5H_{11}$
**1c** R = $C_6H_{13}$

**2a** R = *i*-Pr
**2b** R = Et

**Figure 1** Lactones **1a–c** and **2a**

In continuation of our research on the use of Prins cyclization in total synthesis of biologically active natural products,[4] we herein report an efficient approach for the synthesis of (4*S*,6*S*)-6-hydroxy-4-undecanolide (**1b**), a pheromone of the giant white butterfly *Idea leuconoe*.

In the retrosynthetic analysis (Scheme 1), we envisaged that the target molecule could be prepared from compound **7** via the reductive opening of iodomethyl-substituted tetrahydropyran ring followed by hydroboration/oxidation of the terminal olefin. The pyran derivative **7** could in turn be prepared via the Prins cyclization of a homoallylic alcohol **3** and hexanal. The chemoselective oxidation of 1,4-diol **11** using 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and (diacetoxyiodo)benzene would give the γ-lactone **1b**. In another strategy, 1,4-diol **11** could be alternatively prepared from compound **15** by ozonolytic oxidative cleavage of the olefin **15** followed by alkynylation of the resulting aldehyde and subsequent hydrogenation.



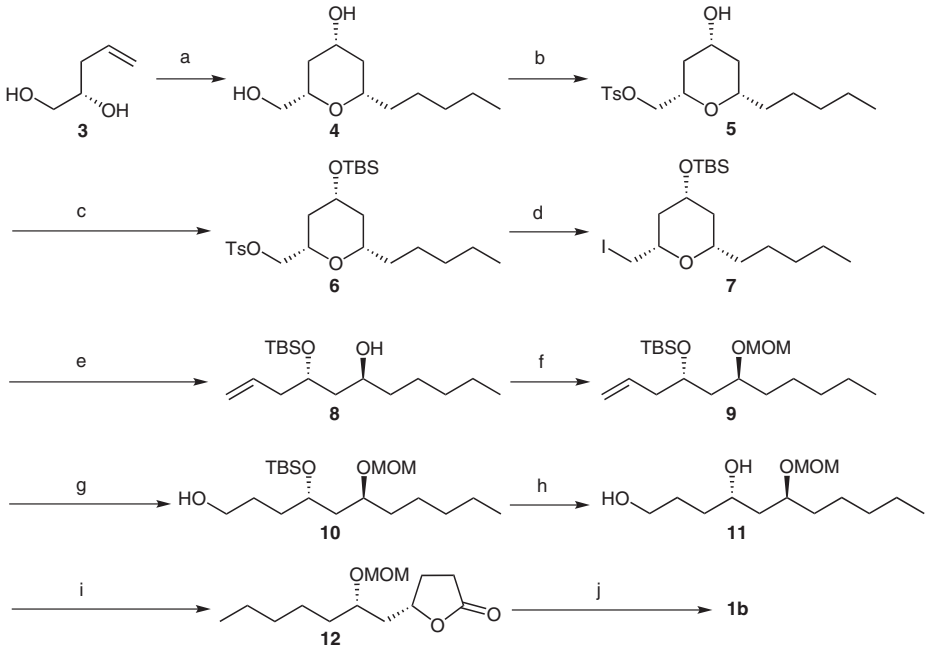

**Scheme 1**

The synthetic approach (route A, Scheme 2) commenced from a chiral homoallylic alcohol **3**, which was prepared via the copper-mediated regioselective opening of (*S*)-benzylglycidyl ether (obtained via the Jacobsen's HKR methodology)[5] with vinylmagnesium bromide (formed in situ from vinyl bromide and Mg metal in THF) followed by debenzylation with sodium in liquid ammonia (overall yield for two steps 69%). Prins cyclization of the homoallylic alcohol **3** with *n*-hexanal in the presence of trifluoroacetic acid followed by hydrolysis of the resulting trifluoroacetate gave the trisubstituted tetrahydropyran **4**

**SYNTHESIS** 2012, 44, 579–584
Advanced online publication: 16.01.2012
DOI: 10.1055/s-0031-1289671; Art ID: Z97011SS

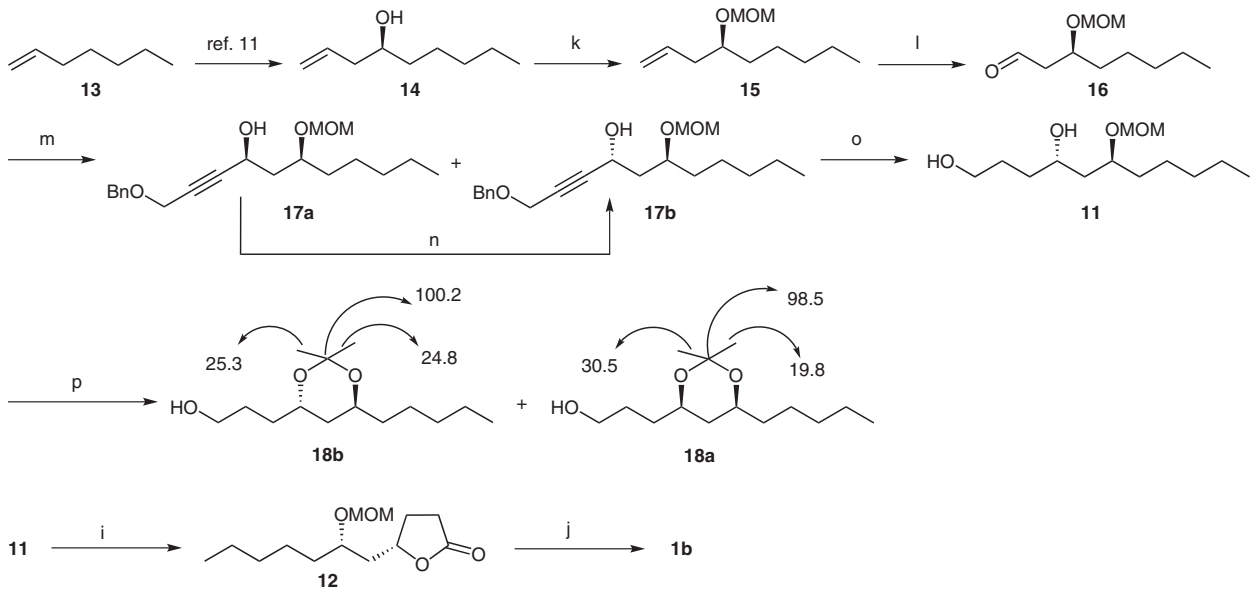
(52%).[6] The stereochemistry was assumed to be in accordance with the literature as it was well examined and established previously.[7] Moreover, the assumption was confirmed when compound **4** was elaborated to synthesize the target molecule **1b** (overall yield 15%), which in all respects was identical with the reported data.[3] Tosylation of the compound **4** with 1.2 equivalents of tosyl chloride in the presence of triethylamine in dichloromethane gave the corresponding primary tosylate **5** (95%). Protection of the secondary alcohol as a silyl ether in the presence of *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane gave the compound **6** (97%). Treatment of tosylate **6** with sodium iodide in refluxing acetone gave the corresponding iodo derivative **7** (95%). Reductive opening of the iodo derivative **7** with activated zinc in refluxing ethanol furnished the compound **8** (92%).[8] The secondary alcohol of compound **8** was protected as its methoxymethyl ether **9** (98%) in the presence of *N*-diisopropylethylamine and methoxymethyl chloride in dichloromethane. Upon exposure of compound **9** to dicyclohexylborane and 30% hydrogen peroxide afforded the primary alcohol **10** (77%).[9] Subsequent removal of the silyl group from compound **10** using tetra-*n*-butylammonium fluoride in tetrahydrofuran furnished the 1,4-diol **11** (97%), which was readily converted into lactone **12** (87%) by chemoselective oxidation using TEMPO and (diacetoxyiodo)benzene in dichloromethane.[10] Deprotection of methoxymethyl ether **12** using trifluoroacetic acid in dichloromethane (1:4) gave the final product **1b** (97%), which in all respects was identical to the reported structure.[3]

The alternative synthetic approach (route B, Scheme 3) commenced from **13**, which was converted into **14** according to a reported procedure[11] in three steps (overall yield 30%). Compound **14** was protected as its methoxymethyl ether gave **15** (98%). Ozonolytic oxidative cleavage of **15** gave the aldehyde **16** (85%), which was then treated with *O*-benzylpropargyl alcohol in the presence of *n*-butyllithium in tetrahydrofuran at –78 °C. The resulting propargylic alcohol was obtained as a mixture of *syn*-**17a** and *anti*-**17b** in a 1:1 ratio. To assign the stereochemistry, both the isomers were converted into the corresponding acetonides **18a** and **18b** in a three-step sequence. Upon exposure of both the isomers **17a/17b** to 10% Pd/C in methanol resulted in the reduction of triple bond with concomitant removal of benzyl group to furnish the diols, which were then treated with aqueous 3 M hydrochloric acid in tetrahydrofuran to give the triols (structures not shown). Upon treatment of the triols with 2,2-DMP in acetone the acetonides **18a** and **18b** were obtained. The stereochemistry of the diastereomers could be established by $^{13}C$ NMR analysis. In **18a**, the two methyl groups resonate at δ = 19.8 and 30.5 ppm and quaternary carbon shows a peak at δ = 98.5 ppm representing the 1,3-*syn* orientation of two hydroxy groups. However, the two methyl groups and quaternary carbon resonate at δ = 24.7, 24.9, and 100.3 ppm, respectively, indicating the 1,3-*anti*-orientation of the two hydroxy groups in **18b**.[12] The undesired isomer **17a** was converted into **17b** (overall yield 70%) under standard Mitsunobu condition.[13] Reduction of the triple bond with a concomitant debenzylation of compound **17b** was achieved using Pd/C in methanol to give the key fragment 1,4-diol **11** (97%). The chemoselective oxidation of 1,4-diol **11** using TEMPO and (diacetoxyiodo)benzene in dichloromethane gave the lactone **12** (87%).[10] Deprotection of the methoxymethyl ether **12** us-




**Scheme 2** Route A. *Reagents and conditions*: (a) *n*-hexanal, TFA, $CH_2Cl_2$, 3 h; then $K_2CO_3$, MeOH, 25 °C, 0.5 h, 52%; (b) $Et_3N$, TsCl, $CH_2Cl_2$, 0–25 °C, 3 h, 95%; (c) TBSCl, imidazole, DMAP, $CH_2Cl_2$, 0 to 25 °C, 3 h, 97%; (d) NaI, acetone, reflux, 24 h, 95%; (e) Zn, EtOH, reflux, 2 h, 92%; (f) MOMCl, DIPEA, DMAP, $CH_2Cl_2$, 0–25 °C, 3 h, 98%; (g) $Cy_2BH$, THF, 30% $H_2O_2$, NaOH, 77%; (h) TBAF, THF, 0–25 °C, 4 h, 97%; (i) TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$, 25 °C, 4 h, 87%; (j) TFA, $CH_2Cl_2$ (1:4 ), 0–25 °C, 2 h, 97%.




**Scheme 3** Route B. *Reagents and conditions*: (a) MOMCl, DIPEA, DMAP, $CH_2Cl_2$, 0 °C to r.t., 3 h, 98%; (b) $O_3$, TPP, $CH_2Cl_2$, –78 °C to r.t.; (c) $BnOCH_2C{\equiv}CH$, *n*-BuLi, THF, –78 °C, 2 h, 85%; (d) DEAD, TPP, *p*-nitrobenzoic acid, THF, 0 °C to r.t., 88%; (e) Pd/C, MeOH, r.t., 4 h, 97%; (f) 1. aq 3 M HCl, THF, 0 °C to r.t., 4 h, 2. 2,2-DMP, acetone, PTSA, r.t., 2 h; (g) TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$, 25 °C, 4 h, 87%; (h) TFA–$CH_2Cl_2$ (1:4), 0– 25 °C, 2 h, 97%.

ing trifluoroacetic acid in dichloromethane (1:4) gave the final product **1b** in 97% yield (overall yield 17%) (Scheme 3), which in all respects was identical to the reported one.[3]

Using the above two synthetic approaches, optically active **1a** and **1c** should be accessed readily.

In summary, we have described a stereoselective formal total synthesis of (4*S*,6*S*)-6-hydroxy-4-undecanolide (**1b**) employing two alternative strategies. These methods would be very useful to generate a wide variety of five-membered-ring lactones.

All reactions were carried out under inert atmosphere. Solvents were dried and purified by conventional methods prior to use. The progress of the reaction was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh) and neutral alumina using $Et_2O$, EtOAc, and hexanes as eluents. Optical rotation values were measured on PerkinElmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on PerkinElmer FT-IR spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded on Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FAB-MS.

### (2*S*,4*R*,6*S*)-2-(Hydroxymethyl)-6-pentyltetrahydro-2*H*-pyran-4-ol (4)

TFA (48.34 mL) was added slowly to a solution of **3** (3 g, 29.40 mmol) and *n*-hexanal (8.82 g, 88.23 mmol) in anhyd $CH_2Cl_2$ (95 mL) at 25 °C under $N_2$ atmosphere. The reaction mixture was stirred at r.t. for 3 h and then diluted with sat. aq $NaHCO_3$ (150 mL). The pH was then adjusted to >7 by the addition of $Et_3N$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 70 mL) and the organic layers were combined and the solvent was removed under reduced pressure. The trifluoroacetate obtained in this reaction was directly used in the next step without purification. The residue was dissolved in MeOH (40 mL) and stirred with $K_2CO_3$ (6.0 g) for 0.5 h. The mixture was extracted with $CH_2Cl_2$ (3 × 30 mL) and the combined organic layers were dried ($Na_2SO_4$) and the solvent was removed under reduced pressure. Purification of the crude by column chromatography on silica gel gave **4** (3.08 g, 52%) as a colorless gummy liquid; $R_f$ = 0.3 (silica gel, 60% EtOAc in hexane); $[\alpha]_D^{20}$ +2.4 (*c* 2.8, $CHCl_3$).

IR (neat): 3380, 2930, 2859, 1722, 1651, 1458, 1373, 1025 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.05–1.64 (m, 10 H), 1.78–1.84 (m, 1 H), 1.88–1.94 (m, 1 H), 3.26–3.60 (m, 4 H), 3.73–3.81 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.0, 31.6, 35.8, 36.7, 40.9, 65.6, 67.7, 75.2, 75.89.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{22}O_3$ + Na: 225.1466; found: 225.1471.

### [(2*S*,4*R*,6*S*)-4-6-Pentyltetrahydro-2*H*-pyran-2-yl]methyl 4-Methylbenzenesulfonate (5)

To stirred solution of diol **4** (2.5 g, 12.3 mmol) in anhyd $CH_2Cl_2$ (25 mL) was added $Et_3N$ (8.68 mL, 61.88 mmol) at 0 °C, and then TsCl (2.82 g, 14.8 mmol) was added over 2 h. The reaction mixture was allowed to warm to 25 °C and then allowed to stir for 3 h. The mixture was then treated with aq 1 M HCl (10 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (15 mL), followed by $H_2O$ (15 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure. Flash chromatography of the crude product afforded tosylate **5** (4.18 g, 95%) as a gummy liquid; $R_f$ = 0.6 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{20}$ –3.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3410, 2930, 2860, 1598, 1454, 1360, 1176, 1097, 1030, 979, 816, 668 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3 H), 1.03–1.49, (m, 10 H), 1.87–1.93 (m, 2 H), 2.44 (s, 3 H), 3.18–3.26 (m, 1 H), 3.50–3.58 (m, 1 H), 3.71–3.82 (m, 1 H), 3.94–4.05 (m, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 21.5, 22.4, 24.9, 31.6, 35.6, 36.7, 40.5, 67.4, 72.0, 72.6, 75.7, 127.8, 129.6, 132.7, 132.7, 144.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{28}O_5S$ + Na: 379.1555; found: 379.156.

**[(2*S*,4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-pentyltetrahydro-2*H*-pyran-2yl]methyl 4-Methylbenzenesulfonate (6)**

To a stirred solution of alcohol **5** (3.8 g, 10.67 mmol) in anhyd $CH_2Cl_2$ (30 mL) at 0 °C were added TBSCl (1.93 g, 12.8 mmol), DMAP (cat.), and imidazole (2.9 g, 42.6 mmol) successively, The mixture was stirred for 3 h at 25 °C, quenched with $H_2O$ (10 mL), and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried ($Na_2SO_4$). Removal of the solvent followed by purification by column chromatography afforded the pure product **6** (4.86 g, 97%) as a colorless liquid; $R_f$ = 0.7 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ –1.6 (*c* 2.0, $CHCl_3$).

IR (neat): 2931, 2857, 1598, 1463, 1364, 1254, 1178, 1122, 1079, 982, 837 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.85–0.9 (m, 12 H), 1.06–1.45 (m, 10 H), 1.69–1.77 (m, 2 H), 2.43 (s, 3 H), 3.16–3.23 (m, 1 H), 3.48–3.56 (s, 1 H), 3.65–3.76 (m, 1 H), 3.92–4.02 (m, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.5, 14.0, 18.0, 21.6, 22.5, 25.0, 25.7, 31.8, 35.7, 37.4, 41.2, 68.2, 72.2, 72.7, 75.8, 127.9, 129.7, 132.9, 144.6.

MS (ESI): *m*/*z* = 493 [M + Na].

***tert*-Butyl[(2*S*,4*R*,6*S*)-2-(iodomethyl)-6-pentyltetrahydro-2*H*-pyran-4-yloxy]dimethylsilane (7)**

To a solution of **6** (3.8 g, 8.08 mmol) in acetone (70 mL) was added NaI (6.06 g, 40.43 mmol) and the mixture was heated to reflux for 24 h. After completion, the solvent was removed under reduced pressure. The residue was quenched with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. Purification of the crude product by column chromatography gave **7** (3.27 g, 95%) as a colorless liquid; $R_f$ = 0.8 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ +10.8 (*c* 1.65, $CHCl_3$).

IR (neat): 2930, 2856, 1465, 1378, 1254, 1148, 1125, 1076, 893, 839, 774 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88–0.93 (m, 12 H), 1.06–1.57 (m, 10 H), 1.66–1.74 (m, 1 H), 1.97–2.06 (m, 1 H), 3.08–3.16 (m, 2 H), 3.21–3.38 (m, 2 H), 3.63–3.81 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.5, 9.0, 14.0, 18.0, 22.6, 25.2, 25.8, 31.7, 35.8, 41.3, 41.2, 68.5, 75.1, 75.9.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{35}IO_2Si$ + Na: 449.1348; found: 449.1365.

**(4*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)undec-1-en-6-ol (8)**

To a solution of iodide **7** (3.0 g, 7.04 mmol) in EtOH (90 mL) was added activated Zn dust (4.6 g, 70.36 mmol). The resulting mixture was stirred under reflux for 2 h and then cooled to 25 °C. Addition of solid $NH_4Cl$ (7.55 g) and $Et_2O$ (110 mL) followed by stirring for 5 min gave a gray suspension, which was filtered through Celite and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography gave **8** (1.94 g, 92%) as a colorless liquid; $R_f$ = 0.5 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ –0.7 (*c* 1.1, $CHCl_3$).

IR (neat): 3379, 2931, 2858, 1641, 1465, 1254, 1073, 999, 913, 835 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.83–0.97 (m, 12 H), 1.21–1.57 (m, 10 H), 2.33 (t, *J* = 7.3 Hz, 2 H), 2.82 (br, OH), 3.85–4.07 (m, 2 H), 4.97–5.09 (m, 2 H), 5.01–5.08 (m, 2 H), 5.61–5.82 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.5, –4.8, 14.0, 17.9, 22.6, 25.2, 25.7, 31.8, 37.9, 41.0, 41.2, 68.1, 71.2, 117.3, 134.6.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{36}O_2Si$ + Na: 323.2382; found: 323.2389.

**(5*S*,7*S*)-7-Allyl-9,9,10,10-tetramethyl-5-pentyl-2,4,8-trioxa-9-silaundecane (9)**

To a solution of alcohol **8** (1.8 g, 6 mmol) in anhyd $CH_2Cl_2$ (15 mL) at 0 °C were added successively DIPEA (3.10 mL, 17.95 mmol), DMAP (cat.), and MOMCl (0.96 g, 11.99 mmol). The mixture was stirred for 3 h at 25 °C, quenched with $H_2O$ (10 mL), and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford the pure product **9** (2.02 g, 98%) as a colorless liquid; $R_f$ = 0.7 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ +19.0 (*c* 1.5, $CHCl_3$).

IR (neat): 3076, 2953, 2930, 1640, 1466, 1379, 1253, 1150, 1044, 1001, 916, 834 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.88–0.92 (m, 12 H), 1.25–1.63 (m, 10 H), 2.20–2.24 (t, *J* = 6.4 Hz, 2 H), 3.34 (s, 3 H), 3.55–3.63 (m, 1 H), 3.81–3.89 (m, 1 H), 4.59 (s, 2 H), 5.01–5.05 (m, 2 H), 5.71–5.85 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.5, –4.0, 14.0, 18.0, 22.6, 24.7, 25.8, 31.9, 35.2, 42.3, 42.6, 55.4, 69.2, 75.7, 95.8, 116.9, 134.7.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{40}O_3Si$ + Na: 367.2644; found: 367.2631.

**(4*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(methoxymethoxy)undecan-1-ol (10)**

To a stirred solution of cyclohexene (2.64 mL, 26 mmol) in anhyd THF (2 mL) was added $Me_2S{\cdot}BH_3$ (1.22 mL, 13 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, and then a solution of **9** (1.50 g, 4 mmol) in anhyd THF (15 mL) was added slowly over 10–15 min at 0 °C. The resulting solution was allowed to warm to 25 °C and then allowed to stir for 6 h. Upon completion, the mixture was quenched at 0 °C with EtOH (5 mL), and treated with 1 M aq NaOH (21.8 mL, 21.8 mmol) and 30% $H_2O_2$ (10 mL, 87 mmol). After stirring at r.t. for 1 h, the resulting mixture was quenched with 1 M aq $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with 1 M aq $Na_2S_2O_3$ (10 mL) followed by brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography to afford the alcohol **10** (1.21 g, 77%) as a colorless liquid; $R_f$ = 0.3 (silica gel, 20% EtOAc in hexane); $[\alpha]_D^{20}$ +15.8 (*c* 1.2, $CHCl_3$).

IR (neat): 3417, 2931, 2858, 1466, 1380, 1253, 1212, 1150, 1041, 919, 835 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.88–0.89 (m, 12 H), 1.29–1.88 (m, 15 H), 3.34 (s, 3 H), 3.53–3.61 (m, 3 H), 3.83–3.90 (m, 1 H), 4.59 (s, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = –4.6, –4.1, 13.9, 18.0, 22.5, 24.0, 24.5, 25.4, 25.8, 27.7, 31.9, 41.9, 55.4, 69.3, 70.2, 75.6, 95.6.

MS (ESI): *m*/*z* = 385 [M + Na].

**(4*S*,6*S*)-6-(Methoxymethoxy)undecan-1,4-diol (11)**

To an ice cold solution of silyl ether **10** (0.75 g, 2.07 mmol) in anhyd THF (10 mL) was added TBAF (2.48 mL, M in THF, 2.48 mmol). After stirring for 15 min, the reaction mixture was brought to 25 °C and the stirring was continued for 4 h. The mixture was then cooled to 0 °C and quenched with sat. aq $NH_4Cl$ (10 mL) and

extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography to afford the alcohol **11** (0.49 mg, 97%) as a colorless gummy liquid; $R_f$ = 0.2 (silica gel, 20% EtOAc in hexane); $[\alpha]_D^{20}$ –17.1 (*c* 1.2, $CHCl_3$).

IR (neat): 3413, 2931, 1639, 1456, 1377, 1214, 1148, 1097, 1036, 914 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.7 Hz, 3 H), 1.12–1.28 (m, 6 H), 1.43–1.71 (m, 8 H), 2.74 (br, OH), 3.35 (s, 3 H), 3.56–3.66 (m, 2 H), 3.70–3.91 (m, 2 H), 4.58–4.68 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.0, 29.2, 31.8, 34.5, 34.7, 41.2, 55.7, 62.7, 67.7, 76.1, 96.2.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{28}O_4$ + Na: 271.1909; found: 271.1894.

**(4*S*)-4-(Methoxymethoxy)non-1-ene (15)**

To a solution of alcohol **14** (5.0 g, 35.2 mmol) in anhyd $CH_2Cl_2$ (25 mL) at 0 °C were added successively DIPEA (12.13 mL, 70.4 mmol), DMAP (20 mg, cat.), and MOMCl (8.02 mL, 105.5 mmol). The mixture was stirred for 3 h at 25 °C, quenched with $H_2O$ (25 mL), and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography to afford the pure product **15** (6.35 g, 97%) as a colorless liquid; $R_f$ = 0.8 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ –17.8 (*c* 1.5, $CHCl_3$).

IR (neat): 3367, 3019, 1215, 1096, 1038 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.26–1.47 (m, 8 H), 2.23–2.27 (m, 2 H), 3.33 (s, 3 H), 3.52–3.58 (m, 1 H), 4.57–4.63 (m, 2 H), 5.00–5.06 (m, 2 H), 5.72–5.83 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.9, 31.8, 34.0, 38.8, 55.3, 76.7, 95.2, 116.8, 134.7.

MS (ESI): *m*/*z* = 209 [M + Na].

**(3*S*)-3-(Methoxymethoxy)octanal (16)**

$O_3$ was bubbled through a solution of **15** (4.5 g, 24.19 mmol) in $CH_2Cl_2$ (35 mL) at –78 °C until no unreacted starting material was observed on TLC (eluent: 10% EtOAc in hexanes). The reaction mixture was then purged with $N_2$ to remove the excess $O_3$ and cooled to 0 °C. $Ph_3P$ (7.6 g, 29.0 mmol) was added and the mixture was stirred for 2 h and concentrated in vacuo. After adding hexane (10 mL), the mixture was filtered through a Celite pad and the residue was washed with hexane (30 mL). The filtrate was dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford the pure product **16** (3.64 g, 80%) as a colorless liquid; $R_f$ = 0.6 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{20}$ +20.1 (*c* 1.5, $CHCl_3$).

IR (neat): 3019, 2932, 1724, 1215, 1036, 758 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.7 Hz, 3 H), 1.16–1.60 (m, 8 H), 2.50–2.56 (m, 2 H), 3.28 (s, 3 H), 3.97–4.06 (m, 1 H), 4.57–4.63 (m, 2 H), 9.73 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.8, 31.7, 34.8, 48.7, 55.5, 73.1, 95.7, 201.4.

MS (ESI): *m*/*z* = 209 [M + Na].

**(4*S*,6*S*)-1-(Benzyloxy)-6-(methoxymethoxy)undec-2-yn-4-ol (17b)**

A solution of *n*-BuLi in hexane (14.73 mL, 19.14 mmol, 1.3 M solution in hexane) was added to a solution (10 mL) of *O*-benzylpropargyl alcohol (2.79 g, 19.11 mmol) in THF at –78 °C under $N_2$ atmosphere and the mixture was allowed to stir for 20 min. To this mixture, a solution of aldehyde **16** (3.0 g, 15.95 mmol) in anhyd THF (15 mL) was added. After stirring the mixture for 2 h at –78 °C, the reaction was quenched by sat. aq $NH_4Cl$ (15 mL), extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried ($Na_2SO_4$). Evaporation of the solvent followed by purification on column chromatography afforded alcohols **17b** (2.76 g 43%) and **17a** (2.70 g, 42%). Unwanted **17a** was converted into **17b** by Mitsunobu inversion; **17b** (total yield: 4.53 g, 70%) was obtained as a viscous liquid; $R_f$ = 0.4 ($SiO_2$, 30% EtOAc in hexane); $[\alpha]_D^{20}$ +23.5 (*c* 0.9, $CHCl_3$).

IR (neat): 3399, 3019, 2930, 1215, 1095, 757 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 6.7 Hz, 3 H), 1.26–1.30 (m, 6 H), 1.45–1.50 (m, 2 H), 1.79–1.84 (m, 2 H), 3.31 (s, 3 H), 3.36–3.41 (m, 1 H), 3.71–3.76 (m, 1 H), 4.14 (s, 2 H), 4.51 (s, 2 H), 4.55–4.63 (m, 2 H), 7.27 (m, 5 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.4, 31.8, 34.3, 42.4, 53.5, 55.7, 57.3, 71.5, 76.0, 80.6, 87.3, 95.3, 127.7, 127.9, 128.3, 137.3.

MS (ESI): *m*/*z* = 357 [M + Na].

**(4*S*,6*S*)-6-(Methoxymethoxy)undecan-1,4-diol (11)**

To a solution of **17b** (2.0 g) in anhyd MeOH (15 mL) was added a catalytic amount of 10% Pd/C and the resulting mixture was stirred under $H_2$ atmosphere at r.t. for 4 h. After completion, the catalyst was filtered and then washed with EtOAc (3 × 10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to afford the alcohol **11** (1.44 g, 97%) as a colorless gummy liquid; $R_f$ = 0.2 (silica gel, 20% EtOAc in hexane); $[\alpha]_D^{20}$ –17.1 (*c* 1.2, $CHCl_3$).

IR (neat): 3413, 2931, 1639, 1456, 1377, 1214, 1148, 1097, 1036, 914 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.7 Hz, 3 H), 1.12–1.28 (m, 6 H), 1.43–1.71 (m, 8 H), 2.74 (br, OH), 3.35 (s, 3 H), 3.56–3.66 (m, 2 H), 3.70–3.91 (m, 2 H), 4.58–4.68 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.0, 29.2, 31.8, 34.5, 34.7, 41.2, 55.7, 62.7, 67.7, 76.1, 96.2.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{28}O_4$ + Na: 271.1909; found: 271.1894.

**(*S*)-5-[(*S*)-2-(Methoxymethoxy)heptyl]dihydrofuran-2(3*H*)-one (12)**

To a stirred solution of diol **11** (0.23 g, 0.92 mmol) in anhyd $CH_2Cl_2$ (5 mL) were added sequentially $PhI(OAc)_2$ (943 mg, 2.93 mmol) and TEMPO (33 mg, 0.21 mmol). After stirring the reaction mixture at 25 °C for 3.5 h, sat. aq $Na_2S_2O_3$ (10 mL) was added, and the mixture was extracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (10 mL) and brine (6 mL), and concentrated in vacuo. The residue was subjected to column chromatography to afford the lactone **12** (0.196 g, 87%) as a colorless liquid; $R_f$ = 0.5 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{20}$ +48.5 (*c* 1.9, $CHCl_3$).

IR (neat): 2933, 1773, 1730, 1455, 1333, 1278, 1181, 1102, 1035, 918, 798, 737, 651 $cm^{-1}$.

$^1H$ NMR (300 MHz $CDCl_3$): δ = 0.90 (t, *J* = 6.7 Hz, 3 H), 1.30–1.61 (m, 8 H), 1.71–1.91 (m, 3 H), 2.28–2.39 (m, 1 H), 2.46–2.53 (m, 2 H), 3.35 (s, 3 H), 3.71–3.79 (m, 1 H), 4.57–4.71 (m, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.3, 24.2, 28.3, 29.6, 31.7, 34.7, 41.1, 55.4, 74.6, 77.7, 95.8, 176.8.

MS (ESI): *m*/*z* = 245 [M + 1].

**(*S*)-5-[(*S*)-2-Hydroxyheptyl]dihydrofuran-2(3*H*)-one (1b)**

To a solution of **12** (0.13 g, 0.53 mmol) in anhyd $CH_2Cl_2$ (0.92 mL) was added TFA (0.23 mL, 2.13 mmol) dropwise at 25 °C. After stirring the mixture at the same temperature for 2 h, it was quenched with sat. aq $NaHCO_3$ (6 mL) and extracted with $CH_2Cl_2$ (2 × 6 mL).

The combined organic extracts were washed with brine (6 mL) and concentrated in vacuo. The residue was purified by column chromatography to afford the pure alcohol **1b** (0.103 g, 97%) as a colorless oil; $R_f$ = 0.3 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{20}$ +59.6 (*c* 1.2, $Et_2O$).

IR (neat): 3445, 2929, 2859, 1767, 1460, 1420, 1359, 1185, 1036, 917, 766, 653 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.6 Hz, 3 H), 1.18–1.46 (m, 8 H), 1.69 (ddd, *J* = 3.5, 9.8, 14.3 Hz, 1 H), 1.78 (ddd, *J* = 2.8, 9.2 Hz, 1 H), 1.90 (ddt, *J* = 8.4, 9.4, 12.6 Hz, 1 H), 2.13 (br, OH), 2.25–2.36 (m, 1 H), 2.45–2.51 (m, 2 H), 3.76–3.85 (m, 1 H), 4.70–4.78 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.0, 28.4, 28.8, 31.6, 37.9, 43.1, 68.3, 78.1, 177.2.

HRMS (ESI): *m/z* calcd for $C_{11}H_{20}O_3$ + Na: 223.1310; found: 223.1336.

## Acknowledgment

P.A.N.R. and H.A. thank CSIR, New Delhi for the award of fellowships. The correspondence author acknowledges the partial support by King Saud University for Global Research Network for Organic Synthesis (GRNOS).

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