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Enantioselective synthesis of α-benzyloxy-ω-alkenals: application to the synthesis of (+)-*exo*-brevicomin, (+)-iso-*exo*-brevicomin, and (−)-isolaurepan

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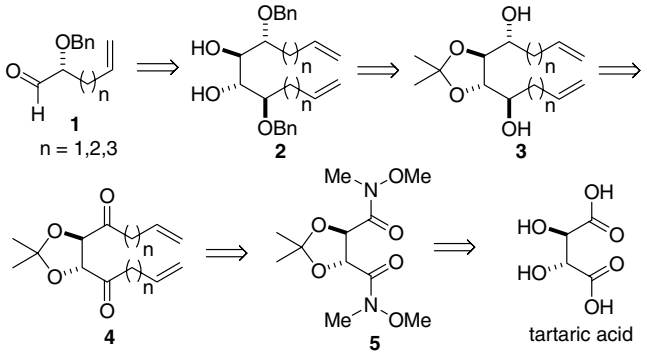
Abstract—The enantioselective synthesis of α-benzyloxy aldehydes containing a terminal alkene was carried out from chiral pool L-(+)-tartaric acid by employing the stereoselective reduction of a 1,4-diketone as the key step. The synthetic utility of these aldehydes was demonstrated in the synthesis of pine beetle pheromones (+)-*exo*-brevicomin, (+)-iso-*exo*-brevicomin and a formal synthesis of 2,7-*cis*-disubstituted oxepane (−)-isolaurepan.

1. Introduction

The synthesis of bio-active natural products from chiral pool sources is an attractive method in organic synthesis.[1] In this context, naturally occurring α-hydroxy carbonyl compounds have been extensively explored in natural product synthesis.[2] However, their higher homologues bearing a longer carbon chain with or without further functionalities are limited from chiral pool sources. These types of carbonyl compounds serve as excellent building blocks for the synthesis of 1,2-amino alcohols and 1,2-diols, which have numerous applications in the enantioselective synthesis of natural products.[3] We became interested in the synthesis of α-hydroxy aldehydes with an alkene tether, which could be further applied to the synthesis of a number of oxygen-containing heterocycles. Herein, we report, in detail, a general method[4] for the synthesis of α-hydroxy aldehydes having an alkene tether. Application of these aldehydes in the synthesis of pine beetle pheromones (+)-*exo*-brevicomin, (+)-iso-*exo*-brevicomin and a formal approach to 2,7-*cis*-disubstituted oxepane, (−)-isolaurepan, is demonstrated.

2. Results and discussion

Our approach for the synthesis of unsaturated α-benzyloxy aldehydes **1** is based on the cleavage of the 1,2-diol **2**, which is obtained by elaboration of the protected 1,4-diol **3**. The synthesis of **3** via the stereoselective reduction of the corresponding diketone **4** was envisaged. Bis-Weinreb amide **5**, derived from tartaric acid, was identified as the precursor for the synthesis of **4** (Scheme 1).



Scheme 1. Retrosynthesis of unsaturated α-benzyloxy aldehydes.

Thus diketones **4a–c** were prepared by addition of the respective Grignard reagents to bis-Weinreb amide **5**[5] derived from tartaric acid. The subsequent reduction of

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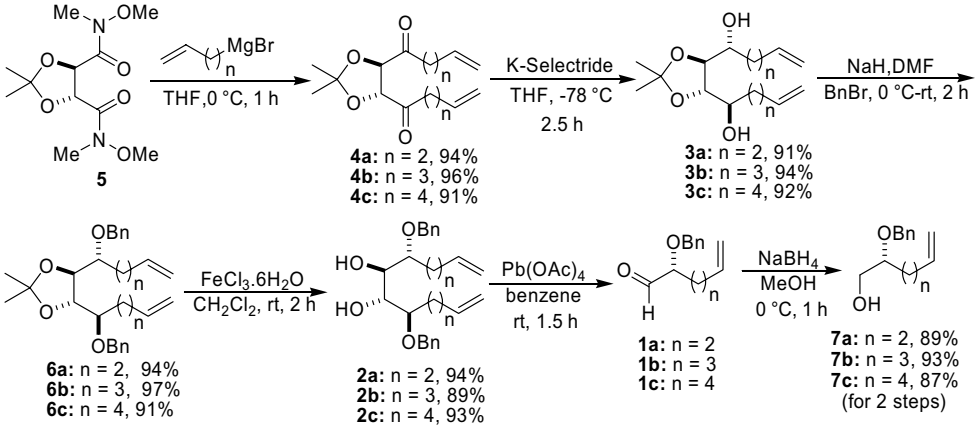


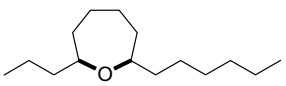
Scheme 2. Synthesis of unsaturated α-benzyloxy aldehydes.

4a–**c** with K-selectride resulted in a single diastereomer of diols **3a**–**c** in very high yields. The formation of the other possible two diastereomers (C_1-symmetric diastereomer and other C_2-symmetric diastereomer) was not observed within detectable limits by ^{1}H NMR. Protection of the diols as benzyl ethers **6a**–**c** was carried out with sodium hydride and benzyl bromide in almost quantitative yield. Facile deprotection of the acetonide in **6a**–**c** was accomplished by employing $FeCl_3{\cdot}6H_2O$ to afford 1,2-diols **2a**–**c** in good yields.[6] Reaction of **2a**–**c** with $Pb(OAc)_4$ in benzene resulted in the formation (2 mol) of aldehydes **1a**–**c**. Stereochemical integrity was preserved all through the transformations. The configuration at the newly formed stereogenic center was further established by comparing the specific rotation of alcohol **7b** {$[\alpha]_D = -11.8$ (*c* 1.9, $CHCl_3$), lit.[3e] $[\alpha]_D = -12.2$ (*c* 1.8, $CHCl_3$)} obtained from the reduction of aldehyde **1b** (Scheme 2).

The synthetic potential of these hydroxy aldehydes **1a**–**c** is widespread, and they serve as excellent precursors for a number of bio-active oxygen-containing compounds. To demonstrate the utility of these chiral aldehydes, synthesis of pine beetle pheromones (+)-*exo*-brevicomin **8**, (+)-iso-*exo*-brevicomin **9**, and 2,7-*cis*-disubstitued oxepane (−)-isolaurepan **10** was undertaken.

(+)-*exo*-brevicomin **8**

(+)-iso-*exo*-brevicomin **9**



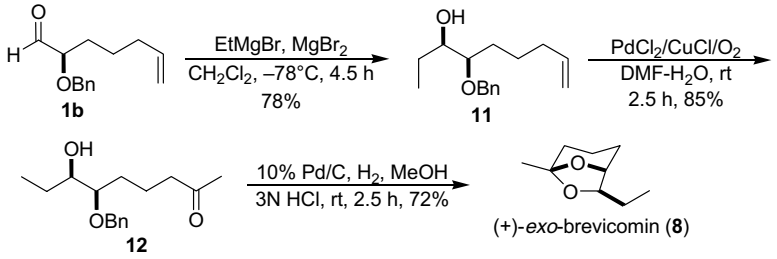
isolaurepan **10**

(+)-*exo*-Brevicomin **8**,[7] and (+)-iso-*exo*-brevicomin **9**[8] are aggregation pheromones produced by the Western pine beetle *Dendroctonus brevicomis* and *Dendroctonus ponderosae*, respectively, a principle pest in the timber regions of west coast of North America.

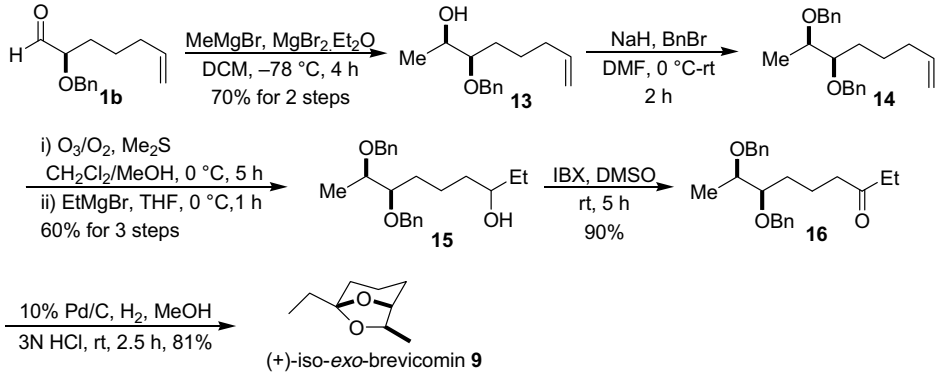
The synthesis of (+)-*exo*-brevicomin **8** is outlined in Scheme 3. Aldehyde **1b** was treated with ethylmagnesium bromide in the presence of $MgBr_2{\cdot}Et_2O$ in CH_2Cl_2 to yield the corresponding *threo* alcohol **11** as a single diastereomer in 78% yield.[9] Wacker oxidation[10] of alcohol **11** with $PdCl_2$/CuCl produced ketone **12** {$[\alpha]_D = -12.8$ (*c* 1.3, $CHCl_3$); lit.[11] $[\alpha]_D = +13.0$ (*c* 1.7, $CHCl_3$) for the corresponding enantiomer} in 85% yield. Hydrogenation of **12** with Pd/C in MeOH containing a trace of 3 N HCl resulted in (+)-*exo*-brevicomin **8** {$[\alpha]_D = +66.6$ (*c* 0.3, Et_2O); lit.[9] $[\alpha]_D = +66.7$ (*c* 1.40 Et_2O)} in 72% yield, formed via simultaneous debenzylation and intramolecular ketalization.

The synthesis of (+)-iso-*exo*-brevicomin **9**, was accomplished as shown in Scheme 4. The addition of MeMgBr to aldehyde **1b** under similar conditions to those employed for **11** furnished *threo* alcohol **13** in 70% yield. Protection of the hydroxyl group in **13** as the corresponding benzylether with NaH and benzyl bromide resulted in the dibenzylether **14**.[12] Ozonolysis of **14** furnished the corresponding aldehyde, which upon treatment with ethylmagnesium bromide afforded **15** as a mixture of diastereomers. Oxidation of alcohol **15** with IBX in DMSO produced ketone **16** in 90% yield. Treatment of **16** with Pd/C in MeOH containing a trace of 3 M HCl, cleanly produced (+)-iso-*exo*-brevicomin {$[\alpha]_D = +54$ (*c* 0.5, $CHCl_3$); lit.[8a] $[\alpha]_D = -54.3$ (*c* 1.34, $CHCl_3$)} in 81% yield.

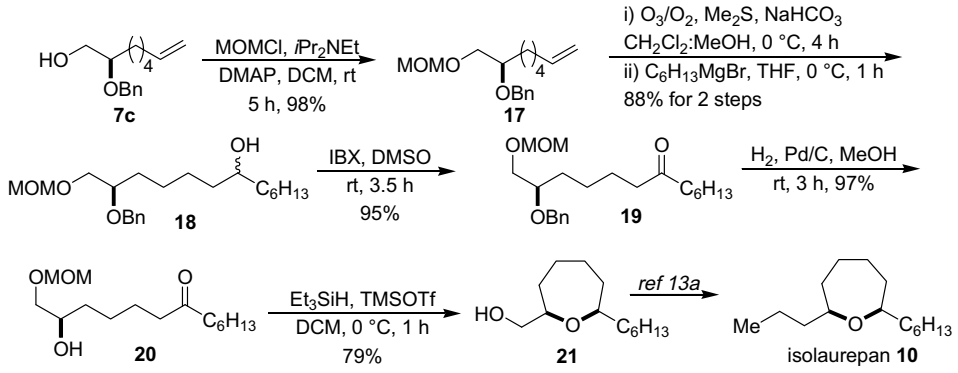
The synthesis of (−)-isolaurepan **10** began with the protection of alcohol **7c** to the corresponding MOM ether employing methoxymethyl chloride (MOMCl) and Hunig's base in the presence of a catalytic amount of DMAP furnished **17** in 98% yield. Ozonolysis of the alkene in **17**, followed by addition of *n*-hexylmagnesium bromide furnished alcohol **18** as a mixture of diastereomers. The diastereomeric ratio is of no consequence as it is oxidized to ketone **19** with IBX in DMSO. Hydrogenation of **19** with 10% Pd/C as catalyst in MeOH resulted in alcohol **20** in 97% yield. The reaction of **20** with Et_3SiH in the presence of TMSOTf cleanly produced alcohol **21** in 79% yield. Since the conversion of **21** to isolaurepan **10** is already reported in the literature,[13a] the present sequence constitutes a formal synthesis of (−)-isolaurepan **10** (Scheme 5).



Scheme 3. Synthesis of (+)-*exo*-brevicomin **8**.



Scheme 4. Synthesis of (+)-iso-*exo*-brevicomin **9**.



Scheme 5. Formal synthesis of (−)-isolaurepan **10**.

3. Conclusion

In conclusion, we have developed an efficient enantioselective strategy for the synthesis of unsaturated α-benzyloxy aldehydes from chiral pool tartaric acid. The sequence is highly selective comprising simple transformations. The utility of these aldehydes was further demonstrated by applying it to the stereoselective synthesis of pheromones, such as (+)-*exo*-brevicomin, (+)-iso-*exo*-brevicomin and 2,7-disubstituted oxepane (−)-isolaurepan.

4. Experimental

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points are uncorrected. Unless otherwise stated, ^{1}H NMR and ^{13}C NMR spectra were recorded either on a bruker AC400 or on a JEOL300 machine in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all the reactions were performed under inert atmosphere.

4.2. General procedure for the preparation of (4*R*,5*R*)-4,5-dialkenoyl-2,2-dimethyl-1,3-dioxolanes 4a–c

In an oven dried two neck 50 mL round-bottomed flask equipped with magnetic stir bar and an argon inlet, was placed bis-Weinreb amide **5** (0.5 g, 1.8 mmol) dissolved in

5 mL of THF. The reaction mixture was cooled to 0 °C and a THF solution of alkenylmagnesium bromide (12 mL of 0.6 M solution in THF, 7.2 mmol) was added dropwise over 10 min under argon atmosphere. The reaction mixture was stirred for 2.5 h at the same temperature, during which the reaction was complete (TLC). It was then quenched with saturated NH_4Cl (5 mL), poured into water (10 mL), and extracted with diethyl ether (3×10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography of the residue using petroleum ether–ethyl acetate (9:1) as an eluent yielded diketones **4a**–**c**.

4.2.1. (4*R*,5*R*)-4,5-Bis(pent-4-enoyl)-2,2-dimethyl-1,3-dioxolane 4a. Colorless oil; Yield: 94%; $[\alpha]_D = +10.5$ (*c* 1.8, $CHCl_3$); IR (neat): 2987, 2919, 1720, 1382, 1211, 1081, 998, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (ddt, $J = 16.8$, 10.5, 6.6 Hz, 2H), 5.04–4.89 (m, 4H), 4.51 (s, 2H), 2.80–2.59 (m, 4H), 2.36–2.24 (m, 4H), 1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.6, 136.6, 115.4, 112.4, 81.3, 38.1, 26.9, 26.1; HRMS for $C_{15}H_{22}O_4$+Na calcd 289.1416; found 289.1434.

4.2.2. (4*R*,5*R*)-4,5-Bis(hex-5-enoyl)-2,2-dimethyl-1,3-dioxolane 4b. Colorless oil; Yield 96%; $[\alpha]_D = +11.6$ (*c* 1.2, $CHCl_3$); IR (neat): 2937, 1725, 1455, 1375, 1259, 1153, 995, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.77 (ddt, $J = 17.1$, 10.2, 6.6 Hz, 2H), 5.08–4.95 (m, 4H), 4.55 (s, 2H), 2.76–2.55 (m, 4H), 2.14–2.03 (m, 4H), 1.78–1.66 (m, 4H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 137.8, 115.4, 112.4, 81.5, 38.2, 32.9, 26.2, 22.1; HRMS for $C_{17}H_{26}O_4$+Na calcd 317.1729; found 317.1742.

4.2.3. (4*R*,5*R*)-4,5-Bis(hept-6-enoyl)-2,2-dimethyl-1,3-dioxolane 4c. Colorless oil; Yield 91%; $[\alpha]_D = +10.0$ (*c* 1.0, $CHCl_3$); IR (neat): 2937, 2865, 1724, 1640, 1456, 1383, 1212, 1085, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (ddt, $J = 17.1$, 10.5, 6.6 Hz, 2H), 5.09–4.93 (m, 4H), 4.55 (s, 2H), 2.69 (dt, $J = 18.0$, 7.5 Hz, 2H), 2.62 (dt, $J = 18.0$, 7.2 Hz, 2H), 2.16–2.02 (m, 4H), 1.72–1.56 (m, 4H), 1.54–1.34 (m, 4H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5, 138.3, 114.7, 112.3, 81.4, 38.8, 33.4, 28.3, 26.1, 22.5; HRMS for $C_{19}H_{30}O_4$+Na calcd 345.2042; found 345.2032.

4.3. General procedure for the preparation of (4*S*,5*S*)-4,5-bis((*R*)-1-hydroxyalkenyl)-2,2-dimethyl-1,3-dioxolanes 3a–c

To a solution of **4a**–**c** (1.1 mmol) in 8 mL of THF at −78 °C under an argon atmosphere was added K-Selectride (4 mL of 1 M solution in THF, 4 mmol) dropwise over a period of 10 min. The reaction mixture was stirred for 2.5 h at −78 °C, quenched with 4 mL of 2 M NaOH and 2 mL of 30% H_2O_2 (w/v in water) at the same temperature and stirred for 3 h at room temperature. It was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (30 mL). The combined ethereal layer was washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether–ethyl acetate (8:2) as an eluent afforded **3a**–**c**.

4.3.1. (4*S*,5*S*)-4,5-Bis((*R*)-1-hydroxypent-4-enyl)-2,2-dimethyl-1,3-dioxolane 3a. Colorless oil; Yield 91%; $[\alpha]_D = -7.8$ (*c* 2.8, $CHCl_3$); IR (neat): 3445, 2985, 1641, 1454, 1379, 1245, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (ddt, $J = 17.1$, 10.5, 6.6 Hz, 2H), 5.12–4.95 (m, 4H), 3.92 (s, 2H), 3.54 (br s, 2H), 2.37–2.10 (m, 4H), 2.09–1.96 (br m, 2H, exchangeable with D_2O), 1.75–1.49 (m, 4H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 115.1, 109.3, 79.8, 69.3, 34.0, 29.9, 27.3; HRMS for $C_{15}H_{26}O_4$+Na calcd 293.1729; found 293.1723.

4.3.2. (4*S*,5*S*)-4,5-Bis((*R*)-1-hydroxyhex-5-enyl)-2,2-dimethyl-1,3-dioxolane 3b. Colorless oil; Yield 94%; $[\alpha]_D = -7.5$ (*c* 1.1, $CHCl_3$); IR (neat): 3446, 2985, 1457, 1380, 1240, 1166, 1072, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 2H), 5.07–4.93 (m, 4H), 3.90 (s, 2H), 3.50 (br s, 2H), 2.15–2.04 (m, 4H), 2.03–1.94 (br m, 2H, exchangeable with D_2O), 1.71–1.35 (m, 8H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 114.8, 109.3, 79.9, 69.9, 34.3, 33.5, 27.3, 24.9; HRMS for $C_{17}H_{30}O_4$+Na calcd 321.2042; found 321.2043.

4.3.3. (4*S*,5*S*)-4,5-Bis((*R*)-1-hydroxyhept-6-enyl)-2,2-dimethyl-1,3-dioxolane 3c. Colorless oil; Yield 92%; $[\alpha]_D = -8.6$ (*c* 3.0, $CHCl_3$); IR (neat): 3459, 2932, 2859, 1640, 1457, 1380, 1240, 1120, 1071, 992, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (ddt, $J = 16.9$, 10.5, 6.6 Hz, 2H), 5.12–4.88 (m, 4H), 3.91 (s, 2H), 3.49 (br m, 2H), 2.15–2.01 (m, 6H), 1.65–1.34 (m, 12H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 114.4, 109.2, 79.9, 69.9, 34.7, 33.6, 28.7, 27.3, 25.2; HRMS for $C_{19}H_{34}O_4$+Na calcd 349.2355; found 349.2359.

4.4. General procedure for the preparation of (4*S*,5*S*)-4,5-bis((*R*)-1-benzyloxyalkenyl)-2,2-dimethyl-1,3-dioxolanes 6a–c

To a solution of **3a**–**c** (0.9 mmol) in 5 mL of dry DMF at 0 °C was added NaH (0.15 g of 60% suspension in mineral oil, 3.6 mmol) portionwise. After stirring the reaction mixture for 45 min at 0 °C, benzyl bromide (0.4 mL, 3.6 mmol) was introduced to the suspension dropwise at the same temperature and stirred for 2 h at 0 °C. After the reaction was complete (monitored by TLC), it was cautiously quenched with water (1.5 mL), poured into water (10 mL), and extracted with diethyl ether (3×10 mL). The combined ether layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent under reduced pressure followed by column chromatography of the resultant residue using petroleum ether–ethyl acetate (95:5) as an eluent yielded dibenzylethers **6a**–**c**.

4.4.1. (4*S*,5*S*)-4,5-Bis((*R*)-1-(benzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane 6a. Colorless oil; Yield 94%; $[\alpha]_D = -7.6$ (*c* 1.7, $CHCl_3$); IR (neat): 2984, 2933, 1640, 1453, 1370, 1250, 1072, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.23 (m, 10H), 5.77 (ddt, $J = 17.2$, 10.2, 6.6 Hz, 2H), 5.06–4.92 (m, 4H), 4.59 and 4.53 (AB q, $J = 11.4$ Hz, 4H), 4.12 (s, 2H), 3.46–3.39 (br m, 2H), 2.23–2.06 (m, 4H), 1.74–1.63 (m, 4H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.2, 128.3, 127.8,

127.6, 114.9, 108.8, 77.9, 77.4, 72.4, 30.0, 29.9, 27.2; HRMS for $C_{29}H_{38}O_4$+Na calcd 473.2668; found 473.2663.

4.4.2. (4*S*,5*S*)-4,5-Bis((*R*)-1-(benzyloxy)hex-5-enyl)-2,2-dimethyl-1,3-dioxolane 6b. Colorless oil; Yield 97%; $[\alpha]_D = -8.1$ (*c* 2.5, $CHCl_3$); IR (neat): 2983, 2861, 1639, 1454, 1369, 1249, 1072, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 10H), 5.77 (ddt, $J = 17.4$, 10.2, 6.6 Hz, 2H), 5.03–4.91 (m, 4H), 4.60 and 4.52 (AB q, $J = 11.7$ Hz, 4H), 4.10 (s, 2H), 3.41–3.35 (m, 2H), 2.08–1.98 (m, 4H), 1.65–1.36 (m, 8H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.5, 128.3, 127.9, 127.6, 114.7, 108.8, 78.1, 78.0, 72.4, 33.7, 30.3, 27.2, 25.2; HRMS for $C_{31}H_{42}O_4$+Na calcd 501.2981; found 501.3000.

4.4.3. (4*S*,5*S*)-4,5-Bis((*R*)-1-(benzyloxy)hept-6-enyl)-2,2-dimethyl-1,3-dioxolane 6c. Colorless oil; Yield 91%; $[\alpha]_D = -6.4$ (*c* 2.5, $CHCl_3$); IR (neat): 2932, 2860, 1639, 1454, 1379, 1270, 1070, 911, 751, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.20 (m, 10H), 5.78 (ddt, $J = 17.1$, 10.2, 6.6 Hz, 2H), 5.06–4.90 (m, 4H), 4.60 and 4.51 (AB q, $J = 11.7$ Hz, 4H), 4.10 (s, 2H), 3.36 (br t, $J = 6.3$ Hz, 2H), 2.08–1.98 (m, 4H), 1.66–1.54 (m, 4H), 1.48–1.27 (m, 8H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.5, 128.3, 127.8, 127.5, 114.4, 108.6, 77.9, 72.3, 33.6, 30.6, 28.9, 27.2, 25.5; HRMS for $C_{33}H_{46}O_4$+Na calcd 529.3294; found 529.3294.

4.5. General procedure for the preparation of bis(benzyloxy)-alkene-diols 2a–c

To a solution of **6a**–**c** in 5 mL of dry dichloromethane at room temperature was added $FeCl_3{\cdot}6H_2O$ (0.85 g, 3.2 mmol) under an argon atmosphere. The reaction mixture was stirred for 2.5 h at room temperature, and then filtered through a short pad of Celite. The Celite pad was then washed with dichloromethane (25 mL). The combined organic layer was washed with satd $NaHCO_3$ (3×15 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of resultant residue by column chromatography using petroleum ether–ethyl acetate (3:1) resulted in **2a**–**c**.

4.5.1. (5*R*,6*R*,7*R*,8*R*)-5,8-Bis(benzyloxy)dodeca-1,11-diene-6,7-diol 2a. Colorless oil; Yield 94%; $[\alpha]_D = -24.4$ (*c* 1.8, $CHCl_3$); IR (neat): 3440, 3295, 2923, 2850, 1641, 1454, 1398, 1099, 997, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.25 (m, 10H), 5.81 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 2H), 5.07–4.94 (m, 4H), 4.64 and 4.49 (AB q, $J = 11.4$ Hz, 4H), 3.66 (t, $J = 3.9$ Hz, 2H), 3.56 (q, $J = 5.4$ Hz, 2H), 2.80 (d, $J = 4.5$ Hz, 2H), 2.22–2.08 (m, 4H), 1.87–1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 138.1, 128.5, 127.9, 127.8, 114.9, 80.1, 72.3, 71.7, 29.4, 29.2; HRMS for $C_{26}H_{34}O_4$+Na calcd 433.2355; found 433.2346.

4.5.2. (6*R*,7*R*,8*R*,9*R*)-6,9-Bis(benzyloxy)tetradeca-1,13-diene-7,8-diol 2b. Colorless oil; Yield 89%; $[\alpha]_D = -25.8$ (*c* 2.1, $CHCl_3$); IR (neat): 3437, 2930, 2862, 1638, 1455, 1088, 910, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 10H), 5.78 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 2H), 5.06–4.93 (m, 4H), 4.64 and 4.48 (AB q, $J = 11.4$ Hz, 4H), 3.63 (t, $J = 4.2$ Hz, 2H), 3.54 (q, $J = 5.4$ Hz, 2H), 2.80 (d, $J = 4.2$ Hz, 2H), 2.12–2.00 (m, 4H), 1.79–1.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.2, 128.5, 127.9, 127.8, 114.8, 80.5, 72.3, 71.9, 33.8, 29.4, 24.5; HRMS for $C_{28}H_{38}O_4$+Na calcd 461.2668; found 461.2657.

4.5.3. (7*R*,8*R*,9*R*,10*R*)-7,10-Bis(benzyloxy)hexadeca-1,15-diene-8,9-diol 2c. White solid; Yield 93%; mp 49.5–50.5 °C; $[\alpha]_D = -27.7$ (*c* 2.7, $CHCl_3$); IR (KBr): 3460, 2929, 2859, 1639, 1496, 1454, 1207, 1069, 910, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.22 (m, 10H), 5.79 (ddt, $J = 16.9$, 10.2, 6.6 Hz, 2H), 5.07–4.91 (m, 4H), 4.63 and 4.47 (AB q, $J = 11.4$ Hz, 4H), 3.63 (br t, $J = 4.2$ Hz, 2H), 3.60–3.49 (m, 2H), 2.82 (d, $J = 4.2$ Hz, 2H, exchangeable with D_2O), 2.13–1.98 (m, 4H), 1.79–1.52 (m, 4H), 1.50–1.29 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.1, 128.4, 127.9, 127.8, 114.4, 80.5, 72.1, 71.8, 33.6, 29.6, 29.1, 24.6; HRMS for $C_{30}H_{42}O_4$+Na calcd 489.2981; found 489.2984.

4.6. General procedure for the preparation of (*R*)-2-(benzyloxy)alken-1-ol 7a–c

To a solution of **2a**–**c** (0.34 mmol) in 3 mL of benzene at room temperature was added $Pb(OAc)_4$ (0.27 g, 0.6 mmol) under an argon atmosphere. The reaction mixture was stirred for 1.5 h at the same temperature, quenched with 0.2 mL of water and then stirred for 10 min at room temperature after which it was filtered through a short pad of Celite. The Celite pad was washed with dichloromethane (25 mL) and the combined organic layers dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield α-benzyloxy aldehyde **1a**–**c** as colorless oil, which was used as such without further purification.

To a solution of α-benzyloxy aldehyde **1a**–**c** (obtained above) in 5 mL of MeOH at 0 °C was added $NaBH_4$ (52 mg, 1.36 mmol) under an argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature. It was quenched by the cautious addition of water and extracted with diethyl ether (3×5 mL). The ether layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. The residue thus obtained was subjected to column chromatography using petroleum ether–ethyl acetate (8:2) as an eluent to yield **7a**–**c**.

4.6.1. (*R*)-2-(Benzyloxy)hex-5-en-1-ol 7a. Colorless oil; Yield 89%; $[\alpha]_D = -10.8$ (*c* 3.5, $CHCl_3$); IR (neat): 3413, 2923, 2863, 1639, 1454, 1058, 912, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 5H), 5.79 (ddt, $J = 17.1$, 10.2, 6.6 Hz, 1H), 5.07–4.91 (m, 2H), 4.60 and 4.54 (AB q, $J = 11.4$ Hz, 2H), 3.74–3.62 (m, 1H), 3.59–3.46 (m, 2H), 2.18–2.07 (m, 3H), 1.79–1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 138.1, 128.4, 127.7, 114.9, 79.1, 71.5, 64.0, 30.0, 29.5; HRMS for $C_{13}H_{18}O_2$+Na calcd 229.1204; found 229.1193.

4.6.2. (*R*)-2-(Benzyloxy)hept-6-en-1-ol 7b. Colorless oil; Yield 93%; $[\alpha]_D = -11.8$ (*c* 1.9, $CHCl_3$); lit.[3e] $[\alpha]_D = -12.2$ (*c* 1.8, $CHCl_3$); IR (neat): 3415, 2933, 2861, 1639, 1454, 1396, 1066, 910, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):

δ 7.40–7.22 (m, 5H), 5.79 (ddt, $J = 17.1$, 10.5, 6.6 Hz, 1H), 5.06–4.89 (m, 2H), 4.62 and 4.55 (AB q, $J = 11.7$ Hz, 2H), 3.76–3.63 (m, 1H), 3.58–3.42 (m, 2H), 2.11–1.96 (m, 3H), 1.70–1.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.5, 127.7, 114.8, 79.6, 71.5, 64.2, 33.7, 30.2, 24.6.

4.6.3. (*R*)-2-(Benzyloxy)oct-7-en-1-ol 7c. Colorless oil; Yield 87%; $[\alpha]_D = -14.7$ (*c* 1.9, $CHCl_3$); IR (neat): 3425, 2931, 2859, 1639, 4545, 1349, 1207, 1068, 910, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.21 (m, 5H), 5.79 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.06–4.90 (m, 2H), 4.61 and 4.53 (AB q, $J = 11.7$ Hz, 2H), 3.75–3.66 (m, 1H), 3.59–3.44 (m, 2H), 2.19–1.96 (m, 3H), 1.75–1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.4, 128.4, 127.7, 127.7, 114.4, 79.7, 71.5, 64.2, 33.6, 30.6, 28.9, 24.8; HRMS for $C_{15}H_{22}O_2$+Na calcd 257.1517; found 257.1517.

4.7. Preparation of (3*R*,4*R*)-4-(benzyloxy)non-8-en-3-ol 11

A suspension of **1b** (0.11 g, 0.50 mmol) and $MgBr_2{\cdot}Et_2O$ (0.19 g, 0.75 mmol) in 3 mL of dichloromethane at −78 °C, under an argon atmosphere was stirred for 1 h. Ethylmagnesium bromide (0.25 mL of 3 M solution in diethyl ether, 0.75 mmol) was introduced dropwise via syringe over a period of 2 min at the same temperature. The reaction mixture was stirred for 2 h at −78 °C and quenched with saturated NH_4Cl (5 mL). It was extracted with diethyl ether (3 × 10 mL) and the combined ethereal extracts were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue using petroleum ether–ethyl acetate (97:3) as an eluent resulted in **11** as colorless oil in 78% (0.1 g) yield. $[\alpha]_D = +18.3$ (*c* 3.0, Et_2O); IR (neat): 3433, 2931, 2869, 1640, 1454, 1067, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 5H), 5.80 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.07–4.93 (m, 2H), 4.65 and 4.50 (AB q, $J = 11.4$ Hz, 1H), 3.50–3.43 (m, 1H), 3.30 (q, $J = 6.0$ Hz, 1H), 2.12–2.02 (m, 2H), 1.70–1.40 (m, 6H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 138.4, 128.4, 127.8, 127.7, 114.8, 81.9, 74.1, 72.4, 33.9, 29.7, 26.3, 24.3, 10.2; HRMS for $C_{16}H_{24}O_2$+Na calcd 271.1674; found 271.1668.

4.8. Preparation of (6*R*,7*R*)-6-(benzyloxy)-7-hydroxynonan-2-one 12

A mixture of $PdCl_2$ (3.5 mg, 0.02 mmol, 5 mol %) and CuCl (196 mg, 2 mmol) in 15 mL of 4:1 DMF–H_2O at room temperature was stirred for 1 h, under an O_2 atmosphere. A DMF solution of **11** (0.1 g, 0.4 mmol) was then introduced at room temperature. The reaction mixture was stirred for 2 h at the same temperature, quenched with 3 M HCl and extracted with diethyl ether (3 × 10 mL). The combined ether layers were washed with brine (10 mL) and dried over Na_2SO_4. Residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether–ethyl acetate (98:2) as eluent to yield **12** as colorless oil (0.09 g, 85%). $[\alpha]_D = -12.8$ (*c* 1.3, $CHCl_3$); lit.[11] $[\alpha]_D = -13.0$ (*c* 1.7, $CHCl_3$); IR (neat): 3455, 2932, 2875, 1710, 1455, 1362, 1163, 1069, 973 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.25 (m, 5H), 4.65 and 4.51 (AB q, $J = 11.3$ Hz, 1H), 3.51–3.44 (m, 1H), 3.43 (q, $J = 5.2$ Hz, 1H), 2.44 (t, $J = 6.8$ Hz, 2H), 2.37–2.26 (br m, 1H), 2.12 (s, 3H), 1.70–1.41 (m, 6H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 138.3, 128.5, 127.9, 127.8, 81.7, 73.9, 72.5, 43.7, 29.9, 29.7, 26.3, 19.3, 10.2; HRMS for $C_{16}H_{24}O_3$+Na calcd 287.1623; found 287.1620.

4.9. Preparation of (+)-*exo*-brevicomin 8

To a methanol (1.5 mL) solution of **12** (40 mg, 0.15 mmol) was added activated 10% Pd/C (10 mg) and 0.02 mL of 3 M HCl at room temperature. The reaction mixture was stirred for 2.5 h under a hydrogen atmosphere (balloon). It was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). Evaporation of the solvent followed by column chromatography of the residue using pentane–diethyl ether (96:4) as an eluent afforded (+)-*exo*-brevicomin **8** as a highly volatile colorless oil in 72% (16 mg) yield. $[\alpha]_D = +66.6$ (*c* 0.3, Et_2O); lit.[9] $[\alpha]_D = +66.7$ (*c* 1.4, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (br s, 1H), 3.94 (t, $J = 6.5$ Hz, 1H), 1.93–1.76 (m, 2H), 1.64–1.41 (m, 6H), 1.42 (s, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.7, 81.1, 78.3, 34.9, 28.5, 27.9, 25.0, 17.2, 9.8.

4.10. Preparation of (2*R*,3*R*)-3-(benzyloxy)oct-7-en-2-ol 13

A suspension of **1b** (0.25 g, 1.1 mmol) and $MgBr_2{\cdot}Et_2O$ (0.44 g, 1.7 mmol) in 5 mL of dichloromethane at −78 °C was stirred for 1 h, under an argon atmosphere. Methylmagnesium bromide (0.6 mL of 3 M solution in diethyl ether, 1.8 mmol) was introduced dropwise via syringe over a period of 5 min at the same temperature. The reaction mixture was stirred for 2 h, quenched with saturated NH_4Cl (6 mL), and extracted with diethyl ether (3 × 10 mL). Combined ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether–ethyl acetate (97:3) as an eluent to afford **13** as a colorless oil in 70% (0.18 mg). $[\alpha]_D = -24.3$ (*c* 1.1, $CHCl_3$); IR (neat): 3440, 2925, 1455, 1070, 910, 734, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.23 (m, 5H), 5.79 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.05–4.93 (m, 2H), 4.65 and 4.49 (AB q, $J = 11.4$ Hz, 1H), 3.74 (quin, $J = 6.3$ Hz, 1H), 3.22 (q, $J = 5.7$ Hz, 1H), 2.10–2.02 (m, 2H), 1.69–1.42 (m, 4H), 1.17 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.3, 128.4, 127.8, 127.7, 114.7, 83.8, 72.4, 68.8, 33.8, 29.4, 24.0, 18.9; HRMS for $C_{15}H_{22}O_2$+Na calcd 257.1517; found 257.1514.

4.11. Preparation of (7*R*,8*R*)-7,8-bis(benzyloxy)nonan-3-ol 15

To a pre-cooled (0 °C) DMF (3 mL) solution of **13** (0.15 g, 0.64 mmol) was added NaH (0.05 g of 60% suspension in mineral oil, 1.3 mmol) portionwise. The reaction mixture was stirred for 1 h at 0 °C and benzyl bromide (0.9 mL, 7.5 mmol) was introduced. The reaction mixture was stirred for an additional 1 h at 0 °C and quenched by the cautious addition of water (4 mL). It was extracted with diethyl ether (3 × 10 mL) and the combined ether layers

were washed with brine (5 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was used as such for the next step.

Ozone was bubbled through a pre-cooled (−78 °C) solution of the benzyl ether (obtained above) in dichloromethane–methanol (4:1, 12.5 mL) containing solid $NaHCO_3$ (10 mg) till the pale blue color persisted. Excess ozone was flushed off with oxygen and Me_2S (0.2 mL) was added and stirred for 5 h at 0 °C. The reaction mixture was concentrated under reduced pressure and dissolved in diethyl ether. It was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (20 mL). The ether layers were combined and evaporation of solvent afforded the crude aldehyde, which was subjected to Grignard reaction without further purification.

To a pre-cooled (0 °C) THF solution (3 mL) of aldehyde (obtained above), under an argon atmosphere was added a THF solution of ethylmagnesium bromide (1 mL, 1 M solution in THF, 1 mmol) dropwise over a period of 3 min. The reaction mixture was stirred for 1 h at the same temperature. After the reaction was complete (as indicated by TLC), it was quenched with saturated NH_4Cl (3 mL), poured into water (15 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether–ethyl acetate (85:15) as eluent to yield **15** (mixture of diastereomers) as a colorless oil (0.13 g, 60% for three steps). IR (neat): 3413, 2921, 2857, 1454, 1369, 1099, 1027, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (for the mixture of diastereomers): δ 7.37–7.24 (m, 10H), 4.68–4.47 (m, 4H), 3.67 (quin, $J = 6.0$ Hz, 1H), 3.48–3.38 (m, 2H), 1.61–1.20 (m, 8H), 1.17 (d, $J = 6.3$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 138.8, 128.5, 128.3, 127.6, 127.5, 127.4, 126.9, 81.4, 75.8, 75.7, 73.2, 73.1, 72.8, 72.7, 71.2, 36.9, 30.1, 30.0, 29.7, 29.6, 21.9, 21.8, 15.0, 9.8; HRMS for $C_{23}H_{32}O_3$+Na calcd 379.2249; found 379.2267.

4.12. Preparation of (7*R*,8*R*)-7,8-bis(benzyloxy)nonan-3-one 16

A mixture of **15** (0.1 g, 0.28 mmol) and IBX (0.19 g, 0.7 mmol) in 5 mL of DMSO was stirred for 5 h at room temperature. After the reaction was complete (indicated by TLC), it was quenched with 1 mL of water at 0 °C and stirred for 5 min. The white precipitate, which was formed, was filtered off through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). The ether layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using petroleum ether–ethyl acetate (9:1) as eluent gave **16** in 90% (0.09 g) yield as a colorless oil. $[\alpha]_D = +9.1$ (*c* 3.2, $CHCl_3$); IR (neat): 2931, 2873, 1712, 1454, 1376, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.23 (m, 10H), 4.63 and 4.51 (AB q, $J = 11.4$ Hz, 2H), 4.61 and 4.50 (AB q, $J = 11.7$ Hz, 2H), 3.67 (quin, $J = 6.0$ Hz, 1H), 3.44–3.38 (m, 1H), 2.40–2.31 (m, 4H), 1.76–1.41 (m, 4H), 1.16 (d, $J = 6.0$ Hz, 3H), 1.02 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.5, 138.8, 138.7, 128.2, 127.9, 127.6, 127.5, 127.4, 81.1, 75.6, 72.7, 71.2, 42.3, 35.7, 29.2, 20.2, 14.9, 7.8; HRMS for $C_{23}H_{30}O_3$+Na calcd 377.2093; found 377.2082.

4.13. Preparation of (+)-iso-*exo*-brevicomin 9

To a methanol (1.5 mL) solution of **16** (45 mg, 0.13 mmol) was added activated 10% Pd/C (15 mg) and 0.02 mL of 3 M HCl at room temperature. The reaction mixture was stirred for 2.5 h under a hydrogen atmosphere (balloon). It was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). Evaporation of the solvent followed by column chromatography of the residue using pentane–diethyl ether (96:4) as an eluent afforded (+)-iso-*exo*-brevicomin **9** in 81% (16 mg) yield as a highly volatile colorless oil. $[\alpha]_D = +54$ (*c* 0.5, $CHCl_3$); lit.[8a] $[\alpha]_D = -54.3$ (*c* 1.34, $CHCl_3$) for the enantiomer; ^1H NMR (300 MHz, $CDCl_3$): δ 4.21 (q, $J = 6.3$ Hz, 1H), 4.05 (br s, 1H), 1.95–1.45 (m, 8H), 1.18 (d, $J = 6.3$ Hz, 3H), 0.95 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.6, 79.9, 75.5, 33.5, 30.5, 28.0, 21.5, 17.1, 7.2.

4.14. Preparation of (*R*)-2-benzyloxy-1-(methyoxymethoxy)-oct-7-ene 17

To a stirred CH_2Cl_2 (2 mL) solution of **7c** (0.1 g, 0.43 mmol), DMAP (10 mg, 0.08 mmol), and diisopropylethylamine (0.2 mL), was added methoxymethyl chloride (MOMCl) (0.08 mL, 1 mmol) dropwise at 0 °C under an argon atmosphere. It was stirred for 5 h at room temperature, poured into water (15 mL), and extracted with diethyl ether (3 × 10 mL). The combined ether extracts were washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether–ethyl acetate (92:8) as eluent resulting in **17** as colorless oil in 98% (0.11 g) yield. $[\alpha]_D = +12.5$ (*c* 1.2, $CHCl_3$); IR (neat): 2932, 1639, 1302, 1454, 1212, 1151, 1112, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.23 (m, 5H), 5.79 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.06–4.90 (m, 2H), 4.68 and 4.56 (AB q, $J = 11.7$ Hz, 2H), 4.65 (s, 2H), 3.65–3.51 (m, 3H), 3.37 (s, 3H), 2.11–1.99 (m, 2H), 1.67–1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 128.3, 127.7, 127.4, 114.3, 96.6, 77.9, 71.8, 69.7, 55.2, 33.6, 31.6, 28.9, 24.9; HRMS for $C_{17}H_{26}O_3$+Na calcd 301.1780; found 301.1787.

4.15. Preparation of (*R*)-2-(benzyloxy)-1-(methoxymethoxy)tridecan-7-ol 18

Ozone was bubbled through a pre-cooled (–78 °C) solution of **17** (0.1 g, 0.36 mmol) in dichloromethane–methanol (4:1, 10 mL) containing solid $NaHCO_3$ (10 mg) till the pale blue color persisted. Excess ozone was flushed off with oxygen and Me_2S (0.2 mL) was added and stirred for 4 h at 0 °C. The reaction mixture was concentrated under reduced pressure and dissolved in diethyl ether. It was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (20 mL). The ether layers were combined and evaporation of solvent afforded the crude aldehyde, which was subjected to a Grignard reaction without further purification.

To a stirred THF solution (3 mL) of the aldehyde (obtained above) in 0 °C, under an argon atmosphere was added a THF solution of hexylmagnesium bromide (1.6 mL of 0.5 M solution in THF, 0.8 mmol) dropwise. The reaction mixture was stirred for 1 h at the same temperature. After the reaction was complete (as indicated by TLC), it was quenched with saturated NH_4Cl (3 mL), poured into water (15 mL), and extracted with diethyl ether (3×10 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using petroleum ether–ethyl acetate (8:2) as eluent to yield **18** as a mixture of diastereomers as a colorless oil in 88% yield for two steps. (0.11 g). IR (neat): 3376, 2929, 2856, 1455, 1412, 1115, 1041, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.23 (m, 5H), 4.68 and 4.56 (AB q, $J = 11.7$ Hz, 2H), 4.65 (s, 2H), 3.64–3.51 (m, 4H), 3.37 (s, 3H), 1.73–1.19 (m, 18H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 128.2, 127.7, 127.4, 96.6, 77.8(4), 77.8(1), 71.8, 71.7, 69.7, 55.2, 37.4, 37.3, 31.8, 29.3, 25.6(4), 25.6(1), 25.5, 25.4, 22.6, 14.0; HRMS for $C_{22}H_{38}O_4$+Na calcd 389.2668; found 389.2661.

4.16. Preparation of (*R*)-2-(benzyloxy)-1-(methoxymethoxy)tridecan-7-one 19

A mixture of **18** (0.1 g, 0.27 mmol) and IBX (0.19 g, 0.68 mmol) in 4 mL of DMSO was stirred for 3.5 h at room temperature. After the reaction was complete (as indicated by TLC), it was cooled to 0 °C, quenched by addition of water (1 mL) and almost stirred for 5 min at room temperature. The white precipitate that was formed while quenching was filtered off through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). The ether layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using petroleum ether–ethyl acetate (9:1) as an eluent gave the **19** in 95% yield (0.094 g) as colorless oil. $[\alpha]_D = +13.7$ (*c* 1.6, $CHCl_3$); IR (neat): 2931, 2859, 1714, 1602, 1455, 1372, 1212, 1150, 1112, 1044, 918, 737, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.21 (m, 5H), 4.68 and 4.55 (AB q, $J = 11.7$ Hz, 2H), 4.64 (s, 2H), 3.63–3.50 (m, 3H), 3.37 (s, 3H), 2.37 (t, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 7.2$ Hz, 2H), 1.69–1.20 (m, 14H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 138.7, 128.3, 127.7, 127.5, 96.6, 77.7, 71.8, 69.6, 55.2, 42.8, 42.6, 31.6, 31.5, 28.8, 25.0, 23.8, 22.4, 14.0; HRMS for $C_{22}H_{36}O_4$+Na calcd 387.2511; found 387.2530.

4.17. Preparation of (*R*)-2-hydroxy-1-(methoxymethoxy)tridecan-7-one 20

To a methanol (1.5 mL) solution of **19** (80 mg, 0.22 mmol) was added activated 10% Pd/C (20 mg) at room temperature. The reaction mixture was stirred for 3 h under a hydrogen atmosphere (balloon). It was then filtered through a short pad of Celite and the Celite pad washed with diethyl ether (15 mL). The residue obtained after evaporation of solvent was purified column chromatography using petroleum ether–ethyl acetate (6:4) as eluent afforded **20** in 97% (58 mg) yield as colorless oil. $[\alpha]_D = +15$ (*c* 1.4, $CHCl_3$); IR (neat): 3460, 2931, 2861, 1712, 1599, 1513, 1462, 1375, 1213, 1114, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.67 and 4.65 (AB q, $J = 6.6$ Hz, 2H), 3.76 (br s, 1H), 3.61 (dd, $J = 10.5$, 3.0 Hz, 1H), 3.45–3.32 (m, 1H), 3.38 (s, 3H), 2.65 (br s, 1H, exchangeable with D_2O), 2.42 (t, $J = 7.2$ Hz, 2H), 2.39 (t, $J = 7.2$ Hz, 2H), 1.71–1.22 (m. 14H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 96.9, 73.1, 70.3, 55.4, 42.8, 42.5, 32.8, 31.5, 28.9, 25.1, 23.8, 23.6, 22.4, 14.0; HRMS for $C_{15}H_{30}O_4$+Na calcd 297.2042; found 297.2041.

4.18. Preparation of (2*R*,7*R*)-7-hexyl-2-(hydroxymethyl)oxepane 21

To a stirred solution of **20** (50 mg, 0.18 mmol) in 1.5 mL of THF was added triethylsilane (0.15 mL, 0.9 mmol). It was cooled to 0 °C after which trimethylsilyl triflate (0.03 mL, 0.2 mmol) was added dropwise and stirred for 1 h at same temperature. After the reaction was complete (as indicated by TLC), it was quenched with water (5 mL) and extracted with diethyl ether (3×5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of resultant residue using petroleum ether–ethyl acetate (8:2) as eluent afforded oxepane **21** as colorless oil in 79% yield. $[\alpha]_D$ +6.6 (*c* 1.8, MeOH); lit.[13a] $[\alpha]_D = -6.5$ (*c* 1.7, MeOH); IR (neat): 3431, 2929, 2857, 1601, 1455, 1377, 1112, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66–3.55 (m, 1H), 3.54–3.39 (m, 3H), 2.21 (dd, $J = 9.0$, 3.3 Hz, 1H, exchangeable with D_2O), 1.83–1.19 (m, 18H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.1, 80.3, 66.5, 37.2, 36.7, 31.6, 31.8, 29.3, 26.3, 25.3, 25.1, 22.6, 14.1; HRMS for $C_{13}H_{26}O_2$+Na calcd 237.1830; found 237.1840.

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