Total Synthesis of Nonenolide

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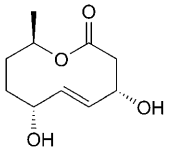
A novel synthetic route has been reported for the synthesis of nonenolide. The syntheses of fragments were initiated from commercially available and inexpensive starting materials. The synthesis involves key steps like *Sharpless* epoxidation, *Jacobsen*'s resolution, lactonization, and cross-metathesis.

Introduction. – Nature gave us many biologically active metabolites. For example, the genus *Cordyceps*, an abundant source of biologically active secondary metabolites, *e.g.*, antimalarial erythrostominones [1], antimalarial cordypyridones [2], and anti-tumor sterols [3]. It has been widely used as food and herbal medicine in Asia over the past years. The rich source of the secondary active metabolites ranging from simple to structural complex molecules such nonenolide **1** and cephalosporolides **2** [4] continues to stimulate organic chemists. The ten-membered lactone **1** was isolated from the entomopathogenic fungus *cordyceps militaris* BCC 2816 in 2004. It is a white solid and exhibits good antimalarial activity. The structure was deduced from spectroscopic data and X-ray crystallographic analysis [5].



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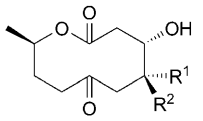

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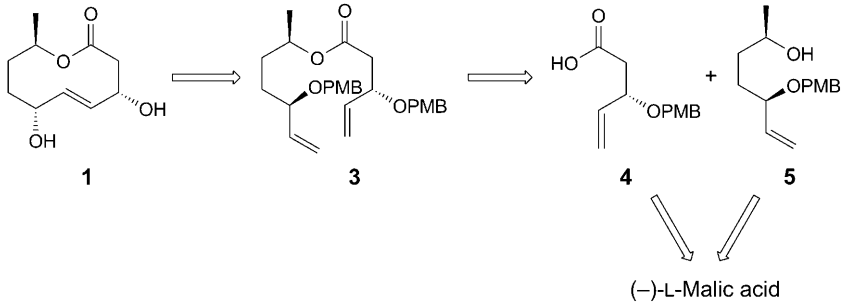
There are two reported syntheses [6] starting from mannitol and propylene oxide, respectively. In both syntheses, ring-closing metathesis (RCM) is the key step, and *Grubb*'s catalyst has been used to accomplish the reaction. It has been shown previously that the nonenolide **1** could be derived by RCM reaction of compound **3** [6a], which can be obtained by the coupling of subunits **4** and **5** [6a]. Here, we show that these subunits can be traced back to L-malic acid (*Scheme 1*).

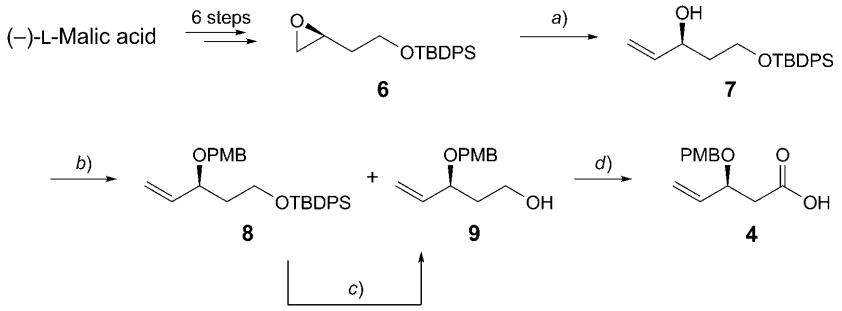
Results and Discussion. – The importance and new aspect of the present synthesis lie in the fact that the same starting material is used for both fragments. The synthesis of compound **4** is depicted in *Scheme 2*. Thus, the synthesis of fragment **4** commenced from L-malic acid. It was converted into **6** in six steps (42%) according to a literature procedure [7]. The epoxide **6**, on exposure to trimethylsulfonium iodide [8] in THF,

Scheme 1



afforded a secondary allylic alcohol **7** in good yield (87%). Protection of **7** with *para*-methoxybenzyl bromide (PMB-Br) in the presence of NaH gave a mixture of compounds **8** and **9** (60:40). As the *tert*-butyl(diphenyl)silyl ((*t*-Bu)Ph_2Si, TBDPS) group on the primary OH group has to be removed, we treated the crude compound with Bu_4NF (TBAF) to give the required primary alcohol, which was converted into acid **4** in two steps with 90% yield (*Scheme 2*).

Scheme 2

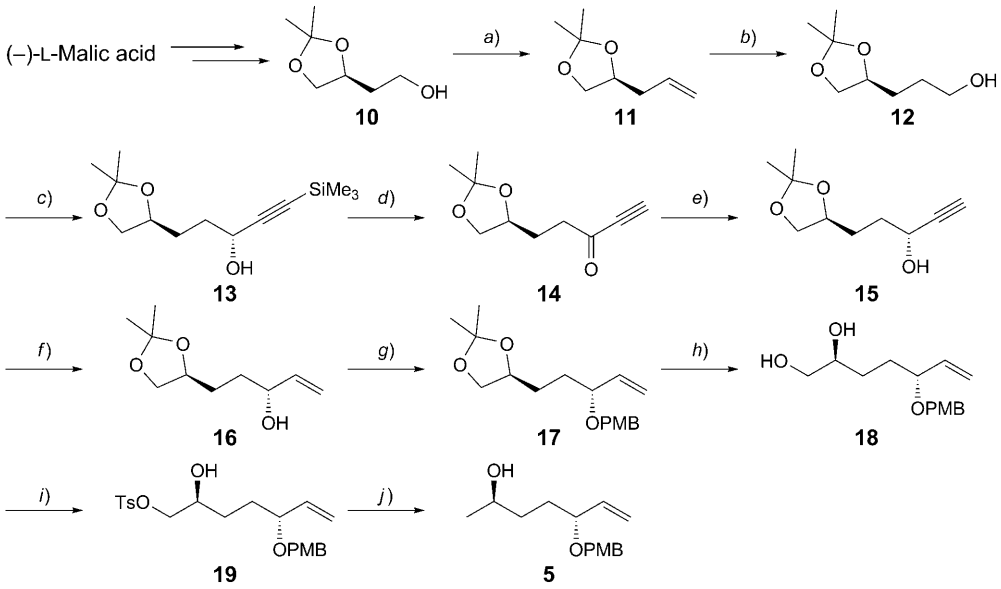


a) $(Me)_3S^+I^-$, BuLi, THF, $-10°$, 1 h; 90%. *b*) NaH, 4-methoxybenzyl bromide (PMB-Br), Bu_4NI (TBAI), THF, 0° – room temperature. *c*) Bu_4NF (TBAF), THF, room temperature. *d*) 1. $(COCl)_2$, DMSO, CH_2Cl_2, $-78°$; 2. NaH_2PO_4, $NaClO_2$, MeCN, H_2O, 2-methylbut-2-ene, room temperature; 90%.

Oxidation of alcohol **10** [9] with PCC gave the corresponding aldehyde, which, without further purification, was treated with the C_1 *Wittig* reagent [10] to provide allyl derivative **11** (47%). The latter was subjected to hydroboration with $BH_3 \cdot SMe_2$ in THF, followed by oxidation with H_2O_2 [11], to give primary alcohol **12** in 84% yield in two steps. Oxidation of **12** with 2-iodoxybenzoic acid (IBX) furnished the intermediate aldehyde, and subsequent addition of (trimethylsilyl)acetylene [12] gave a 1:1 mixture of diasteroisomers **13** (*Scheme 3*).

Removal of the TMS group in **13** with K_2CO_3 in MeOH, followed by oxidation of the secondary alcohol with *Dess–Martin* periodinane (DMP) [13], provided the desired ketone **14** in 90% yield. *Corey*'s chiral oxazaborolidine protocol [14] was applied to reduce **14** to give **15** in 95% yield (de 86%). The propargylic alcohol was reduced by using *Lindlar*'s catalyst to furnish the allylic alcohol **16** in 92% yield [15].

Scheme 3



a) 1. Pyridinium chlorochromate (PCC), CH_2Cl_2, room temperature; 2. $Ph_3PMe^+I^-$, *t*-BuOK, THF, 0°. *b*) 1. $BH_3 \cdot Me_2S$, THF; 2. H_2O_2, NaOH. *c*) 1. 2-Iodoxybenzoic acid (IBX), CH_2Cl_2, DMSO, 0°, room temperature; 2. (trimethylsilyl)acetylene, BuLi, THF, −78°. *d*) 1. K_2CO_3, MeOH; 2. *Dess–Martin* periodinane (DMP) oxidation, CH_2Cl_2, 0°; 90%. *e*) (*R*)-2-methyl-CBS-oxazaborlidine (CBS = *Corey–Bakshi–Shibata*), $BH_3 \cdot DMS$, THF, −78°. *f*) Pd–$CaCO_3$, H_2, AcOEt, room temperature. *g*) NaH, PMB-Br, TBAI, THF, 0° – room temperature. *h*) TsOH, MeOH. *i*) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, room temperature. *j*) $LiAlH_4$, THF, 0° – room temperature.

The secondary OH group was protected as its *para*-methoxybenzyl (PMB) ether to give **17** in 80% yield. The isopropylidene moiety of **17** was hydrolyzed under acidic conditions with TsOH, in MeOH at room temperature, to furnish **18** in 92% yield. The fragment **5** was obtained from diol **18** by selective monotosylation [16], followed by lithium aluminium hydride (LAH) reduction [17] (*Scheme 3*).

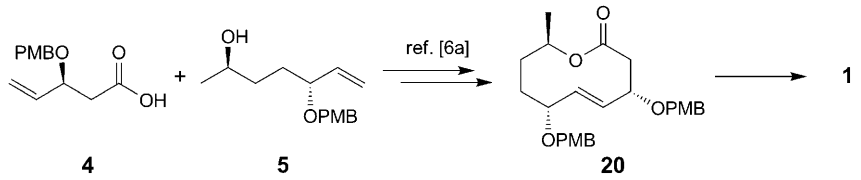
The acid **4** was coupled with alcohol **5** according to *Yamaguchi* conditions [18] to give diene ester **3** in 91% yield. Further, we have successfully performed the RCM reaction on PMB-protected hydroxy compound according to the protocol of *Grubbs* and co-workers [6a] and obtained lactone **20** as the major product in 75% yield along with minor (*Z*)-isomer. Finally, deprotection of the PMB ether groups gave **1** (*Scheme 4*).

The authors *D. A. K.* and *P. R.* thank *CSIR*, New Delhi, for the award of fellowships.

Experimental Part

General. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals*. TLC: precoated silica-gel plates (*60 F_{254}*, 0.2-mm layer; *E. Merk*). ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm, *J* in Hz. Mass spectra: *VG Autospec*; in *m/z*.

Scheme 4



*(3S)-5-{[(*tert*-Butyl)(diphenyl)silyl]oxy}pent-1-en-3-ol* (**7**). To a suspension of $(Me)_3S^+I^-$ (2.44 g, 12 mmol, 3 equiv.) in dry THF (36 ml) was added BuLi (1.6M in hexane; 7.43 ml; 11.9 mmol, 2.9 equiv.). After 30 min, *(*tert*-butyl){2-[(2S)-oxiran-2-yl]ethoxy}diphenylsilane* (**6**; 1.14 g, 4.0 mmol) in THF (8 ml) was introduced producing a milky suspension. The mixture was allowed to warm to 0° over *ca.* 30 min and then to r.t., and was stirred for 2 h. The reaction was quenched with H_2O at 0°, the mixture was extracted with Et_2O, and the combined org. layers were dried (Na_2SO_4). Chromatography of the crude material (SiO_2; AcOEt/hexane 1:9) afforded **7** (1.02 g, 85%). Colorless oil. $[\alpha]_D^{25} = -11.2$ ($c = 1.25$, $CHCl_3$). IR (KBr): 3455, 2931, 2858, 1612, 1512, 1247, 1103, 1036, 821, 705. ^{1}H-NMR: 1.06 (*s*, 9 H); 1.77 (*m*, 2 H); 2.92 (br. *s*, 1 H); 3.90 (*m*, 2 H); 4.40 (*m*, 1 H); 5.11 (*d*, $J = 10.2$, 1 H); 5.31 (*d*, $J = 16.5$, 1 H); 5.81–5.90 (*m*, 1 H); 7.36–7.43 (*m*, 6 H); 7.65–7.69 (*m*, 4 H). ^{13}C-NMR: 19.0; 26.7; 38.2; 55.2; 69.8; 114.2; 129.7; 130.0; 134.4; 138.7. ESI-MS: 363 (90, $[M + Na]^+$). HR-ESI-MS: 363.1743 ($[M + Na]^+$, $C_{21}H_{28}NaO_2Si^+$; calc. 363.1756).

*(*tert*-Butyl)({(3S)-3-[(4-methoxybenzyl)oxy]pent-4-en-1-yl}oxy)diphenylsilane* (**8**). To a soln. of **7** (2.5 g, 13.4 mmol) in dry THF (40 ml) was added NaH (0.8 g, 33.5 mmol; 60% dispersion in mineral oil) at 0°, the mixture was stirred for 30 min, PMB-Br (2.5 g, 16.0 mmol) was added, and the mixture was stirred for additional 3 h at r.t. The reaction was quenched by addition of cold H_2O, and the aq. layer was washed with AcOEt (2 × 25 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and purification of the residue by column chromatography (CC; 10% AcOEt/light petroleum ether) to afforded **8**. $[\alpha]_D^{25} = -5.7$ ($c = 1.5$, $CHCl_3$). IR (KBr): 3029, 2985, 2851, 1555, 1229, 1056, 747. ^{1}H-NMR: 1.01 (*s*, 9 H); 1.64–1.88 (*m*, 2 H); 3.63–3.70 (*m*, 1 H); 3.73–3.80 (*m*, 1 H); 3.77 (*s*, 3 H); 3.99 (*q*, $J = 11.3$, 1 H); 4.22 (*d*, $J = 11.3$, 1 H); 4.47 (*d*, $J = 11.3$, 1 H); 5.15–5.22 (*m*, 2 H); 5.76–5.76 (*m*, 1 H); 6.76 (*d*, $J = 8.3$, 2 H); 7.15 (*d*, $J = 8.3$, 2 H); 7.28–7.40 (*m*, 6 H); 7.58–7.61 (*m*, 4 H). ^{13}C-NMR: 19.3; 27.0; 38.6; 55.0; 60.1; 69.8; 76.9; 113.6; 116.8; 127.6; 129.1; 129.5; 130.8; 133.9; 135.5; 139.2; 159.0. ESI-MS: 483 (88, $[M + Na]^+$). HR-ESI-MS: 483.2347 ($[M + Na]^+$, $C_{29}H_{36}NaO_3Si^+$; calc. 483.2331).

(3S)-3-[(4-Methoxybenzyl)oxy]pent-4-en-1-ol (**9**). To compound **8** (0.9 g, 1.9 mmol) in dry THF (10 ml) was added TBAF (1.9 ml, 1.9 mmol; 1M soln. in THF) dropwise at 0°, and the mixture was stirred for 30 min. H_2O (2 ml) was added, and the mixture was extracted with AcOEt. The org. extracts were washed with brine and dried (anh. Na_2SO_4). Evaporation of the solvent afforded **9** (0.35 g, 80%). Liquid. $[\alpha]_D^{25} = -34$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3428, 2933, 2862, 1612, 1513, 1301, 1247, 1176, 1092, 820. ^{1}H-NMR: 1.69–1.87 (*m*, 2 H); 3.53–3.68 (*m*, 2 H); 3.79 (*s*, 3 H); 4.25–4.31 (*m*, 1 H); 4.42 (*s*, 2 H); 5.06 (*td*, $J = 1.5$, 1.8, 1 H); 5.23 (*td*, $J = 1.5$, 1.7, 1 H); 6.83 (*d*, 2 H, $J = 8.6$); 7.20 (*d*, 2 H, $J = 8.6$). ^{13}C-NMR: 37.5; 55.0; 59.9; 72.6; 78.9; 113.6; 117.2; 128.3; 129.2; 138.0; 158.9. ESI-MS: 245 (69, $[M + Na]^+$). HR-ESI-MS: 245.2753 ($[M + Na]^+$, $C_{13}H_{18}NaO_3^+$; calc. 245.1154).

(3S)-3-[(4-Methoxybenzyl)oxy]pent-4-enoic acid (**4**). To a soln. of oxalyl chloride (18.8 ml, 215.5 mmol) in CH_2Cl_2 (500 ml) at −78° was added DMSO (19.4 ml, 273.0 mmol) over 20 min. The resulting mixture was stirred for an additional 15 min, and then **9** (31.9 g, 143.7 mmol), dissolved in CH_2Cl_2 (100 ml), was added dropwise. The mixture was stirred for 30 min, and Et_3N (120.2 ml, 862.1 mmol) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 30 min. After completion of the reaction, H_2O was added (400 ml), and the aq. phase was extracted with CH_2Cl_2 (2 × 200 ml). The combined org. layers were washed with brine and dried (anh. Na_2SO_4), removal of the solvent afforded the corresponding aldehyde (28.5 g, 90%) as a colorless liquid.

To a stirred soln. of the intermediate aldehyde in *t*-BuOH (1 ml) was added methyl-2-butene (0.5 ml) in *t*-BuOH (0.5 ml). The mixture was cooled (0°) and treated with a soln. of $NaClO_2$ (36 mg, 0.3 mmol)

and NaH_2PO_4 (142 mg, 0.91 mmol) in H_2O (1 ml). After 1.5 h, the mixture was diluted with brine (3 ml) and Et_2O (3 ml). The org. phase was separated, and the aq. phase was extracted with Et_2O. The combined org. phases were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (FC; Et_2O) afforded **4** (38.2 mg, 58%). R_f (SiO_2, 30% AcOEt in hexane) 0.25. $[\alpha]_D^{25} = +29.14$ ($c = 1$, $CHCl_3$). IR (KBr): 3412, 2929, 1716, 1624, 1513, 1248, 1039, 827. ^{1}H-NMR: 2.48 (*dd*, $J = 5.27, 15.41$, 1 H); 2.64 (*dd*, $J = 8.08, 15.41$, 1 H); 3.80 (*s*, 3 H); 4.24 (*m*, 1 H); 4.32 (*d*, $J = 11.24$, 1 H); 4.52 (*d*, $J = 11.24$, 1 H); 5.26–5.38 (*m*, 2 H); 5.76 (*m*, 1 H); 6.83–6.87 (*m*, 2 H); 7.21–7.26 (*m*, 2 H). ^{13}C-NMR: 41.0; 55.17; 70.22; 76.20; 113.76; 118.30; 130.0; 137.0; 159.20; 176.17. ESI-MS: 259 (85, $[M + Na]^+$). HR-ESI-MS: 259.0935 ($[M + Na]^+$, $C_{13}H_{16}NaO_4^+$; calc. 259.0946).

*(3*R*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]pent-1-yn-3-ol* (**15**). (*R*)-2-methyl-CBS-oxazaborolidine (10 ml, 1.0M in toluene) was added to a soln. of ketone **14** (1.82 g, 10 mmol) in 10 ml of toluene, and the mixture was cooled it to −78°. $BH_3 \cdot DMS$ (20 ml, 1.0M in THF) was added dropwise, and stirring was continued for 12 h at −78°. The reaction was quenched with 15 ml of MeOH, and the mixture was allowed to warm to r.t. The mixture was diluted with Et_2O (50 ml) and washed with 1N NaOH, saturated with $NaHCO_3$, until the aq. washings were colorless. The org. layer was washed with brine, dried (anh. Na_2SO_4), and concentrated *in vacuo*. Purification by FC gave **15** (1.58 g, 8.6 mmol, 86%). Yellow liquid. $[\alpha]_D^{25} = +24.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3436, 3097, 2979, 2871, 2230,1643, 1457, 1369, 1226, 1055, 922. ^{1}H-NMR: 1.31 (*s*, 3 H); 1.37 (*s*, 3 H); 1.62–1.98 (*m*, 4 H); 2.37 (*d*, $J = 2.19$, 1 H); 3.49 (*t*, $J = 8.05$, 1 H); 3.88–3.98 (*m*, 2 H); 4.30–4.44 (*m*, 1 H). ^{13}C-NMR: 25.1; 26.6; 34.1; 61.9; 67.6; 72.6; 79.9; 84.7; 108.9. ESI-MS: 207 (80, $[M + Na]^+$). HR-ESI-MS: 207.0980 ($[M + Na]^+$, $C_{10}H_{16}NaO_3^+$; calc. 207.0997).

*(3*R*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pent-1-en-3-ol* (**16**). *Lindlar*'s catalyst (0.03 g) and quinoline (0.12 g) were added to a soln. of **15** (1.84 g, 10 mmol) in AcOEt (12 ml), and the mixture was stirred under H_2 for 2 h. The heterogeneous soln. was filtered through *Celite*. The org. layer was concentrated *in vacuo*. Purification by CC (SiO_2) gave **16** (1.71 g, 9.2 mmol, 92%). Yellow syrup. $[\alpha]_D^{25} = +12.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058, 922, 757. ^{1}H-NMR: 1.35 (*s*, 3 H); 1.41 (*s*, 3 H); 1.58–1.75 (*m*, 4 H); 2.15 (br. *s*, 1 H); 3.51 (*t*, $J = 6.8$, 1 H); 4.01–4.16 (*m*, 3 H); 5.08–5.29 (*m*, 2 H); 5.78–5.95 (*m*, 1 H). ^{13}C-NMR: 25.7; 26.8; 29.2; 33.1; 69.4; 72.4; 76.0; 108.8; 114.6; 140.9. ESI-MS: 209 (87, $[M + Na]^+$). HR-ESI-MS: 209.1147 ($[M + Na]^+$, $C_{10}H_{18}NaO_3^+$; calc. 209.1153).

*(4*S*)-4-{(3*R*)-3-[(4-Methoxybenzyl)oxy]pent-4-en-1-yl}-2,2-dimethyl-1,3-dioxolane* (**17**). To a soln. of **16** (1.87 g, 10.05 mmol) in dry DMF (30 ml) was added NaH (0.6 g, 25.1 mmol; 60% dispersion in mineral oil) at 0°, and the mixture was stirred for 30 min. Then, PMB-Br (1.87 g, 12.0 mmol) was added, and the soln. was stirred for additional 3 h at r.t. The reaction was quenched by cold H_2O, and the aq. layer was extracted with AcOEt (2 × 25 ml) and dried (anh. Na_2SO_4). Evaporation of the solvent *in vacuo* gave a residue which was purified by CC (10% AcOEt/light petroleum ether) to afford **17** (2.73 g, 8.9 mmol, 89%). Yellow syrup. $[\alpha]_D^{25} = +14.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3067, 2986, 2868, 1645, 1460, 1362, 1051, 752. ^{1}H-NMR: 1.34 (*s*, 3 H); 1.39 (*s*, 3 H); 1.46–1.78 (*m*, 4 H); 3.36–3.80 (*m*, 3 H); 3.80 (*s*, 3 H); 3.97 (*d*, $J = 11.4$, 1 H); 4.26 (*d*, $J = 11.5$, 1 H); 4.55 (*m*, 1 H); 5.18–5.28 (*m*, 2 H); 5.64–5.85 (*m*, 1 H); 6.84–6.89 (*m*, 2 H); 7.22–7.27 (*m*, 2 H). ^{13}C-NMR: 26.2; 29.0; 55.8; 69.2; 72.8; 76.2; 82.8; 109.2; 114.1; 115.7; 129.6; 139.8; 159.7. ESI-MS: 307 (84, $[M + H]^+$). HR-ESI-MS: 307.1904 ($[M + H]^+$, $C_{18}H_{27}O_4^+$; calc. 307.1909).

*(2*S*,5*R*)-5-[(4-Methoxybenzyl)oxy]hept-6-ene-1,2-diol* (**18**). A soln. of **17** (1.83 g, 6.0 mmol) in 80% AcOH (25 ml) was stirred for 6 h at r.t., and the reaction was quenched with sat. $NaHCO_3$ soln. The aq. layer was washed with AcOEt (2 × 30 ml), dried (anh. Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by CC (SiO_2, 60–120 mesh; 50% EtOAc/hexane) to give **18** (1.46 g, 5.52 mmol, 92%). Colorless liquid. $[\alpha]_D^{25} = +17.3$ ($c = 1$, $CHCl_3$). IR (KBr): 3409, 3076, 3000, 2936, 2868, 1612, 1514, 1442, 1302, 1248, 1174, 1072, 995, 821. ^{1}H-NMR: ($CDCl_3$, 200 MHz): 1.43–1.57 (*m*, 2 H); 1.64–1.75 (*m*, 2 H); 2.41 (br. *s*, 2 H); 3.38 (*m*, 1 H); 3.53–3.75 (*m*, 3 H); 3.79 (*s*, 3 H); 4.24 (*d*, $J = 11.4$, 1 H); 4.50 (*d*, $J = 11.3$, 1 H); 5.16–5.29 (*m*, 2 H); 5.66–5.84 (*m*, 1 H); 6.83–6.87 (*m*, 2 H); 7.19–7.26 (*m*, 2 H). ^{13}C-NMR: 28.9; 31.5; 55.1; 66.5; 69.8; 71.9; 80.2; 113.7; 117.3; 129.4; 130.3; 138.6; 159.1. ESI-MS: 266 (56, M^+). HR-ESI-MS: 266.1513 (M^+, $C_{15}H_{22}O_4^+$; calc. 266.1519).

*(2*S*,5*R*)-2-Hydroxy-5-[(4-methoxybenzyl)oxy]hept-6-en-1-yl 4-Methylbenzenesulfonate* (**19**). To a soln. of **18** (1.0 g, 3.75 mmol) in dry CH_2Cl_2 (30 ml) were added Et_3N (0.44 g, 4.27 mmol), Bu_2SnO (0.47 g, 1.89 mmol), 4-(dimethylamino)pyridine (DMAP; 13.8 mg, 0.12 mmol), and TsCl (0.74 g,

3.84 mmol) at 0°. The mixture was stirred for 12 h at r.t., and the reaction was quenched with a sat. soln. of $NaHCO_3$. The aq. layer was extracted with AcOEt (2 × 25 ml), and the combined org. layer was washed with brine, dried (anh. Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (SiO_2, 60–120 mesh; 15% AcOEt/hexane) to afford **19** (1.2 g, 2.85 mmol, 76%). Colorless liquid. $[\alpha]_D^{25} = +23.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3410, 3067, 2998, 2925, 2852, 1606, 1512, 1420, 1239, 1070, 820. ^{1}H-NMR: 1.43–1.71 (*m*, 4 H); 2.45 (*s*, 3 H); 3.66–3.78 (*m*, 2 H); 3.80 (*s*, 3 H); 3.85–3.98 (*m*, 2 H); 4.21 (*d*, $J = 11.5$, 1 H); 4.49 (*d*, $J = 11.4$, 1 H); 5.16–5.26 (*m*, 2 H); 5.71 (*m*, 1 H); 6.83–6.87 (*m*, 2 H); 7.18–7.22 (*m*, 2 H); 7.31–7.35 (*m*, 2 H); 7.76–7.80 (*m*, 2 H). ^{13}C-NMR: 21.3; 28.0; 28.9; 55.6; 70.9; 72.6; 73.7; 82.8; 114.4; 115.7; 128.4; 129.6; 129.8; 130.5; 139.8; 140.3; 144.4; 159.7. ESI-MS: 421 (80, $[M+H]^+$). HR-ESI-MS: 421.1697 ($[M+H]^+$, $C_{22}H_{29}O_6S^+$; calc. 421.1685).

*(2*R*,5*R*)-5-[(4-Methoxybenzyl)oxy]hept-6-en-2-ol* (**5**). To a soln. of **19** (0.420 g, 1 mmol) in dry THF (20 ml) at 0° was added LAH (0.152 g, 4.0 mmol), and the mixture was stirred for 3 h. Excess of LAH was removed by addition of a sat. Na_2SO_4 soln. (3 ml). The solid formed was filtered through *Celite* pad, washed with AcOEt, and the filtrate was concentrated *in vacuo* and purified by CC (SiO_2; 20% AcOEt/hexane) to afford **5** (0.220 g, 0.88 mmol, 88%). Colorless liquid. $[\alpha]_D^{25} = +19.6$ ($c = 1.1$, $CHCl_3$). IR (KBr): 3436, 3079, 2986, 2871, 1644, 1455, 1379, 1216, 1058, 922, 757. ^{1}H-NMR: 1.15 (*d*, $J = 6.0$, 3 H); 1.44–1.53 (*m*, 2 H); 1.62–1.68 (*m*, 2 H); 2.14 (br. *s*, 1 H); 3.70–3.73 (*m*, 2 H); 3.80 (*m*, 3 H); 4.24 (*d*, $J = 11.3$, 1 H); 4.47 (*d*, $J = 11.3$, 1 H); 5.16–5.26 (*m*, 2 H); 5.78 (*m*, 1 H); 6.84–6.84 (*m*, 2 H); 7.21–7.26 (*m*, 2 H). ^{13}C-NMR: 23.1; 31.9; 34.6; 55.1; 67.4; 69.7; 80.1; 113.5; 116.0; 128.6; 130.4; 135.8; 159.0. ESI-MS: 250 (92, M^+). HR-ESI-MS: 250.1574 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.1568).

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