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Synthesis of a C(4)–C(9) eleutheside template from D-glucal☆

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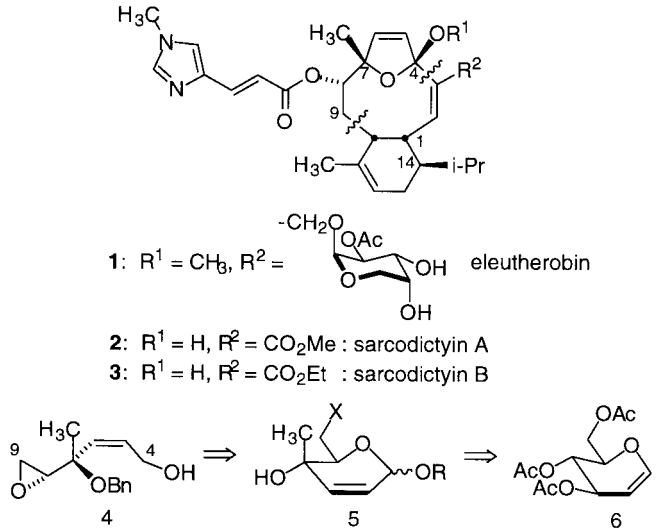
Abstract—D-Glucal is converted to epoxy allylic alcohol **4** using an eight-step sequence that features a stereoselective methyl Grignard addition to an iodo-hexenulose. Epoxide formation via intramolecular iodide displacement occurs subsequent to an unusual hemiacetal reduction protocol involving $LiBH_4$ in *n*-octanol. Alcohol **4** and the corresponding aldehyde (*Z*)-**14** are potential C(4)–C(9) templates for eleutheside syntheses.

Eleutherobin (**1**, Scheme 1), first reported by Fenical and co-workers,[1] is a potent cytotoxic marine natural product that mimics the action of paclitaxel (taxol[2]) by binding to tubulin and effectively stabilizing microtubules.[3] This action leads to mitotic arrest and is the subject of considerable recent interest given that paclitaxel, eleutherobin, and other notable microtubule-stabilizing natural products such as epothilones A and B[4] and discodermolide[5] appear to operate by binding to a common site on the microtubule polymer.[6,7] Total syntheses of eleutherobin, and the closely related sarcodictyins A and B (**2**, **3**),[8] have been reported by Nicolaou et al.[9] and Danishefsky and co-workers.[10] To date, the correlation of activity for tubulin polymerization with structure has been examined for eleutherobin and sarcodictyin derivatives wherein structural alterations resided either within the core 10-membered ring or the accompanying side chains.[11,12] The relative scarcity of these marine natural products has hampered further biological evaluations.[13]

We[14] and other investigators recently presented new approaches to eleutherobin and eleutheside analogs.[15–18] Our current aim is to synthesize the eleutheside core



Scheme 1. D-Glucal as a progenitor of eleutheside C(4)–C(9).

☆ A preliminary account of this work was presented at the 219th National Meeting of the American Chemical Society, San Francisco, CA; see: By, K.; Kelly, P. A.; Kurth, M. J.; Nantz, M. H. *ACS Books of Abstracts*, 26–30 March 2000, ORGN-851.

Keywords: eleutheside; epoxide; stereoselective; D-glucal; hexenulose.

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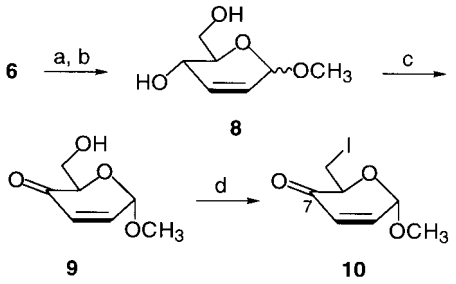
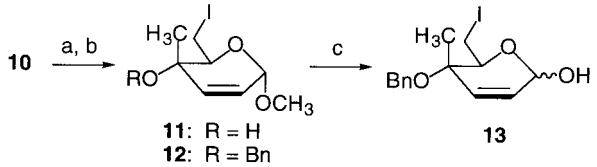


Scheme 2. (a) $BF_3{\cdot}Et_2O$, MeOH, C_6H_6, rt, 45 min; (b) KCN, MeOH, rt, 4 h, 95% (2 steps); (c) MnO_2, CH_2Cl_2, rt, 2 h, 55%; (d) $[(PhO)_3PCH_3]I$, DMF, rt, 2 h, 72%.

structure via intramolecular Diels–Alder reaction of a dienophile tethered to C(8).[14b] This strategy requires an enantioenriched C(4)–C(9) template. In this regard, we present herein a stereoselective synthesis of epoxy allylic alcohol **4** (Scheme 1), whose origin is traced through pyranoside **5** to commercially available tri-*O*-acetyl-D-glucal (**6**).

Using a combination of literature procedures, tri-*O*-acetal-D-glucal **6** was readily converted in four steps to hexenulose **10** (Scheme 2).[19] Exposure of **6** to boron trifluoride etherate and methanol in benzene afforded methyl 4,6-di-*O*-acetyl-2,3-dideoxy-2-enopyranoside (**7**).[20] The acetate esters were cleaved using potassium cyanide in methanol to obtain diol **8**[21] as an 8:1 mixture of α:β anomers and subsequent treatment with excess manganese dioxide afforded hex-2-en-4-ulose **9** as a single diastereomer.[22] Comparison of the specific activity with that of the literature revealed that these transformations occurred without loss of optical activity (compound **9**: $[\alpha]_D^{25} = +33.2°$ (c=0.78, $CHCl_3$), literature $[\alpha]_D^{23} = +36.1°$ (c=2.66, $CHCl_3$).[23] An alcohol-to-iodide conversion was then conducted using methyltriphenoxyphosphonium iodide according to Landauer and Rydon to give iodo-hexenulose **10**.[24]

We envisioned introduction of the eleutheside C(7) methyl by stereoselective nucleophilic addition to the β-face of hexenulose **10**. Indeed, prior work by Achmatowicz et al. has shown that treatment of a trityl-protected hexenulose analogous to **9** with MeLi or BuLi gave the corresponding *erythro* products as the major isomers.[25] We found that treatment of **10** with MeMgBr in Et_2O gave a 14:1 mixture of methyl adducts (Scheme 3).[26] Single crystal X-ray analysis confirmed the major product to be α-hydroxy adduct **11**.[27] Subsequent benzylation gave **12** and set the stage for acetal hydrolysis. The methyl glycoside linkage of **12** was unexpectedly resistant to hydrolysis and required heating in aqueous acetic acid to deliver hemiacetal **13** as a 5:1 mixture of anomers.



Scheme 3. (a) MeMgBr, Et_2O, 0°C–rt, 6 h, 80%; (b) NaH, BnBr, TBAI, THF, 0°C–rt, 10 h, 77%; (c) 1.7:3:1, 1,4-dioxane:H_2O:AcOH, reflux, 4.5 h, 84%.

Table 1. Base-catalyzed reaction of **13**→**14**+**15**

Entry	Reaction conditions[a]	Aldehyde **14** Yield, %[b] (*Z*:*E*)[c]	Anhydro **15** Yield, %[b]
1	NaH, THF, 0°C, 1 h	0	65
2	KH, THF, 0°C, 2 h	0	75
3	KO*t*-Bu, CH_2Cl_2, 0°C–rt, 16 h	49 (10:1)	44
4	KO*t*-Bu, THF, 0°C–rt, 8 h	0	77
5	DBU, CH_2Cl_2, 0°C–rt, 14 h	11 (0:100)	50
6	$NaOCH_3$, CH_3OH, 0°C–rt, 8 h	0	60
7	K_2CO_3, acetone, rt, 16 h	34 (100:0)	22
8	Cs_2CO_3, acetone, rt, 16 h	26 (10:1)	35
9	$LiCH_2S(O)CH_3$, DMSO, rt, 2 h	3 (0:100)	75

[a] For each entry, **13** (0.2–0.3 mmol) was treated with excess base (ca. 4 equiv.).
[b] Isolated.
[c] Determined by ^1H NMR integration.[25]

At this stage, our strategy was to facilitate the hemiacetal equilibrium to an open form δ-oxido aldehyde wherein intramolecular iodide displacement would yield the corresponding C(8)-epoxide.[28] To our dismay, we found that treatment of **13** with a variety of bases provided a mixture of products principally consisting of (*E*)- and (*Z*)-epoxy aldehydes **14**[29] and the *anhydro*-1,6-pyranoside **15** (Table 1). Although formation of desired (*Z*)-**14** was influenced by selection of base and solvent, we were unable to thwart the formation of **15** as a major product. Additionally, alkene isomerization appeared to be problematic in the presence of excess homogeneous base. The use of K_2CO_3 in acetone (entry 7) afforded the best ratio of (*Z*)-**14** but in low yield. Consequently, we sought to obtain aldehyde **14** by reduction of the hemiacetal moiety to circumvent *anhydro*-pyranoside formation.

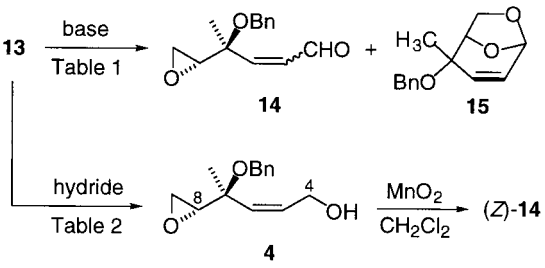


Table 2. Formation of epoxy alcohol **4**

Entry	Reaction conditions[a]	% Yield (**4**)
1	$NaBH_4$, MeOH, 0°C–rt	34
2	$LiAlH_4$, THF, −78 to −30°C	33
3	$(n\text{Bu})_4NBH_4$, THF, 0°C–rt	20
4	Dibal-H,[b] pentane, 0°C–rt	<10
5	$LiBH_4$, Et_2O, 0°C	44
6	$LiBH_4$, 10:1 Et_2O:CH_3OH, 0°C–rt	47
7	$LiBH_4$, CH_3OH, 0°C–rt	57
8	$LiBH_4$, $CH_3(CH_2)_6CH_2OH$, 0°C–rt	88

[a] For all entries except 4, **13** at a concentration of 0.1–0.2 M was treated with excess hydride (ca. 8 equiv.); all crude reaction mixtures were subsequently treated with KOH (s) in CH_2Cl_2 at 0°C and followed by chromatography to isolate **4**.
[b] 2.0 equiv.

Hydride reduction of **13** gave a mixture of products that included the expected C(4),C(8)-diol (not depicted). Base treatment of the crude reaction mixture after work-up (KOH (s), CH_2Cl_2, 0°C) gave rise to epoxide **4** in varying yields (Table 2). The reduction was sensitive to temperature in that warming above room temperature led to the formation of **15**. Olefin isomerization was not observed under any of the conditions. The use of ether or THF for this reaction resulted in significant product mixtures containing unreacted starting material, a problem that was somewhat ameliorated by a change in solvent to methanol. The use of $LiBH_4$ in methanol (entry 7) was slightly more effective than $NaBH_4$ in methanol (entry 1). We were gratified to find that substitution of methanol with *n*-octanol (entry 8) further enhanced the formation of **4**. The underlying basis for this improvement in yield is unclear and is the subject of current studies. MnO_2 oxidation of **4** conveniently afforded aldehyde (*Z*)-**14** in 82% yield. Although MnO_2 oxidation of (*Z*)-4-(benzyloxy)-but-2-en-1-ol has been shown to afford mixtures of *E* and *Z* isomers,[30] no (*E*)-isomer was detected in the oxidation of **4** presumably due to the non-enolizable nature of **14**.

In summary, an eight-step synthesis of a C(4)–C(9) template for eleutheside synthesis has been achieved from D-glucal in 17% overall yield. We are currently examining the elaboration of **4** via epoxide cleavage reactions at C(9) and are using aldehyde **14** for chain extensions at C(4).

1. Experimental section

1.1. General

All reactions were carried out under an atmosphere of nitrogen. CH_2Cl_2 was distilled from calcium hydride immediately prior to use. THF and Et_2O were distilled from sodium benzophenone ketyl immediately prior to use, and benzene was distilled from sodium. Column chromatography was carried out using 230–400 mesh silica gel, slurry packed in glass columns, eluting with the solvents indicated. TLC was performed on Kieselgel 60 F_{254} plates, staining with an ethanolic solution of *p*-anisaldehyde containing 5% conc. H_2SO_4. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$. High resolution mass spectrometry was performed by Mass Spectrometry Service Labs of the University of California, Davis, the University of Minnesota (Minneapolis) and the University of California, Riverside. Infrared (IR) data were obtained on neat samples. Elemental analyses were performed by Midwest Microlab, LLC (Indianapolis).

1.1.1. Methyl 2,3-dideoxy-α-D-*glycero*-4-pyranosidulose (9). To a solution of diol **8** (6.5 g, 41 mmol) in CH_2Cl_2 (2.70 l) was added MnO_2 (70 g, 0.59 mol). The suspension was stirred 2 h at room temperature and then filtered through a pad of celite. After removal of the solvent by rotary evaporation, the residue was chromatographed (9:1 EtOAc:hexane) to afford **9** (3.33 g, 55%) as a white solid, mp 84–86°C (lit.[22] mp 82.5°C); TLC, R_f=0.58 (EtOAc); $[\alpha]_D^{25}$ = 33.2° (*c*=0.78, $CHCl_3$); IR 3257, 1697 cm^{-1}; ^1H NMR δ 2.35 (br. s, 1H, —OH), 3.55 (s, 3H), 4.01 (m, 2H), 4.85 (t, *J*=4.5 Hz, 1H), 5.18 (d, *J*=3.6 Hz, 1H), 6.11 (d, *J*=10.2 Hz, 1H), 6.92 (dd, *J*=3.6, 10.2 Hz, 1H); ^{13}C NMR δ 56.7, 61.6, 74.1, 94.1, 127.8, 143.8, 195.7. Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.12; H, 6.29.

1.1.2. Methyl 6-deoxy-6-iodo-2,3-dideoxy-α-D-*glycero*-4-pyranosidulose (10). To a solution of **9** (2.0 g, 12.8 mmol) in dry DMF (100 ml) at room temperature was added methyltriphenoxyphosphonium iodide (11.6 g, 25.6 mmol) in one portion. After stirring 1 h, methanol (8 ml) was added to the dark red reaction mixture and the reaction was stirred an additional 45 min before diluting with Et_2O (200 ml) and quenching by addition of aq. 15% $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted with Et_2O (×2). The combined organic extract was washed with brine and dried ($MgSO_4$). After solvent removal using rotary evaporation, flash chromatography of the residue (8:1 hexane:EtOAc) gave impure **10** (5.8 g). This material was further purified by trituration with Et_2O (5 ml). Filtration of the crystals and subsequent washing with hexane gave **10** (2.2 g) as colorless crystals. The mother liquor was concentrated and the above procedure was repeated to obtain an additional quantity of **10** (0.26 g, 72% overall); mp 89.6–91.5°C; TLC, R_f=0.75 (EtOAc); $[\alpha]_D^{25}$ = 59.8° (*c*=1.45, $CHCl_3$); IR 3029, 2830, 1698, 1629 cm^{-1}; ^1H NMR δ 3.46 (dd, *J*=6.9, 10.8 Hz, 1H), 3.59 (s, 3H), 3.61 (dd, *J*=3.0, 10.8 Hz, 1H), 4.51 (dd, *J*=3.0, 6.9 Hz, 1H), 5.18 (d, *J*=3.6 Hz, 1H), 6.10 (d, *J*=10.2 Hz, 1H), 6.90 (dd, *J*=3.6, 10.2 Hz, 1H); ^{13}C NMR δ 1.9, 56.8, 73.6, 94.5, 127.2, 144.0, 193.4. Anal. calcd for $C_7H_9O_3I$: C, 31.36, H, 3.38. Found: C, 30.97; H, 3.21.

1.1.3. Methyl 6-deoxy-6-iodo-4-methyl-2,3-dideoxy-α-D-*erythro*-pyranoside (11). To a solution of **10** (2.42 g, 9.03 mmol) in Et_2O (180 ml) at 0°C was added MeMgBr (3.6 ml of 3.0 M solution in Et_2O, 10.8 mmol) dropwise. After 30 min, the reaction mixture was warmed to room temperature and stirred 6.5 h before diluting with Et_2O and quenching by addition of water. The layers were separated and the aqueous layer was extracted with Et_2O (×2). The combined organic extract was washed with brine and dried ($MgSO_4$). After solvent removal via rotary evaporation, the residue was chromatographed (5:1 hexane:EtOAc) to obtain **11** (2.05 g, 80%) as a white solid, mp=86–87°C; TLC, R_f=0.39 (1:1 hexane:EtOAc); $[\alpha]_D^{25}$ = 134° (*c*=10.1, CH_2Cl_2); IR 3434, 2967, 2830, 1679 cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 2.06 (s, 1H, —OH), 3.15 (t, *J*=10.8, 1H), 3.56 (m, 1H), 3.60 (s, 3H), 4.00 (dd, *J*=1.8, 11.1, 1H), 4.89 (d, *J*=3.0 Hz, 1H), 5.65 (dd, *J*=2.7, 9.9 Hz, 1H), 5.80 (d, *J*=10.8 Hz, 1H); ^{13}C NMR δ 3.0, 19.5, 56.5, 69.9, 76.4, 95.9, 125.0, 137.7. A sample of **11** was recrystallized from Et_2O:hexane to obtain needles suitable for X-ray crystallographic analysis (see Supporting information).

1.1.4. Methyl 6-deoxy-6-iodo-4-*O*-benzyl-4-methyl-2,3-dideoxy-α-D-*erythro*-glucopyranoside (12). To a suspension of sodium hydride (0.48 g, 9.1 mmol) in THF (95 ml) at 0°C was added a solution of **11** (1.85 g, 6.5 mmol) in THF (25 ml) via cannula. The reaction was allowed to warm to room temperature and then recooled to 0°C after 45 min whereupon benzyl bromide (0.93 ml, 7.8 mmol) and tetrabutylammonium iodide (0.53 g, 1.3 mmol) were added successively. The reaction was stirred at room temperature for 10 h and then diluted with Et_2O and quenched by addition of water. The layers were separated and the

aqueous layer was extracted with Et_2O (×2). The combined organic extract was washed with brine and dried ($MgSO_4$). After removal of the solvents via rotary evaporation, chromatography (5:1 hexane:EtOAc) gave **12** (1.92 g, 77%) as a light yellow oil; TLC, R_f=0.66 (4:1 hexane:EtOAc); $[\alpha]_D^{23}$=58.2° (*c*=2.42, $CHCl_3$); IR 2927, 1698, 1635 cm^{-1}; ^1H NMR δ 1.21 (s, 3H), 3.16 (t, *J*=10.8 Hz, 1H), 3.52 (dd, *J*=1.5, 10.8 Hz, 1H), 3.62 (s, 3H), 4.37 (dd, *J*=1.5, 11.1 Hz, 1H), 4.50 (dd, *J*=11.7, 14.4 Hz, 2H), 4.90 (d, *J*=2.7 Hz, 1H), 5.80 (dd, *J*=2.7, 10.2 Hz, 1H), 5.95 (d, *J*=10.2 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR δ 3.6, 19.2, 56.5, 65.6, 72.2, 75.3, 95.9, 127.1, 127.2, 127.5, 128.4, 135.4, 138.6; HRMS *m/z* calcd for $[M+Na]^+$ 397.02785, found 397.0276.

1.1.5. 6-Deoxy-6-iodo-4-*O*-benzyl-4-methyl-2,3-dideoxy-α-D-*erythro*-glucopyranose (13). To a solution of **12** (0.50 g, 1.34 mmol) in a solvent mixture of 1,4-dioxane (5 ml) and water (9 ml) at room temperature was added acetic acid (3 ml). The reaction was heated to reflux for 4.5 h and then allowed to cool to room temperature before quenching by slow addition of saturated aq. $NaHCO_3$ to a pH 5–6. The reaction mixture was extracted with Et_2O and the combined organic extract was washed with brine and dried (Na_2SO_4). After solvent removal via rotary evaporation, the residue was chromatographed (5:1 hexane:EtOAc) to obtain **13** (0.41 g, 84%) as a light yellow oil; TLC, R_f=0.49 (1:1 hexane:EtOAc); $[\alpha]_D^{23}$=7.09° (*c*=1.60, $CHCl_3$); IR 3414, 3030, 2869, 1692, 1653 cm^{-1}; ^1H NMR δ 1.21 (s, 3H), 3.10 (t, *J*=10.8 Hz, 1H), 3.55 (dd, *J*=1.8, 10.8 Hz, 1H), 4.50 (m, 1H), 4.52 (d, *J*=3, 2H), 5.46 (d, *J*=2.4 Hz, 1H), 5.90 (dd, *J*=2.7, 10.2 Hz, 1H), 5.97 (d, *J*=10.5 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR δ 3.9, 19.0, 65.6, 72.3, 75.2, 89.3, 127.2, 127.6, 127.8, 128.5, 135.3, 138.6. Anal. calcd for $C_{14}H_{17}$: C, 46.68; H, 4.76. Found: C, 46.78; H, 4.76.

1.1.6. 4-[(2*R*)-Oxiran-2-yl)-(4*S*)-(2*Z*)-4-(phenylmethoxy)]-pent-2-enal (*Z*-14). To a solution of **13** (155 mg, 0.43 mmol) in dry acetone (30 ml) was added anhydrous potassium carbonate (640 mg, 4.64 mmol). The suspension was stirred at room temperature for 17 h and then diluted with ether (30 ml). The reaction mixture was filtered through a pad of celite and the filtrate was concentrated by rotary evaporation. The residue was chromatographed (4:1 hexane:EtOAc) to obtain **14** (34 mg, 34%) and **15** (22 mg, 22%) as oils. (*Z*)-**14**: TLC, R_f=0.27 (7:3 hexane: EtOAc); $[\alpha]_D^{23}$=−37.5° (*c*=0.79, $CHCl_3$); IR 3033, 1716 (C=O), 1277 cm^{-1}; ^1H NMR δ 1.58 (s, 3H), 2.62 (dd, *J*=2.7, 4.5 Hz, 1H), 2.83 (t, *J*=4.2 Hz, 1H), 3.26 (dd, *J*=3.2, 3.9 Hz, 1H), 4.58 (s, 2H), 6.05 (dd, *J*=7.8, 12 Hz, 1H), 6.22 (d, *J*=12 Hz, 1H), 7.31 (m, 5H), 10.39 (d, *J*=7.8 Hz, 1H); ^{13}C NMR δ 22.7, 42.9, 55.9, 65.7, 78.5, 127.5, 128.5, 133.2, 137.8, 145.6, 155.7, 193.7; HRMS *m/z* calcd for $[M+Na]^+$ 255.0997, found 255.1003. Anal. calcd for $C_{14}H_{16}O_3 \cdot 0.5H_2O$: C, 69.69; H, 7.10. Found: C, 69.35; H, 6.74.

1.1.7. 1,6-Anhydro-4-*O*-benzyl-4-methyl-2,3-dideoxy-α-D-*erythro*-pyranoside (15). TLC, R_f=0.58 (1:1 hexane: EtOAc); IR 3031, 2973, 1633, 985 cm^{-1}; ^1H NMR δ 1.31 (s, 3H), 3.70 (d, *J*=7.8 Hz, 1H), 3.88 (t, *J*=7.8 Hz, 1H), 4.58 (dd, *J*=5.4, 11.7 Hz, 2H), 4.80 (d, *J*=11.7 Hz, 1H), 5.57 (d, *J*=3.0 Hz, 1H), 5.65 (dd, *J*=1.4, 9.6 Hz, 1H), 6.14 (dd, *J*=3.2, 9.5 Hz, 1H), 7.33 (m, 5H); ^{13}C NMR δ 22.6, 63.3, 67.1, 73.2, 80.3, 95.2, 127.2, 127.3, 128.2, 129.5, 131.0, 139.7. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.91; H, 7.00.

1.1.8. 4-[(2*R*)-Oxiran-2-yl)-(4*S*)-(2*Z*)-4-(phenylmethoxy)]-pent-2-en-1-ol (4). To a solution of **13** (2.99 g, 8.30 mmol) in *n*-octanol (50 ml) at 0°C was added lithium borohydride (0.40 g, 18.3 mmol) portion wise over 5 min. After stirring 24 h at room temperature, the reaction was quenched by slow addition of water and the resultant mixture was extracted with Et_2O (3×300 ml). The combined organic extract was washed with brine and dried (Na_2SO_4). The Et_2O was removed by rotary evaporation and the remaining solution was loaded onto a SiO_2 column (ca. 300 g) and eluted with 9:1 hexane:EtOAc to remove the *n*-octanol (TLC). Subsequent elution with EtOAc followed by concentration of the collected fractions afforded a crude mixture of **4** and its diol progenitor. The crude mixture was dissolved in CH_2Cl_2 (100 ml) and cooled to 0°C. To this mixture was added KOH (s) (ca. 0.5 g) in one portion. After stirring 4 h at 0°C, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated by rotary evaporation. Chromatography (4:1 hexane:EtOAc) of the residue gave **4** (1.72 g, 88%) as an oil; TLC, R_f=0.3 (2:1 hexane: EtOAc); $[\alpha]_D^{25}$=15.3° (*c*=3.83, $CHCl_3$); IR 3417, 1454, 1027 cm^{-1}; ^1H NMR δ 1.44 (s, 3H), 2.51 (s, 1H, −OH), 2.60 (dd, *J*=2.7, 4.5 Hz, 1H), 2.75 (apparent t, *J*=4.5 Hz, 1H), 3.16 (dd, *J*=2.7, 4.2 Hz, 1H), 4.18 (m, 1H), 4.39 (m, 1H), 4.50 (s, 2H), 5.20 (d, *J*=12 Hz, 1H), 5.87 (dt, *J*=6.3, 12.0 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR δ 22.9, 43.3, 56.9, 59.1, 65.4, 76.6, 127.3, 127.4, 127.8, 128.3, 135.3, 138.5; HRMS *m/z* calcd for $[M+Na]^+$ 257.1148, found 257.1150.

1.1.9. Supporting information available. ^{13}C NMR spectra for compounds **4**, **12** and (*Z*)-**14** and the ^1H NMR spectrum of **4**, X-ray crystallographic data for **11** (12 pages). This material is available free of charge via the Internet at http://pubs. acs.org.

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