Synthesis P. Jangili et al. Paper

Stereoselective Total Synthesis of Pinolide and Its C2 Epimer and Evaluation of Their Cytotoxic Activity[1]

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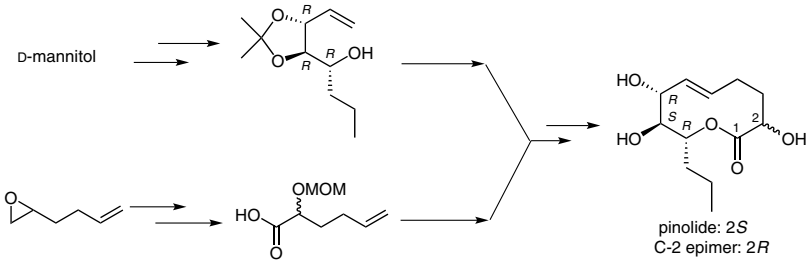

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Abstract Pinolide, a naturally occurring nonenolide and its C2 epimer have been synthesized using D-mannitol and 1,2-epoxyhex-5-ene as the starting materials. The synthesis involves the Jacobsen's hydrolytic kinetic resolution, Yamaguchi esterification, and intramolecular ring-closing metathesis as the key steps. The 2-*epi*-pinolide, the C2 epimer of pinolide, has been synthesized for the first time. The cytotoxic activity of the pinolide and 2-*epi*-pinolide has been studied.

Key words pinolide, total synthesis, D-mannitol, 1,2-epoxyhex-5-ene

The ten-membered lactones (nonenolides) are commonly isolated from fungal sources.[2] These compounds contain interesting structural features with various stereogenic centers and different functionalities. They also possess important biological properties such as cytotoxic, antibacterial, antifungal, and herbicidal activity.[2,3] Pinolide [(2*S*)-**1**], a ten-membered lactone, was isolated[4] from the liquid culture of isolate CO-99 of the fungus *Didymella pinodes*, the causal agent of ascochyta blight on pea plants (*Pisum sativum*). Herein, we report the stereoselective synthesis of pinolide [(2*S*)-**1**] and 2-*epi*-pinolide [(2*R*)-**1**] (Figure 1); we also studied the cytotoxicity of both the epimers (2*S*)-**1** and [(2*R*)-**1**]. While our work was under progress a synthesis of (2*S*)-**1** was published using different starting materials.[5] However, the present work is the first report of the synthesis of 2-*epi*-pinolide [(2*R*)-**1**]. The C2 epimers of different natural nonenolides have been isolated[4] from natural sources, but 2-*epi*-pinolide [(2*R*)-**1**] is naturally unknown. This synthesis provides an access to both the epimers (2*S*)-**1** and (2*R*)-**1** to examine and compare their different other biological properties.

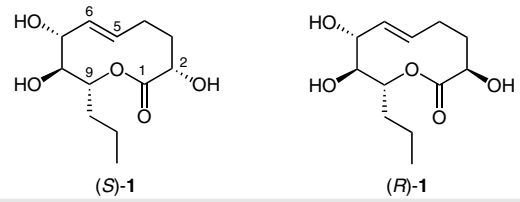
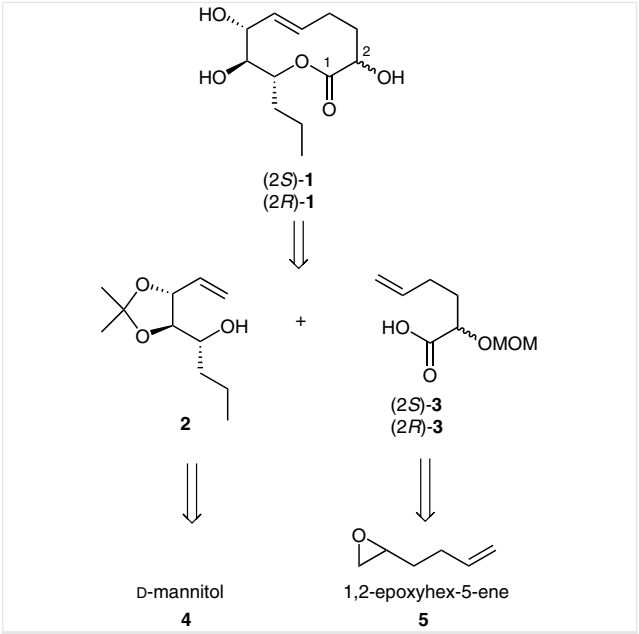


Figure 1 Structures of pinolide [(2*S*)-**1**] and 2-*epi*-pinolide [(2*R*)-**1**]

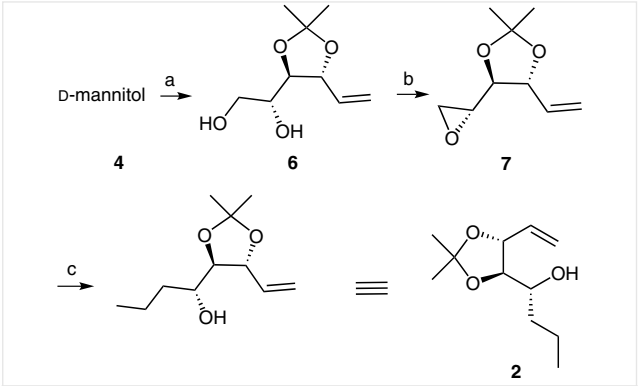
In continuation of our work[6] on the stereoselective construction of natural products, we proposed that compound (2*S*)-**1** could be synthesized from the alcohol fragment **2** and the acid fragment (2*S*)-**3** (Scheme 1). Similarly, (2*R*)-**1** can be prepared from the same alcohol **2** and the enantiomeric acid (2*R*)-**3**. The alcohol **2**, in turn, can be prepared from D-mannitol (**4**) and the acids (2*S*)-**3** and (2*R*)-**3** from 1,2-epoxyhex-5-ene (**5**).

The synthesis was initiated (Scheme 2) by converting D-mannitol (**4**) into the known diol **6** following a reported method.[7] The diol **6** was then treated with dibutyltin oxide and 4-toluenesulfonyl chloride in triethylamine and subsequently with methanolic potassium carbonate to afford the epoxyalkene **7**. The epoxide ring of **7** was then opened with ethylmagnesium bromide using copper(I) iodide to produce the required alcohol **2**.

The synthesis of the acid fragment (2*S*)-**3** was achieved[8] (Scheme 3) from the epoxide **5**, which was subjected to hydrolytic kinetic resolution[9] using Jacobsen's (*R*,*R*)-(Salen)Co(III) complex and acetic acid to generate the diol (2*S*)-**8** (96% ee). The diol (2*S*)-**8** was treated with *tert*-butyldimethylsilyl chloride and imidazole to protect its primary hydroxy group as the *tert*-butyldimethylsilyl ether (2*S*)-**9**. The secondary hydroxy group of (2*S*)-**9** was subsequently protected as methoxymethyl (MOM) ether (2*S*)-**10**



Scheme 1 Retrosynthetic analysis of pinolide [(2*S*)-**1**] and 2-*epi*-pinolide [(2*R*)-**1**]



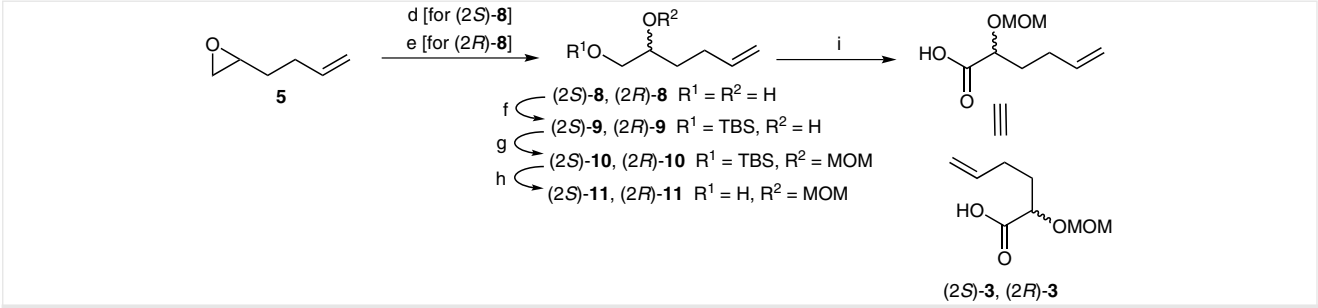
Scheme 2 Synthesis of the alcohol fragment **2**. *Reagents and conditions*: (a) ref. 7; (b) (i) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, r.t., 30 min; (ii) K_2CO_3, MeOH, r.t., 1 h, 75%; (c) EtMgBr, CuI, –20 °C to r.t., 84%.

by reaction with methoxymethyl bromide and diisopropylethylamine. Compound (2*S*)-**10** was converted into the desired acid (2*S*)-**3** by treatment with tetrabutylammonium fluoride to produce the primary alcohol (2*S*)-**11** which was next oxidized[10] with (diacetoxyiodo)benzene and 2,2,6,6-tetramethylpiperidin-1-yloxyl in acetonitrile–water (2:1).

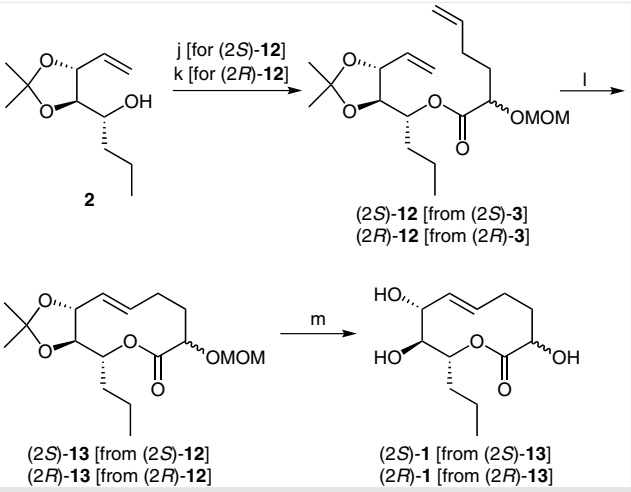
The enantiomeric acid (2*R*)-**3** was also prepared[8] from the same epoxide **5** (Scheme 3). The latter underwent hydrolytic kinetic resolution[9] with Jacobsen's (*S*,*S*)-(Salen)Co(III) complex and acetic acid to furnish the diol (2*R*)-**8** (96% ee). The diol (2*R*)-**8** was then converted into the acid (2*R*)-**3** following the similar methods described above, that is, (i) protection of the primary hydroxy group of (2*R*)-**8** as TBS ether (2*R*)-**9**; (ii) protection of the secondary hydroxy group of (2*R*)-**9** as MOM ether (2*R*)-**10**; (iii) deprotection of TBS ether group of (2*R*)-**10** to primary alcohol (2*R*)-**11**, and (iv) oxidation of primary hydroxy group of (2*R*)-**11** to the acid (2*R*)-**3**.

The alcohol fragment **2** was coupled (Scheme 4) with the acid fragments (2*S*)-**3** and (2*R*)-**3** separately using 2,4,6-trichlorobenzoyl chloride, triethylamine, and 4-(dimethylamino)pyridine under the Yamaguchi esterification protocol[11] to produce the esters (2*S*)-**12** and (2*R*)-**12**, respectively. These two esters underwent intramolecular ring-closing metathesis[12] in the presence of Grubbs II catalyst (Figure 2) to produce the cyclic esters (2*S*)-**13** [from (2*S*)-**12**] and (2*R*)-**13** [from (2*R*)-**12**]. Next, the compounds (2*S*)-**13** and (2*R*)-**13** were subjected to treatment with 4 M hydrochloric acid in acetonitrile to furnish the desired products, pinolide [(2*S*)-**1**] and 2-*epi*-pinolide [(2*R*)-**1**], respectively. The physical (optical rotation) and the spectral (^{1}H and ^{13}C NMR and MS) properties of (2*S*)-**1** were found to be identical to those reported for the naturally occurring compound.[4]

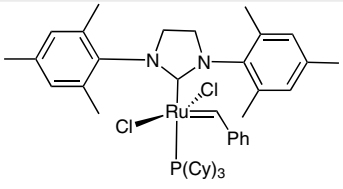
The two compounds, pinolide and 2-*epi*-pinolide were examined for in vitro cytotoxicity against a panel of three cancer cell lines: MDA-MB-231 (human breast adenocarcinoma), HepG2 (human liver carcinoma), and COLO205 (human colon carcinoma). Doxorubicin was used as the positive control. MTT assay (according to the method of Mosmann[13]) was applied to assess the cytotoxic activity of



Scheme 3 Synthesis of the acid fragments (2*S*)-**3** and (2*R*)-**3**. *Reagents and conditions*: (d) (*R*,*R*)-(salen)Co(III)OAc (0.5 mol%), distilled H_2O (0.45 equiv), AcOH, THF, 0 °C, 24 h, 46% (96% ee); (e) (*S*,*S*)-(salen)Co(III)OAc (0.5 mol%), distilled H_2O (0.45 equiv), AcOH, THF, 0 °C, 24 h, 46% (96% ee); (f) TBSCl, imidazole, THF, r.t., 96%; (g) MOMBr, *i*-Pr_2NEt, CH_2Cl_2, 45 °C, 100%; (h) TBAF, THF, 0 °C–r.t., 100%; (i) $PhI(OAc)_2$, TEMPO, MeCN–H_2O (2:1), r.t., 3 h; 84%.



Scheme 4 Coupling of the fragments **2** and (2*S*)-**3**, **2** and (2*R*)-**3**. *Reagents and conditions*: (j) (2*S*)-**3**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, r.t., 93%; (k) (2*R*)-**3**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, r.t., 91%; (l) Grubbs II catalyst, CH_2Cl_2, 50 °C, 83%; (m) 4 M HCl, MeCN, 0 °C to r.t., 8 h, 90%.



A
Grubbs II catalyst

Figure 2

the two compounds. IC_{50} values (in μM) are indicated as the mean ± SD of three independent experiments depicted in Table 1. The results showed that both the compounds exhibited significant cytotoxic activity against all the three cancer cell lines. However, pinolide and 2-*epi*-pinolide exhibited promising activity against MDA-MB-231 cell line (IC_{50} values are 9.8 and 11.2 μM, respectively), and good cytotoxicity against HepG2 and COLO205 cell lines.

Table 1 Cytotoxicity of Pinolide and 2-*epi*-Pinolide Against Human Cancer Cell Lines

Cell line	IC_{50} (μM)		
	Pinolide [(2*S*)-**1**]	2-*epi*-Pinolide [(2*R*)-**1**]	Doxorubicin
MDA-MB-231	9.8 ± 0.31	11.2 ± 0.28	0.7 ± 0.16
Hep G2	13.2 ± 0.26	15.2 ± 0.12	0.6 ± 0.11
COLO205	15.8 ± 0.14	14.1 ± 0.22	0.7 ± 0.09

In conclusion, we have developed a stereoselective total synthesis of the natural nonenolide, pinolide and its C2 epimer. The synthesis utilized D-mannitol and 1,2-epoxyhex-5-ene as the starting materials with Jacobsen's hydrolytic kinetic resolution, Yamaguchi esterification, and intramolecular ring-closing metathesis as the key steps. This is the first report of the synthesis of 2-*epi*-pinolide. The cytotoxic activity of the synthetic compounds pinolide [(2*S*)-**1**] and 2-*epi*-pinolide [(2*R*)-**1**] was evaluated.

NMR spectra were recorded on Gemini 500 MHz and 300 MHz spectrometers using $CDCl_3$ as solvent and TMS as internal standard. ESI-MS were recorded with VG-Autospec micromass. Optical rotations were measured with a Jasco DIP 360 digital polarimeter. All reactions were monitored by TLC using silica gel F_{254} pre-coated plates. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China); PE = petroleum ether.

(4*S*,5*R*)-2,2-Dimethyl-4-[(*R*)-oxiran-2-yl]-5-vinyl-1,3-dioxolane (7)

To a stirred solution of **6** (1 g, 5.31 mmol) in CH_2Cl_2 (20 mL), Et_3N (1.48 mL, 10.62 mmol) and Bu_2SnO (27.0 mg, 0.10 mmol) were added. After 5 min, TsCl (1.11 g, 5.84 mmol) was added and the mixture was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The organic layer was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 10% EtOAc–PE) to give the tosylate as a colorless liquid which was used directly in the next step.

A solution of tosylate in MeOH (10 mL) was treated with K_2CO_3 (1.62 g, 11.78 mmol) and stirred at r.t. for 1 h. The mixture was treated with aq NH_4Cl solution (5 mL). The MeOH was evaporated under reduced pressure and the residue was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (75 mL) and brine (75 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 10% EtOAc–PE) to furnish **7** (0.68 g, 75%) as a colorless liquid. $[\alpha]_D^{25}$ –3.1 (*c* 0.2, $CHCl_3$).

IR (KBr): 2923, 2852, 1597, 1373, 1257, 1177, 1079, 874 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.44 (d, *J* = 16.0 Hz, 1 H), 5.30 (d, *J* = 9.0 Hz, 1 H), 4.38 (t, *J* = 7.0 Hz, 1 H), 3.62 (dd, *J* = 7.0, 5.0 Hz, 1 H), 3.10 (m, 1 H), 2.83 (m, 1 H), 2.72 (m, 1 H), 1.46 (s, 3 H), 1.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.9, 119.0, 109.7, 80.1, 80.0, 51.2, 44.7, 26.8, 26.6.

MS (ESI): *m*/*z* = 171 $[M + H]^+$.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.42; H, 8.33.

(*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol (2)

A suspension of EtMgBr in THF (30 mL) was prepared from EtBr (0.79 mL, 10.59 mmol) and Mg (0.343 g, 14.12 mmol) in the usual manner. The suspension was cooled (–20 °C) and CuI (1.0 g, 5.29 mmol) was added. The mixture was stirred at –20 °C for 15 min. To this cooled organometallic suspension, a solution of epoxide **7** (0.60 g, 3.53 mmol) in THF (20 mL) was added. The mixture was stirred at this temperature for 1 h and then gradually brought to r.t. and stirred overnight. The reaction was quenched by the addition of aq sat. NH_4Cl (10 mL) and extracted with EtOAc. The combined organic layers were

washed with 5% aq HCl, H_2O, and brine and then dried (Na_2SO_4). Solvent removal under reduced pressure gave a residue that was purified by column chromatography (silica gel, 0–10% EtOAc–hexane) to afford pure **2** (0.59 g, 84%) as a colorless liquid. $[\alpha]_D^{25}$ +7.1 (*c* 0.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (m, 1 H), 5.32 (d, *J* = 16.0 Hz, 1 H), 5.18 (d, *J* = 9.0 Hz, 1 H), 4.37 (t, *J* = 7.0 Hz, 1 H), 3.81–3.77 (m, 2 H) 3.64 (dd, *J* = 7.0, 4.0 Hz, 1 H), 1.50–1.41 (m, 2 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.30–1.24 (m, 2 H), 0.82 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.8, 118.8, 108.7, 83.1, 77.3, 70.1, 34.5, 27.0, 19.1, 13.9.

MS (ESI): *m*/*z* = 223 $[M + Na]^+$.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.09; H, 10.03.

(*S*)-Hex-5-ene-1,2-diol [(*S*)-8]

The catalyst (*R*,*R*)-(salen)Co(III)OAc (32 mg, 51 μmol, 0.005 equiv) was dissolved in (±)-1,2-epoxyhex-5-ene (**5**, 1.15 mL, 1 g, 10.20 mmol), AcOH (12 μL, 0.21 mmol, 0.02 equiv), and THF (0.5 mL). The solution was cooled to 0 °C and H_2O (0.082 mL, 4.59 mmol, 0.45 equiv) was added in 1 portion. After 24 h, the residual epoxide was isolated by vacuum transfer into a cooled (–78 °C) receiving flask and (*S*)-hex-5-ene-1,2-diol [(*S*)-**8**, 0.55 g, 46%] was distilled under reduced pressure; 96% ee (chiral chromatography). $[\alpha]_D^{25}$–14.0 (*c* 0.3, $CHCl_3$).

IR (KBr): 3431, 2932, 1640, 1417, 1059 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.11–4.95 (m, 2 H), 3.78–3.60 (m, 4 H), 3.43 (m, 1 H), 2.28–2.03 (m, 2 H), 1.57–1.42 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 115.0, 71.4, 66.0, 32.6, 29.9.

MS (ESI): *m*/*z* = 139 $[M + Na]^+$.

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.18; H, 10.38.

(*S*)-1-(*tert*-Butyldimethylsiloxy)hex-5-en-2-ol [(*S*)-9]

A mixture of (*S*)-hex-5-ene-1,2-diol [(*S*)-**8**, 0.5 g, 4.31 mmol], TBSCl (0.65 g, 4.31 mmol), and imidazole (0.29 g, 4.31 mmol) in THF (20 mL) was stirred for 2 h at r.t. The white precipitate was removed by filtration and washed with Et_2O (30 mL). The combined filtrates were concentrated and purified by flash column chromatography (PE–EtOAc, 10:1) to give (*S*)-**9** (0.95 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 0.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.10–4.92 (m, 2 H), 3.70–3.60 (m, 2 H), 3.42 (m, 1 H), 2.26–2.10 (m, 2 H), 1.59–1.47 (m, 2 H), 0.91 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 115.0, 71.2, 67.2, 32.0, 30.0, 26.1, 18.1, –5.2.

MS (ESI): *m*/*z* = 253 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.43; H, 11.42.

(*S*)-5-(But-3-enyl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane [(*S*)-10]

(*S*)-1-(*tert*-Butyldimethylsiloxy)hex-5-en-2-ol [(*S*)-**9**, 0.8 g, 3.48 mmol] was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. *i*-Pr_2NEt (1.82 mL, 10.40 mmol) was added followed by MOMBr (0.58 mL, 7.10 mmol). The solution was stirred at 0 °C for 0.5 h and then heated under reflux overnight. The mixture was cooled to r.t., acidified with 1 M HCl (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and the filtrate concentrated in vacuo. Flash column chromatography (EtOAc–PE, 1:20) yielded (*S*)-**10** (0.95 g, 100%) as a colorless oil. $[\alpha]_D^{25}$ –56.9 (*c* 0.25, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (m, 1 H), 5.08–4.91 (m, 2 H), 4.79 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 7.0 Hz, 1 H), 3.68–3.53 (m, 3 H), 3.39 (s, 3 H) 2.22–2.02 (m, 2 H), 1.69–1.50 (m, 2 H), 0.88 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 115.0, 96.5, 78.0, 65.9, 55.8, 31.1, 29.8, 26.0, 18.1, –5.2.

MS (ESI): *m*/*z* = 275 $[M + H]^+$.

Anal. Calcd $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.37; H, 11.00.

(*S*)-2-(Methoxymethoxy)hex-5-en-1-ol [(*S*)-11]

To a solution of **10** (0.8 g, 2.90 mmol) in THF (10 mL) at 0 °C, was added 1 M TBAF in THF (3.5 mL). The mixture was stirred for 2 h at r.t. and then it was diluted with EtOAc and the solution was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 5:2) to give (*S*)-**11** (0.47 g, 100%) as a colorless liquid. $[\alpha]_D^{25}$ +40.9 (*c* 0.25, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (m, 1 H), 5.08–4.92 (m, 2 H), 4.71 (d, *J* = 7.0 Hz, 1 H), 4.62 (d, *J* = 7.0 Hz, 1 H), 3.61–3.48 (m, 3 H), 3.42 (s, 3 H), 3.09 (br s, 1 H), 2.20–2.05 (m, 2 H), 1.68–1.48 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 115.2, 97.0, 81.3, 65.5, 55.8, 31.0, 29.9.

MS (ESI): *m*/*z* = 183 $[M + Na]^+$.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.86; H, 10.10.

(*S*)-2-(Methoxymethoxy)hex-5-enoic Acid [(*S*)-3]

To a solution of **11** (0.4 g, 2.50 mmol) in MeCN–H_2O (2:1, 10 mL) were added $PhI(OAc)_2$ (1.77 g, 5.50 mmol) and TEMPO (78 mg, 0.50 mmol); the mixture was stirred at r.t. for 3 h. When the reaction was complete (TLC), the mixture was filtered and extracted with EtOAc (2 × 20 mL). The combined organic phases were dried and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexane–EtOAc 7:3) to give pure (*S*)-**3** (0.36 g, 84%) as a pale yellow liquid. $[\alpha]_D^{25}$ –56.6 (*c* 0.1, $CHCl_3$).

IR (KBr): 3438, 2925, 2853, 1734, 1640, 1444, 1214, 1036 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (br s, 1 H), 5.81 (m, 1 H), 5.16–4.98 (m, 2 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 4.68 (d, *J* = 7.0 Hz, 1 H), 4.17 (t, *J* = 7.0 Hz, 1 H), 3.40 (s, 3 H), 2.26–2.19 (m, 2 H), 1.98–1.84 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 137.5, 116.0, 96.4, 75.0, 56.2, 32.1, 29.2.

MS (ESI): *m*/*z* = 197 $[M + Na]^+$.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.26; H, 8.05.

(*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl (*S*)-2-(Methoxymethoxy)hex-5-enoate [(2*S*)-12]; Typical Procedure

To a stirred solution of acid (*S*)-**3** (87 mg, 0.5 mmol) in anhyd THF (5 mL) were added 2,4,6-trichlorobenzoyl chloride (0.094 mL, 0.6 mmol) and Et_3N (0.35 mL, 2.5 mmol), and the contents were stirred at r.t. When the formation of the mixed anhydride was complete (indicated by TLC), DMAP (122 mg, 1.0 mmol) and a solution of alcohol **2** (100 mg, 0.5 mmol) in toluene (5 mL) were added and the mixture was stirred for 3 h at r.t. The reaction was quenched by the addition of H_2O and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 100–200 mesh, 10% EtOAc–hexane) to afford (2*S*)-**12** (165 mg, 93%) as a colorless liquid. $[\alpha]_D^{25}$ –22.0 (*c* 0.2, $CHCl_3$).

IR (KBr): 2922, 2852, 1748, 1455, 1256, 1037 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83 (m, 2 H), 5.40 (d, *J* = 17.0 Hz, 1 H), 5.27 (d, *J* = 9.0 Hz, 1 H), 5.19 (m, 1 H), 5.09–4.99 (m, 2 H), 4.69 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 7.0 Hz, 1 H), 4.30 (t, *J* = 7.0 Hz, 1 H), 4.13 (dd, *J* = 7.0, 5.0 Hz, 1 H), 3.81 (dd, *J* = 7.0, 6.0 Hz, 1 H), 3.39 (s, 3 H), 2.25–2.19 (m, 2 H), 1.92–1.80 (m, 2 H), 1.70–1.59 (m, 2 H), 1.41 (s, 6 H), 1.38–1.24 (m, 2 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 137.2, 135.8, 118.9, 115.5, 109.4, 96.0, 81.1, 79.4, 74.5, 73.2, 56.0, 33.0, 32.2, 29.4, 26.9, 26.8, 18.4, 13.8.

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

Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 63.91; H, 9.10.

(3a*R*,4*R*,7*S*,11a*R*,*E*)-7-(Methoxymethoxy)-2,2-dimethyl-4-propyl-3a,4,7,8,9,11a-tetrahydro-6*H*-[1,3]dioxolo[4,5-*c*]oxecin-6-one [(2*S*)-13]; Typical Procedure

To a solution of (2*S*)-**12** (100 mg, 0.28 mmol) in degassed anhyd CH_2Cl_2 (75 mL) was added Grubbs II catalyst (43 mg, 0.05 mmol) and the mixture was heated at 50 °C under an argon flow for 12 h. When the reaction was complete (TLC), most of the solvent was evaporated and then air was bubbled to decompose the catalyst. The remaining solvent was evaporated under reduced pressure to afford a dark brown oily residue that was quickly passed through a short silica gel column (20% EtOAc–hexane) to give (2*S*)-**13** (76 mg, 83%) as a colorless liquid. $[\alpha]_D^{25}$ +6.5 (*c* 0.2, $CHCl_3$).

IR (KBr): 2924, 1620, 1384, 1260, 1023, 799 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.65 (ddd, *J* = 15.0, 10.0, 4.0 Hz, 1 H), 5.57 (dd, *J* = 15.0, 10.0 Hz, 1 H), 5.17 (td, *J* = 8.0, 2.0 Hz, 1 H), 4.69 (d, *J* = 7.0 Hz, 1 H), 4.67 (d, *J* = 7.0 Hz, 1 H), 4.28 (dd, *J* = 7.0, 2.0 Hz, 1 H), 4.01 (t, *J* = 8.0 Hz, 1 H), 3.49 (dd, *J* = 10.0, 8.0 Hz, 1 H), 3.40 (s, 3 H), 2.41 (m, 1 H), 2.21–2.14 (m, 2 H), 2.03 (m, 1 H), 1.81 (m, 1 H), 1.67–1.58 (m, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 0.93 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 136.0, 128.8, 108.7, 95.6, 82.1, 79.4, 73.6, 72.7, 55.7, 34.1, 31.8, 27.2, 26.9, 26.8, 17.9, 13.7.

MS (ESI): *m*/*z* = 329 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.09; H, 8.57.

Pinolide [(2*S*)-1]; Typical Procedure

To a solution of compound (2*S*)-**12** (50 mg, 0.15 mmol) in MeCN (10 mL), 4 M aq HCl (1 mL) was added at 0 °C; the mixture was stirred for 8 h at r.t. The mixture was neutralized with aq $NaHCO_3$ (5 mL) and extracted with EtOAc. The combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by purification of the residue by chromatography (50% hexane–EtOAc) provided pure pinolide [(2*S*)-**1**], 33 mg, 90%] as a white solid. $[\alpha]_D^{25}$ –9.8 (*c* 0.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.56–5.53 (m, 2 H), 5.01 (td, *J* = 9.0, 2.5 Hz, 1 H), 4.37 (dd, *J* = 5.0, 2.5 Hz, 1 H), 3.84 (br t, *J* = 9.0 Hz, 1 H), 3.45 (t, *J* = 9.0 Hz, 1 H), 2.92 (br s, 1 H), 2.48–2.38 (m, 2 H), 2.16–1.88 (m, 3 H), 1.73–1.55 (m, 1 H), 1.44–1.25 (m, 2 H), 0.94 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 132.7, 132.1, 77.0, 74.4, 74.3, 69.8, 33.5, 31.3, 26.6, 17.8, 13.8.

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

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.28.

(*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl (*R*)-2-(Methoxymethoxy)hex-5-enoate [(2*R*)-12]

Following the typical procedure for (2*S*)-**12** using (2*R*)-**3a** (87 mg, 0.5 mmol), anhyd THF (5 mL), 2,4,6-trichlorobenzoyl chloride (0.094 mL, 0.6 mmol), and Et_3N (0.35 mL, 2.5 mmol), followed by DMAP (122 mg, 1.0 mmol) and alcohol **2** (100 mg, 0.5 mmol) in toluene (5 mL) afforded (2*R*)-**12** (162 mg, 91%) as a colorless liquid. $[\alpha]_D^{25}$ +5.0 (*c* 0.1, $CHCl_3$).

IR (KBr): 2921, 1624, 1384, 1216, 770 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (m, 2 H), 5.40 (d, *J* = 17.0 Hz, 1 H), 5.27 (d, *J* = 9.0 Hz, 1 H), 5.18 (m, 1 H), 5.10–4.98 (m, 2 H), 4.70 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 7.0 Hz, 1 H), 4.31 (t, *J* = 7.0 Hz, 1 H), 4.12 (dd, *J* = 7.0, 5.0 Hz, 1 H), 3.83 (dd, *J* = 7.0, 6.0 Hz, 1 H), 3.39 (s, 3 H), 2.27–2.16 (m, 2 H), 1.89–1.79 (m, 2 H), 1.69–1.52 (m, 2 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.32–1.20 (m, 2 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 137.2, 135.8, 119.2, 115.5, 109.2, 96.2, 81.1, 79.1, 74.9, 73.0, 56.1, 32.7, 32.1, 29.4, 26.9, 26.8, 18.5, 13.9.

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

Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 63.92; H, 9.08.

(3a*R*,4*R*,7*R*,11a*R*,*E*)-7-(Methoxymethoxy)-2,2-dimethyl-4-propyl-3a,4,7,8,9,11a-tetrahydro-6*H*-[1,3]dioxolo[4,5-*c*]oxecin-6-one [(2*R*)-13]

Following the typical procedure for (2*S*)-**13** using (2*R*)-**12** (80 mg, 0.22 mmol) in degassed anhyd CH_2Cl_2 (75 mL) and Grubbs II catalyst (34 mg, 0.04 mmol) gave (2*R*)-**13** (61 mg, 83%) as a colorless liquid. $[\alpha]_D^{25}$ +4.3 (*c* 0.2, $CHCl_3$).

IR (KBr): 2925, 1749, 1650, 1458, 1380, 1049, 873 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.61 (ddd, *J* = 15.0, 10.0, 4.0 Hz, 1 H), 5.47 (ddd, *J* = 15.0, 10.0, 2.0 Hz, 1 H), 5.02 (td, *J* = 8.0, 4.0 Hz, 1 H), 4.68 (d, *J* = 7.0 Hz, 1 H), 4.61 (d, *J* = 7.0 Hz, 1 H), 4.55 (dd, *J* = 8.0, 7.0 Hz, 1 H), 3.94 (dd, *J* = 10.0, 8.0 Hz, 1 H), 3.56 (t, *J* = 10.0 Hz, 1 H), 3.33 (s, 3 H), 2.29 (m, 1 H), 2.18 (m, 1 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.84 (m, 1 H), 1.65–1.56 (m, 3 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 0.94 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 132.0, 129.2, 109.7, 96.8, 80.0, 76.7, 76.6, 76.1, 56.0, 35.5, 30.3, 27.1, 26.8, 23.8, 17.8, 13.9.

MS (ESI): *m*/*z* = 329 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.25; H, 8.55.

2-*epi*-Pinolide [(2*R*)-1]

Following the typical procedure for (2*S*)-**1** using (2*R*)-**12** (30 mg, 0.09 mmol) in MeCN (5 mL) and 4 M aq HCl (0.5 mL) gave (2*R*)-**1** (20 mg, 90%) as a white solid. $[\alpha]_D^{25}$ –6.0 (*c* 0.25, CD_3OD).

IR (KBr): 3496, 2921, 2851, 1715, 1459, 1383, 1219, 1080 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 5.51–5.30 (m, 2 H), 4.24–4.01 (m, 2 H), 3.67 (br t, *J* = 9.0 Hz, 1 H), 3.55 (br t, *J* = 9.0 Hz, 1 H), 2.22–2.13 (m, 2 H), 2.03 (m, 1 H), 1.91 (m, 1 H), 1.75–1.54 (m, 2 H), 1.39–1.26 (m, 2 H), 0.93 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 175.2, 133.5, 130.1, 77.5, 74.2, 71.6, 70.4, 36.2, 32.8, 25.1, 18.9, 14.4.

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

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.30.

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