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First Total Synthesis of Pinolide

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The first total synthesis of pinolide, a nonsymmetrical ten-membered macrocyclic, is described starting from readily available (–)-tartaric and L-ascorbic acid. The key synthetic steps include Barbier allylation, Yamaguchi esterification and ring-closing metathesis (RCM) reactions. The synthetic strategy has been successful for the construction of the ten-membered core skeleton. A facile and convergent approach enabled the incorporation of all the four stereogenic centers present in the molecule.

Introduction

Lactones are widely produced by fungi, and ten-membered lactones from fungal origin have played particularly important roles in the biochemical fields due to their biological properties.[1] Among these lactone derivatives are important compounds such as stagonolides,[2] herbarumins[3] and nonenolide,[4] which have diverse properties including herbicidal, antibacterial, antifungal and cytotoxic activities. Pinolide (**1**), a naturally occurring nonenolide, was also isolated from a fungal liquid culture CO-99 of *D. Pinodes*[5] along with three other known phytotoxic metabolites, namely Herbarumin I, Herbarumin II, and 2-*epi*-herbarumin II (Figure 1). The structure of pinolide was established on the basis of X-ray diffractometry but, to the best of our knowledge, no synthesis has been reported as a proof of structure.

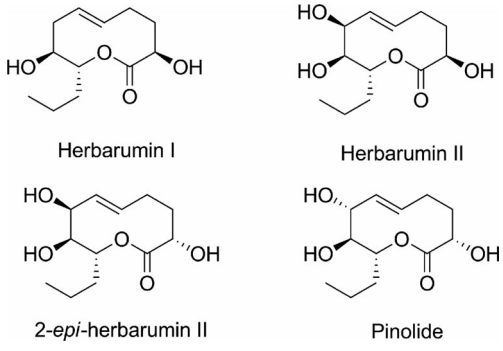

Figure 1. Structure of phytotoxic metabolites from *D. Pinodes*.

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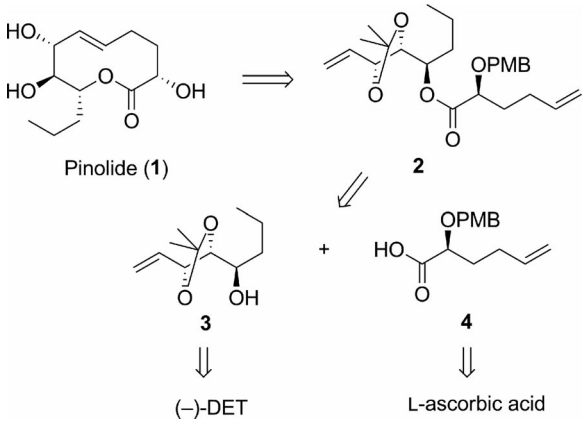
Results and Discussion

Herein, we report the first stereoselective total synthesis of pinolide by using a convergent approach. This approach involves Barbier allylation, Yamaguchi esterification, and ring-closing metathesis RCM reaction as key steps.

The retrosynthetic analysis of the target molecule **1** is depicted in Scheme 1. The macrolactone **1** can be synthesized by the coupling of two fragments, **3** and **4**, through esterification followed by olefin metathesis. Fragment **3** could be prepared from (–)-DET (diethyl tartrate), and the acid fragment **4** from naturally available L-ascorbic acid using established protocols.



Scheme 1. Retrosynthetic analysis for pinolide (**1**).

Initially, the synthesis of fragment **3** was undertaken from commercially available (–)-DET (Scheme 2). Accordingly, (–)-DET was converted into aldehyde **5** by using a known procedure[6] in four steps. Aldehyde **5** was then subjected to Zn-mediated stereoselective allylation (Barbier allylation) to furnish the corresponding homoallylic alcohols **6a** and **6b** as a mixture of diastereomers in a *anti*/*syn* ratio

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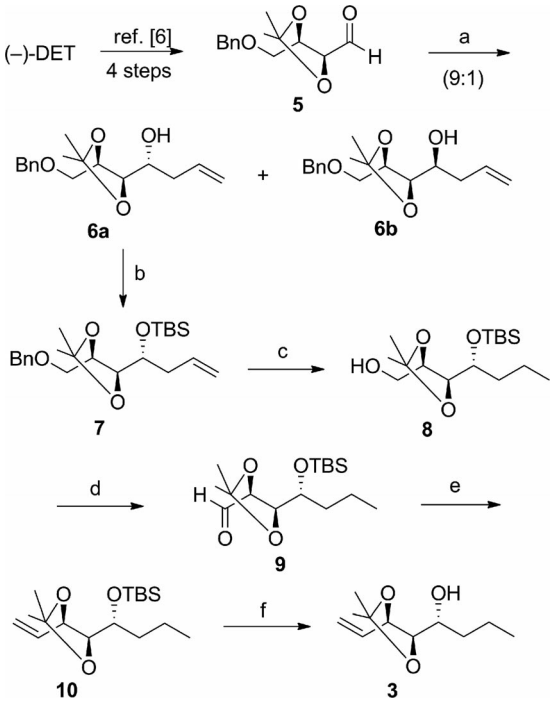
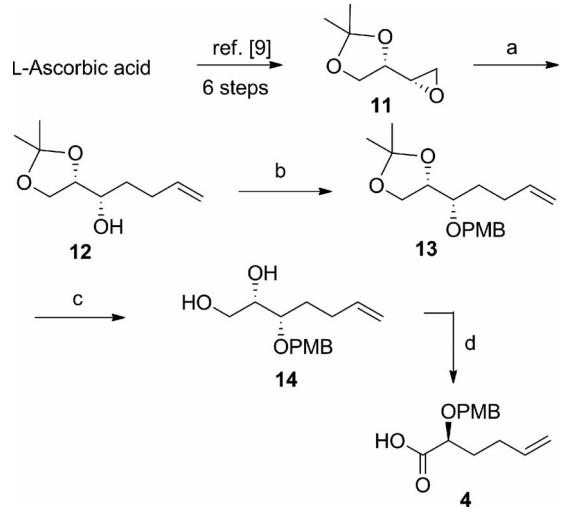
of 9:1 with 92% overall yield, which was separated by silica gel chromatography.[7] The newly generated chiral secondary alcohol **6a** was protected as TBS ether **7** in 97% yield and then hydrogenation by using H_2 in the presence of Pd/C (10%) to afford saturated primary alcohol **8** in 90% yield. Subsequently, oxidation of terminal primary alcohol **8** under Swern conditions provided aldehyde **9**, which was subsequently treated with iodomethyltriphenylphosphane in the presence of *n*BuLi to obtain olefinic compound **10** in 76% overall yield for two steps.[8] The TBS ether in compound **10** was then deprotected by using tetrabutylammonium fluoride (TBAF) to afford the desired fragment **3** in 86% yield.



Scheme 2. *Reagents and conditions:* (a) allyl bromide, zinc, I_2, THF, 0 °C to room temp., 1 h, 92%; (b) TBSCl, CH_2Cl_2, imidazole, 0 °C to room temp., 2 h, 97%; (c) H_2, Pd/C, MeOH, 5 h, 90%; (d) $(COCl)_2$/DMSO, Et_3N, CH_2Cl_2, –78 °C, 1.5 h; (e) $Ph_3P{=}CH_2I$, *n*BuLi, THF, 0 °C, 1 h, 76% (for two steps); (f) TBAF, THF, 0 °C, 2 h, 86%.

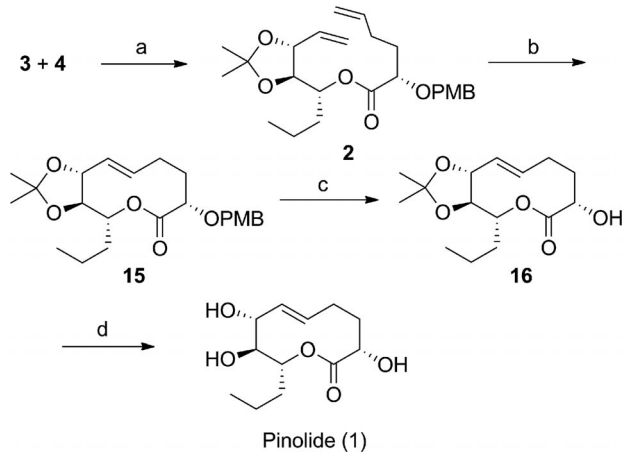
The second fragment **4** was synthesized from naturally available L-ascorbic acid, which was first converted into its epoxide **11** by using a known protocol in six steps as reported (Scheme 3).[9] Opening of epoxide **11** with allylmagnesium chloride afforded secondary alcohol **12** in 93% yield,[10] which was then protected as its PMB ether **13** by using *p*-methoxybenzyl chloride (PMBCl) in the presence of NaH in anhydrous tetrahydrofuran (THF) to afford compound **13** in 92% yield.

The acetonide present in compound **13** was deprotected by using *p*-toluenesulfonic acid (PTSA)/MeOH and the corresponding diol **14** was obtained in 86% yield. The diol was subsequently treated with sodium metaperiodate in CH_2Cl_2 to afford the corresponding aldehyde, and the crude aldehyde was then converted into its acid by using Pinnick's protocol to furnished the desired acid fragment **4** in 70% yield.[11]



Scheme 3. *Reagents and conditions:* (a) allyl chloride, Mg, anhydrous THF, 0 °C, 30 min, 93%; (b) PMB-Cl, NaH, THF, 0 °C, 3 h, 92%; (c) PTSA/MeOH, 2 h, room temp., 86%; (d) i. $NaIO_4$/CH_2Cl_2, $NaHCO_3$(cat), 2 h; ii. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, 0 °C to room temp., 7 h, 70%.

Acid fragment **4** was then coupled with alcohol fragment **3** by using Yamaguchi's protocol [2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-(*N*,*N*-dimethylamino)pyridine (DMAP)] to afford the dienoic ester **2** in 85% yield.[12] The terminal olefins were then subjected to RCM conditions using Grubbs' I catalyst (10 mol-%) under high dilution and reflux conditions (Scheme 4) to give only the *E* isomer of **15** in 73% yield.[13,14] It is noteworthy that no *Z* isomer was detected in the crude HPLC analysis, although traces might be present. In contrast, conducting the RCM reaction with Grubbs' II catalyst under similar conditions led to the formation **15** in an *E*/*Z* ratio of 2:1 based on crude HPLC and



Scheme 4. *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, catalytic DMAP, THF, then alcohol **3** in toluene, 4 h, 85%; (b) Grubbs' I catalyst (10 mol-%), CH_2Cl_2, reflux, 16 h, 73%; (c) DDQ, CH_2Cl_2, 1 h, 85%; (d) 2*N* HCl, THF, reflux, 1 h, 82%.

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^{1}H NMR spectroscopic analyses. The coupling constant value of 14.3 Hz for the olefinic protons confirmed the *E*-geometry of the resulting product. The PMB ether was deprotected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to furnish secondary alcohol **16** in 85% yield.

Finally, deprotection of the acetonide with 2*N* HCl in THF under reflux afforded pinolide (**1**) in 82% yield. The spectroscopic properties and optical rotation of the synthetic compound were similar to those reported for the natural product.[5]

Conclusions

A first total synthesis of pinolide has been achieved in 14 steps by using Barbier allylation, Yamaguchi esterification, and RCM as key steps. The key fragments **3** and **4** were accessed from easily available starting materials and the spectroscopic data of the synthesized target compound were in agreement with those of the natural product,[5] confirming the absolute stereochemistry.[15] The strategy can be conveniently utilized for the synthesis of similar compounds to enhance their availability and allow their further study.

Experimental Section

General: All the reagents and solvents were reagent grade and used without purification unless specified otherwise. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. When used as a reaction solvent, THF was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 and 100–200 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Optical rotations were measured with a digital polarimeter using a 2 mL cell with a 1 dm path length. FTIR spectra were recorded with a Thermo Nicolet Nexus 670 spectrometer as KBr discs or neat. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and [D$_4$]MeOH on 300, 400, 500, or 75 MHz spectrometers (Avance Innova) at ambient temperature.

(*R*)-1-[(4*R*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-but-3-en-1-ol (6a): Zinc (2.3 g, 36 mmol) and a catalytic amount of iodine (50 mg) were added to a solution of aldehyde **5** (3 g, 12.0 mmol) in anhydrous THF (50 mL). The mixture was stirred for 30 min at 0 °C, and then allyl bromide (2 mL 24.0 mmol) was added dropwise over a period of 15 min. After 1 h stirring at room temp. the reaction was quenched by the addition of saturated NH_4Cl, filtered through a small pad of Celite and the residue was washed with ethyl acetate (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure, which gave the diastereomeric mixture of allyl alcohols **6a** and **6b** (9:1 ratio). The crude diastereomeric mixture was purified by silica gel (100–200 mesh) column chromatography (hexane/ethyl acetate, 20%) to afford allylic alcohol **6a** (2.65 g, 82%) as a colorless liquid. $[\alpha]_D^{25}$ = –45.4 (*c* = 0.37, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3451, 2986, 2925, 1640, 1453, 1373, 1214, 1083, 993, 860, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 5.95–5.80 (m, 1 H), 5.19–5.11 (m, 2 H), 4.62–4.58 (m, 2 H), 4.16–4.08 (m, 1 H), 3.76–3.57 (m, 4 H), 2.50–2.39 (m, 1 H), 2.28–2.13 (m, 1 H), 1.40 (br. s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 134.2, 128.4, 127.8, 117.9, 109.0, 81.1, 78.0, 73.6, 71.3, 70.7, 37.9, 26.9, 26.8 ppm. MS (ESI): *m*/*z* = 315 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{17}H_{24}O_4Na$ [M + Na]$^+$ 315.1560; found 315.1566.

{(*R*)-1-[(4*S*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-but-3-enyloxy}(*tert*-butyl)dimethylsilane (7): To a stirred solution of **6a** (2.5 g, 8.5 mmol) in anhydrous CH_2Cl_2 (30 mL), imidazole (1.16 g, 17.1 mmol) was added. After 5 min, TBDMSCl (1.9 g, 12.8 mmol) and cat. DMAP were added and the reaction was stirred at room temp. for 2 h. The reaction was quenched by the addition of water, and the organic layer was collected. The aqueous layer was extracted with CH_2C1_2 (2 × 25 mL) and the combined organic layer was dried with anhydrous Na_2SO_4. The solvent mixture was evaporated and the residue was purified by silica gel (60–120 mesh) column chromatography (EtOAc/hexane, 5%) to afford **7** (3.3 g, 97%) as a colorless liquid. $[\alpha]_D^{25}$ = –13.2 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3450, 2931, 2858, 1637, 1462, 1253, 1092, 834, 773 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 5.90–5.75 (m, 1 H), 5.06 (dd, *J* = 1.5, 12.0 Hz, 2 H), 4.58 (ABq, *J* = 12.1 Hz, 2 H), 4.17 (td, *J* = 2.2, 7.5 Hz, 1 H), 3.85–3.64 (m,3 H), 3.50 (dd, *J* = 6.8, 9.8 Hz, 1 H), 2.42–2.24 (m, 2 H), 1.40 (s, 6 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 133.8, 128.2, 127.6, 12.5, 117.6, 109.1, 78.7, 78.4, 73.4, 72.9, 71.9, 38.8, 27.1, 27.0, 25.8, 18.0, –4.2, –4.3 ppm. MS (ESI): *m*/*z* = 407 [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{39}O_4Si$ 407.2609; found 407.2612.

{(4*R*,5*S*)-5-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)butyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (8): Compound **7** (3 g, 7.3 mmol) was dissolved in methanol (20 mL) and 10% Pd/C (50 mg) was added. The mixture was hydrogenated at 40 psi at room temperature for 5 h, then filtered through Celite and the solvents were evaporated under vacuum and the residue was purified by silica gel (60–120 mesh) column chromatography (EtOAc/hexane, 25%) to afford **8** (2.0 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = –2.5 (*c* = 0.45, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3444, 2957, 2932, 1465, 1252, 1089 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08–4.03 (m, 1 H), 3.85–3.77 (m, 3 H), 3.69–3.61 (m, 1 H), 1.65–1.55 (m, 2 H), 1.52–1.42 (m, 2 H), 1.40 (s, 6 H), 0.94–0.88 (m, 12 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.7, 79.4, 78.3, 72.9, 63.5, 36.7, 27.1, 27.0, 25.8, 17.0, 14.3, –4.3, –4.4 ppm. MS (ESI): *m*/*z* = 341 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{34}O_4NaSi$ 341.2122; found 341.2120.

***tert*-Butyl{(*R*)-1-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]butoxy}dimethylsilane (10):** A solution of DMSO (1.33 mL, 18.8 mmol) in CH_2Cl_2 (10 mL) was added to a solution of oxalyl chloride (0.83 mL, 9.4 mmol) in CH_2Cl_2 (20 mL) at –78 °C. The resulting solution was stirred for 10 min and alcohol **8** (1.5 g, 4.7 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 1 h. Triethylamine (3.28 mL, 23.5 mmol) was added and the mixture was stirred for an additional 10 min, then warmed to room temp. The reaction was quenched by the addition of water, and the organic layer was collected. The aqueous layer was extracted with CH_2C1_2 (2 × 20 mL) and the organic layers were combined, washed with water and brine, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel (60–120 mesh) column chromatography (EtOAc/hexane, 10%) to afford aldehyde **9** as a colorless liquid.

To a suspension of Ph_3PCH_3I (4.9 g, 12.3 mmol) in anhydrous THF (20 mL) under a nitrogen atmosphere cooled to 0 °C was slowly added a solution of *n*-BuLi (1.6 M in hexane, 5.13 mL, 8.22 mmol). The yellow suspension thus obtained was stirred for 10 min at 0 °C and for 1 h at room temperature, then a solution of aldehyde **9** (1.3 g, 4.11 mmol) in anhydrous THF (10 mL) was

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added very slowly at –78 °C. The mixture was slowly adjusted to room temperature and stirred for 15 min, then satd. NH_4Cl (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were dried with Na_2SO_4 and evaporated, and the crude product was purified by flash chromatography (hexane/EtOAc, 5%) to give olefin **10** (972 mg, 76% over two steps) as a liquid. $[\alpha]_D^{25}$ = +10.9 (*c* = 0.45, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2957, 2932, 1465, 1252, 1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.95–5.82 (m, 1 H), 5.38 (d, *J* = 16.9 Hz, 1 H), 5.21 (d, *J* = 10.3 Hz,1 H), 4.41 (t, *J* = 7.3 Hz, 1 H), 3.91–3.83 (m, 1 H), 3.79–3.72 (m, 1 H), 1.56–1.26 (m, 10 H), 0.93–0.85 (m, 12 H), 0.08 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.0, 117.5, 108.5, 82.7, 78.1, 71.5, 36.4, 27.0, 26.8, 25.9, 18.2, 18.1, 14.2, –4.1, –4.4 ppm. MS (ESI): *m*/*z* = 337 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{34}O_3NaSi$ 337.2174; found 337.2168.

(*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butan-1-ol (3): To a solution of **10** (800 mg, 2.54 mmol) in THF (10 mL) at 0 °C, was added TBAF (1 M in THF, 5 mL). After stirring for 2 h at room temp., the mixture was diluted with ethyl acetate, washed with H_2O (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10%) to give **3** (430 mg, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = +7.5 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3452, 2958, 2861, 1637, 1465, 1376, 1252, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.71 (m, 1 H), 5.33 (d, *J* = 17.3 Hz, 1 H), 5.16 (d, *J* = 9.8 Hz, 1 H), 4.37 (t, *J* = 7.5 Hz, 1 H), 3.83–3.75 (m, 1 H), 3.65 (dd, *J* = 3.7, 8.3 Hz, 1 H), 1.51–1.20 (m, 10 H), 0.82 (t, *J* = 3.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4, 118.7, 108.6, 83.0, 77.3, 70.1, 34.3, 26.9, 19.0, 13.8 ppm. MS (ESI): *m*/*z* = 233 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{11}H_{20}O_3Na$ 233.1305; found 233.1304.

(*S*)-1-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]pent-4-en-1-ol (12): A stirred suspension of Mg (640 mg, 3.4 mmol) in anhydrous THF (10 mL) was treated with allyl chloride (2.8 mL, 34.7 mmol) at room temp., and the mixture was stirred for 30 min and allowed come to 0 °C. Epoxide **11** (2.5 g, 17.3 mmol) in anhydrous THF (15 mL) was added dropwise at 0 °C, and the reaction mixture was stirred for 30 min at room temp., then the reaction was quenched by the addition of saturated NH_4Cl (10 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 15%) to give **12** (3 g, 93%) as a colorless liquid. $[\alpha]_D^{25}$ = –7.5 (*c* = 0.44, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3451, 2924, 1636, 1455, 1216, 1065 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.75 (m, 1 H), 5.10–4.95 (m, 2 H), 4.06–3.96 (m, 2 H), 3.79–3.69 (m, 1 H), 3.59–3.48 (m, 1 H), 2.37–2.10 (m, 2 H), 1.67–1.46 (m, 2 H), 1.44 (s, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 115.0, 109.3, 79.0, 71.5, 66.1, 32.9, 29.6, 26.6, 25.3 ppm. MS (ESI): *m*/*z* = 209 $[M + Na]^+$.

(*R*)-4-[(*S*)-1-(4-Methoxybenzyloxy)pent-4-enyl]-2,2-dimethyl-1,3-dioxolane (13): To a cooled (0 °C) suspension of NaH (60% w/w dispersion in paraffin oil, 640 mg, 26.8 mmol) in THF (20 mL) was added dropwise a solution of alcohol **12** (2.5 g, 13.4 mmol) in THF (10 mL). After 15 min, *p*-methoxybenzyl chloride (1.82 mL, 13.4 mmol) was added dropwise at 0 °C and the mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of satd. NH_4Cl (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, 10%) to afford **13** (4.1 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = –24.4 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2985, 1612, 1513, 1247, 1071, 1037, 913, 822 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.85–5.69 (m, 1 H), 5.04–4.92 (m, 2 H), 4.62 (ABq, *J* = 11.3 Hz, 2 H), 4.21 (q, *J* = 6.7 Hz, 1 H), 3.98 (dd, *J* = 6.7, 7.5 Hz, 1 H), 3.80 (s, 3 H), 3.78–3.64 (m, 1 H), 3.49–3.40 (m, 1 H), 2.32–2.01 (m, 2 H), 1.89–1.80 (m, 1 H), 1.63–1.46 (m, 1 H), 1.44 (s, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 138.2, 130.7, 129.5, 114.9, 113.6, 109.2, 78.5, 78.2, 72.8, 65.8, 55.2, 29.9, 29.7, 26.5, 25.3 ppm. MS (ESI): *m*/*z* = 329 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{26}O_4Na$ 329.1717; found 289.1723.

(2*R*,3*S*)-3-(4-Methoxybenzyloxy)hept-6-ene-1,2-diol (14): A solution of **13** (2 g, 6.5 mol) in MeOH (30 mL) was treated with PTSA (0.5 g), and the mixture was stirred at room temp. for 2 h. The reaction was quenched by the addition of satd. $NaHCO_3$ (10 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, 30%) to afford **14** (1.48 g, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = +18.5 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3417, 2928, 1612, 1513, 1247, 1034, 912, 821, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 5.82–5.66 (m, 1 H), 5.02–4.87 (m, 2 H), 4.42 (ABq, *J* = 10.6 Hz, 2 H), 3.73 (s, 3 H), 3.69–3.47 (m, 3 H), 3.41 (dd, *J* = 6.0, 10.5 Hz, 1 H), 2.14–2.03 (m, 2 H), 1.76–1.52 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 138.0, 129.9, 129.5, 115.0, 113.8, 78.6, 72.6, 71.9, 63.9, 55.2, 29.6, 29.3 ppm. MS (ESI): *m*/*z* = 289 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{22}O_4Na$ 289.1405; found 289.1410.

(*S*)-2-(4-Methoxybenzyloxy)hex-5-enoic Acid (4): To a solution of **14** (1 g, 3.7 mmol) in CH_2Cl_2 (10 mL), sodium periodate (0.95 g, 4.13 mmol) and satd. $NaHCO_3$ (catalytic) was added at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then filtered and the filtrate was washed with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and the solvent was evaporated in vacuo to give the crude aldehyde.

To a stirred solution of the above aldehyde (750 mg, 3.2 mmol) and 2-methyl-2-butene (1.5 mL) in *t*BuOH (1.5 mL) was added a freshly prepared mixture of $NaClO_2$ (1.27 mg, 14.1 mmol) and NaH_2PO_4 (2.2 g, 14.1 mmol) in H_2O at 0 °C. After stirring at 0 °C for 7 h, the reaction was quenched by the addition of satd. NH_4Cl and extracted with ethyl acetate. The extract was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 20%) to give **4** (490 mg, 70% yield over two steps) as a yellow liquid. $[\alpha]_D^{25}$ = –45.4 (*c* = 0.37, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3447, 2926, 2854, 1720, 1612, 1461, 1249, 1106, 915, 822, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.78–5.62 (m, 1 H), 4.99–4.88 (m, 2 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 4.35 (d, *J* = 11.1 Hz, 1 H), 3.92 (t, *J* = 6.0 Hz, 1 H), 3.74 (s, 3 H), 2.19–2.03 (m, 2 H), 1.87–1.77 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 159.5, 137.1, 129.8, 129.0, 115.6, 113.9, 72.3, 55.2, 31.7, 29.1 ppm. MS (ESI): *m*/*z* = 251 $[M + H]^+$.

(S)-{(*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl} 2-(4-Methoxybenzyloxy)hex-5-enoate (2): To a stirred solution of acid **4** (250 mg, 1.0 mmol) in anhydrous THF (10 mL) were added 2,4,6-trichlorobenzoyl chloride (0.187 mL, 1.2 mmol) and Et_3N (0.695 mL, 5.0 mmol), and the contents were stirred at ambient temperature. After completion of the mixed anhydride formation (indicated by TLC), DMAP (244 mg, 2.0 mmol) and a solution of alcohol **19** (200 mg, 1.0 mmol) in toluene (10 mL) were added and

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the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched by the addition of water and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (100–200 mesh; EtOAc/hexane, 10%) to afford **2** (367 mg, 85%) as a colorless liquid. $[\alpha]_D^{25}$ = –16.7 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3462, 2925, 2861, 1728, 1455, 1236, 1070 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 6.87 (d, *J* = 8.9 Hz, 2 H), 5.89–5.72 (m, 2 H), 5.39 (d, *J* = 16.9 Hz, 1 H), 5.28–5.20 (m, 2 H), 5.03–4.95 (m, 2 H), 4.65 (dd, *J* = 1.0, 10.9 Hz, 1 H), 4.36–4.28 (m, 2 H), 3.92 (dd, *J* = 1.0, 5.9 Hz, 1 H), 3.82 (dd, *J* = 2.0, 5.9 Hz, 1 H), 3.80 (s, 3 H), 2.26–2.12 (m, 2 H), 1,87–1.81 (m, 2 H), 1.69–1.58 (m, 2 H), 1.41 (s, 6 H), 1.39–1.24 (m, 2 H), 0.92 (t, *J* = 7.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 159.3, 137.3, 135.8, 129.6, 129.5, 118.8, 115.3, 113.7, 109.2, 81.1, 79.3, 76.9, 73.0, 71.9, 55.2, 33.0, 32.2, 29.4, 26.9, 26.8, 18.4, 13.7 ppm. MS (ESI): *m*/*z* = 455 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{25}H_{36}O_6Na$ 455.2397; found 455.2404.

(3a*R*,4*R*,7S,11a*R*,*E*)-7-(4-Methoxybenzyloxy)-2,2-dimethyl-4-propyl-7,8,9,11a-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]oxecin-6(4*H*)-one (15): A degassed solution of Grubbs' first generation catalyst (0.057 g, 0.069 mmol) in CH_2Cl_2 (30 mL) was added over 30 min to a refluxing solution of **2** (300 mg, 0.69 mmol) in CH_2Cl_2 (250 mL) and the mixture was heated to reflux and stirred for 16 h. When the starting material was completely consumed (judged by TLC), the reaction was stopped and allowed to come to room temperature. The solvent was removed under reduced pressure to give a dark-brown residue. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 7%) to afford the single *E* isomer **15** (170 mg, 73%) as a colorless liquid. $[\alpha]_D^{25}$ = +4.8 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2928, 1725, 1612, 1513, 1459, 1244, 1065, 974, 825 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.27 (d, *J* = 8.3 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 5.72–5.63 (m, 1 H), 5.57 (dd, *J* = 9.0, 14.3 Hz, 1 H), 5.18 (td, *J* = 2.2, 9.0 Hz, 1 H), 4.68 (d, *J* = 11.3 Hz, 1 H), 4.38 (d, *J* = 11.3 Hz, 1 H), 4.06–3.96 (m, 2 H), 3.82 (s, 3 H), 3.49 (t, *J* = 9.0 Hz, 1 H), 2.51–2.36 (m, 1 H), 2.18–1.97 (m, 3 H), 1.91–1.77 (m, 1 H), 1.73–1.58 (m, 3 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 0.95 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.8, 159.2, 135.9, 129.0, 128.8, 113.7, 108.7, 82.2, 79.4, 75.5, 73.5, 72.0, 55.2, 34.2, 32.0, 27.0, 26.9, 26.7, 18.0, 13.7 ppm. MS (ESI): *m*/*z* = 427 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{22}H_{29}O_6Na$ 427.2083; found 427.2091.

(3a*R*,4*R*,7*S*,11a*R*,*E*)-7-Hydroxy-2,2-dimethyl-4-propyl-7,8,9,11a-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]oxecin-6(4*H*)-one (16): To a stirred solution of **15** (100 mg, 0.24 mmol) in CH_2Cl_2/H_2O (19:1; 10 mL) was added DDQ (56 mg, 0.24 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (2× 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried on Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/*n*-hexane, 10%) to afford alcohol **16** (59 mg, 85%) as a liquid. $[\alpha]_D^{25}$ = +4.9 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3462, 2925, 1728, 1455, 1236, 1070, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.74–5.60 (m, 1 H), 5.52 (dd, *J* = 9.2, 15.2 Hz, 1 H), 5.17 (td, *J* = 2.2, 9.4 Hz, 1 H), 4.37 (d, *J* = 4.3 Hz, 1 H), 4.01 (t, *J* = 8.8 Hz, 1 H), 3.44 (t, *J* = 8.8 Hz, 1 H), 2.54–2.36 (m, 2 H), 2.25–2.06 (m, 4 H), 1.93–1.76 (m, 1 H), 1.71–1.44 (m, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.8, 136.5, 128.2, 108.8, 82.0, 79.2, 74.4, 69.7, 33.9, 32.0, 26.8, 26.7, 26.5, 17.8, 13.6 ppm. MS (ESI): *m*/*z* = 307 $[M + Na]^+$.

Pinolide (1): A solution of **16** (30 mg, 0.10 mmol) in THF (5 mL) and aq. HCl (0.5 mL, 2*N*) was stirred at 60 °C for 1 h. The reaction mixture was neutralized with aq. $NaHCO_3$ (5 mL) and the combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation of the solvent followed by purification of the residue by chromatography (hexane/EtOAc, 50%) provided **1** (20 mg, 82%) as a white solid. $[\alpha]_D^{25}$ = –9.2 (*c* = 0.4, $CHCl_3$) {ref.[5] $[\alpha]_D^{25}$ = –8.8 (*c* = 0.2)}. IR (neat): $\tilde{\nu}$ = 3434, 2925, 2854, 1709, 1463, 1377, 1272, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.55 (dd, *J* = 7.1, 14.9 Hz, 1 H), 5.53 (ddd, *J* = 3.9, 9.8, 14.9 Hz, 1 H), 5.0 (td, *J* = 2.2, 8.8 Hz, 1 H), 4.41–4.33 (m, 1 H), 3.84 (br. t, *J* = 7.1 Hz, 1 H), 3.46 (dd, *J* = 8.8, 9.0 Hz, 1 H), 2.56–2.26 (m, 2 H), 2.19–1.86 (m, 3 H), 1.71–1.52 (m, 1 H), 1.46–1.29 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 132.6, 132.0, 77.0, 74.4, 74.3, 69.8, 33.5, 31.3, 26.5, 17.8, 13.8 ppm. MS (ESI): *m*/*z* = 267 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{20}O_5Na$ 267.1206; found 267.1202.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for certain important compounds and intermediates.

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[15] The spectroscopic data of the isolated natural product and synthetic product are compared in the Supporting Information.

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