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Synthesis of the C_1–C_6 subunit of discodermolide from furan

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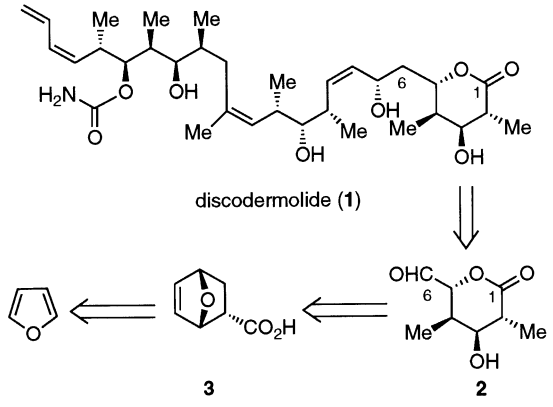
Abstract—The synthesis of the C_1–C_6 subunit of the potent antitumor agent discodermolide has been performed using 7-oxanorbornene derivatives, derived from furan, as key intermediates to control the stereochemistry of the incoming functional groups.

Discodermolide **1** is a polyhydroxylated lactone first isolated in 1990 by Gunasekera et al.[1] from a Caribbean marine sponge, *Discodermia dissoluta* (Scheme 1). This unique polyketide displays potent activity as an antimitotic agent, with a similar mechanism of action to taxol, namely by stabilizing microtubules and promoting the polymerization of tubulin.[2] Discodermolide inhibits the growth of human breast cancer cell in vitro, as well as taxol-resistant ovarian and colon cancer cells.[3] The exceptional pharmacological potential and extreme scarcity of the natural material [0.002% (w/w) from frozen sponge] have stimulated intensive synthetic effort. To date, several total syntheses of both, the natural (+)-discodermolide and its antipodal (−)-discodermolide have been reported.[4]

Herein, we report the synthesis of the subunit C_1–C_6, **2**, of discodermolide using 7-oxanorbornene derivative **3**[5] as precursor, readily available from furan via Diels–Alder cycloaddition with acrylic acid (Scheme 1).[6]

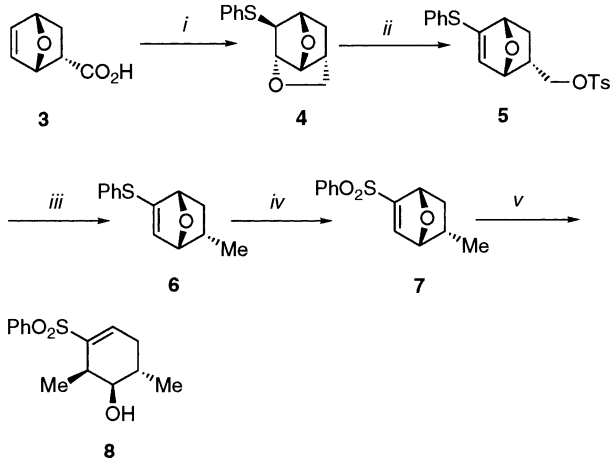


Scheme 1.

1. Results and discussion

The synthesis of the tetrasubstituted δ-lactone **2** was accomplished starting from vinyl sulfone **8**,[7] obtained in six steps (46% overall yield) from **3**. Treatment of tricyclic compound **4**[7] with *n*-BuLi followed by addition of TsCl afforded tosylate **5**. Chemoselective reduction of the tosylate function and further oxidation of the resulting sulfide **6** yielded **7**. Alkylative oxa-bridge opening[8] using MeLi finally gave rise to cyclohexenyl sulfone **8** (Scheme 2).

Epoxidation of **8** using lithium *tert*-butylperoxide,[9] followed by protection of the hydroxyl group afforded α,β-epoxysulfone **10**. Treatment with $MgBr_2$[10] gave rise to a mixture of α-bromoketones **11** and **12** in a ratio **11**:**12**, 2.2:1 and 85% overall yield.[11] Final transformation of this mixture into enone **13** was achieved using $CaCO_3$ in DMF.[12] Alternatively, epoxysulfone **10** was transformed



Scheme 2. (*i*) Two steps, 85%. See Ref. 8; (*ii*) *n*-BuLi, THF, −78°C. Then TsCl, −78°C to rt, 83%; (*iii*) $LiAlH_4$, Et_2O, 0°C, 5 h, 81%; (*iv*) MMPP, MeOH, 0°C to rt, 12 h, 86%; (*v*) MeLi, THF, −78°C, 1 h, 94%.

Keywords: discodermolide; polypropionates; 7-oxanorbornene derivatives.

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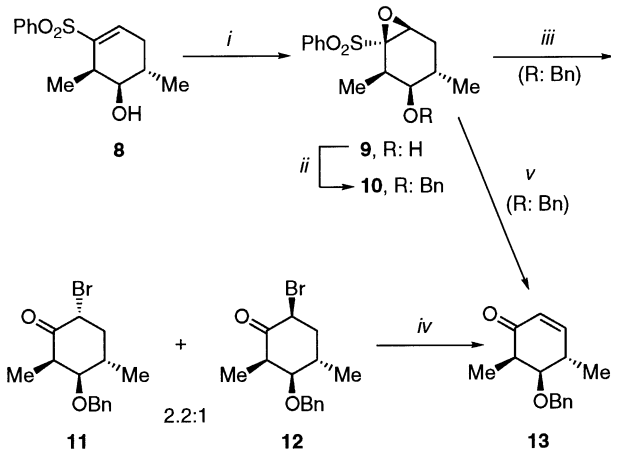
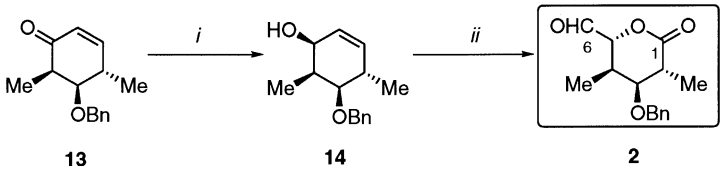


Scheme 3. (*i*) *t*-BuO_2Li, THF, −78°C to rt, 92%; (*ii*) BnBr, NaH, TBAI, THF, 0°C, 96%; (*iii*) $MgBr_2$, Et_2O, rt, 5 h, 85%; (*iv*) $CaCO_3$, DMF, 150°C, 32%; (*v*) LDA, ether–hexane, −78°C to rt, 65%.



Scheme 4. (*i*) $NaBH_4$, $CeCl_3$, MeOH, −78°C, 81%; (*ii*) (a) O_3, $NaHCO_3$, CH_2Cl_2, −78°C. (b) Ac_2O, pyr, CH_2Cl_2, rt, 61% (overall).

directly into **13** upon reaction with lithium diisopropylamide in ether-hexane. A *syn*-β-elimination could be a reasonable pathway for this transformation (Scheme 3).[13,14]

Reduction of enone **13** under Luche's conditions[15] afforded the allylic alcohol **14**,[16] which was subjected to ozonolysis, in absence of MeOH, following Schreiber's procedure[17] to afford the desired δ-lactone **2**[18] in 61% overall yield (Scheme 4).

In summary, an efficient synthesis of a key fragment, the δ-lactone **2**, of discodermolide has been performed in a stereocontrolled fashion and starting from readily available materials, easily obtained from furan.

2. Experimental

2.1. General

Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone; methylene chloride, diethylamine and diisopropylamine from calcium hydride, all under argon. The remaining solvents and chemicals were commercial and used as received. All products were purified by flash chromatography using 230–400 mesh silica gel. Analytical TLC was carried out on silica gel plates. Melting points are uncorrected. ^1H- and ^{13}C NMR were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. When peak multiplicities are reported, the following abbreviations are used: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets); dt (doublet of triplets). Chemical shifts (δ) are reported in ppm from $(CH_3)_4Si$ as internal standard and J values are given in Hertz. IR spectra were recorded on a FT-IR spectrometer as thin films or KBr disks. Elemental analyses were performed at the Universidad Complutense de Madrid.

2.1.1. 2-(Phenylsulfenyl)-5-*endo*-(*p*-toluensulfonyloxymethyl)-7-oxabicyclo[2.2.1] hept-2-ene (5). To a solution of **4**[7] (1.43 g, 6.11 mmol) in 30 mL of THF cooled at −78°C, 5.73 mL of a 1.6 M *n*-BuLi solution in hexane (1.5 equiv.) was added dropwise. After stirring for 1 h at −78°C, TsCl (3.50 g, 18.3 mmol) was added and the reaction stirred for an additional hour and led to reach rt. The reaction mixture was quenched with water, extracted with AcOEt and the organic layer was dried over $MgSO_4$. Elimination of the solvent under reduced pressure and further purification by flash chromatography of the residue eluting with hexanes/ethyl acetate (5:1) produced 1.96 g of **5** as a colorless oil (83%): IR ($CHCl_3$) ν 2980, 1710, 1365, 1190; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.73 (dd, 1H, J=11.6, 4.2 Hz), 1.86 (ddd, 1H, J=11.9, 9.4, 4.9 Hz), 2.38 (s, 3H), 2.48–2.60 (m, 1H), 3.42 (t, 1H, J=10.2 Hz), 3.91 (dd, 1H, J=9.9, 5.7 Hz), 4.62 (d, 1H, J=4.7 Hz), 4.90 (d, 1H, J=4.5 Hz), 5.72 (s, 1H), 7.20–7.36 (m, 7H), 7.70 (d, 2H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 28.0, 40.1, 71.9, 80.3, 80.9, 127.5, 127.8, 127.9, 129.1, 129.3, 129.9, 130.8, 131.2, 144.3, 145.0. Anal. Calcd for $C_{20}H_{19}O_4S_2$: C, 61.85; H, 5.15. Found: C, 61.70; H, 5.32.

2.1.2. 5-*endo*-Methyl-2-(phenylsulfenyl)-7-oxabicyclo-[2.2.1]hept-2-ene (6). To a suspension of $LiAlH_4$ (124 mg, 3.25 mmol) in 6.5 mL of ether at 0°C, 505 mg (1.30 mmol) of **5** dissolved in 6.5 mL of ether were added. After being stirred for 5 h at 0°C, the mixture was diluted with water and ether. The resulting crude was extracted over 10 h and the combined organic extracts were dried over $MgSO_4$. Concentration under reduced pressure and purification via flash chromatography eluting with hexanes/ethyl acetate (10:1) provided 230 mg of **6** (81%) as a colorless oil: IR ($CHCl_3$) ν 2980, 2870, 1460, 1270; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (dd, 1H, J=11.1, 4.4 Hz), 0.83 (d, 3H, J=6.7 Hz), 2.01 (ddd, 1H, J=11.1, 9.1, 5.0 Hz), 2.26–2.36 (m, 1H), 4.68 (d, 1H, J=5.0 Hz), 4.81 (d, 1H, J=4.7 Hz), 6.10 (s, 1H), 7.34–7-46 (m, 3H), 7.41 (d, 2H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.9, 33.2, 34.7, 81.2, 83.3, 127.4, 129.0, 129.2, 129.6, 131.0, 142.9. Anal. Calcd for $C_{13}H_{14}OS$: C, 71.56; H, 6.42. Found: C, 71.45; H, 6.30.

2.1.3. 5-*endo*-Methyl-2-(phenylsulfonyl)-7-oxabicyclo-[2.2.1]hept-2-ene (7). A solution of **6** (490 mg, 2.25 mmol) in 22 mL of MeOH was cooled to 0°C and

MMPP (2.22 g, 4.50 mmol) was added. After stirring for 12 h the reaction was quenched with saturated aqueous $NaHCO_3$ solution and concentrated in vacuo. The residue was diluted with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and removal of the solvent under vacuum followed by purification via flash chromatography eluting with hexanes/ethyl acetate (2:1) afforded 485 mg of **7** (86%) as a white solid: mp 71–72°C; IR (KBr) ν 2980, 1580, 1440, 1150; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (d, 3H, J=7.1 Hz), 0.87 (dd, 1H, J=11.1, 4.0 Hz), 2.10 (ddd, 1H, J=11.4, 9.1, 4.7 Hz), 2.28–2.40 (m, 1H), 4.87 (d, 1H, J=5.0 Hz), 4.90 (d, 1H, J=5.0 Hz), 6.97 (s, 1H), 7.51 (t, 2H, J=7.7 Hz), 7.60 (t, 1H, J=7.1 Hz), 7.88 (d, 2H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.6, 33.2, 33.5, 79.3, 83.3, 128.0, 129.5, 134.0, 142.7, 147.0, 150.2. Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.40; H, 5.60. Found: C, 62.26; H, 5.51.

2.1.4. (1*S,2*S**,6*R**)-3-(Phenylsulfonyl)-2,6-dimethylcyclohex-3-en-1-ol (8).** To a solution of **7** (471 mg, 1.88 mmol) in 9.4 mL of THF cooled at −78°C, 3.53 mL of a 1.6 M MeLi solution in ether (5.63 mmol) was added dropwise. After stirring for an hour at −78°C, the reaction was quenched with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was chromatographed eluting with hexanes/ethyl acetate (1:1) to give **8** (470 mg, 94%) as a white solid: mp 112–113°C; IR (KBr) ν 3400–3200, 1450, 1310, 720; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, 3H, J=6.4 Hz), 1.00 (d, 3H, J=6.7 Hz), 1.80–1.98 (m, 3H), 2.46–2.65 (m, 2H), 3.29 (dd, 1H, J=10.4, 5.0 Hz), 6.90 (dd, 1H, J=4.0, 2.7 Hz), 7.48 (t, 2H, J=7.7 Hz), 7.57 (t, 1H, J=7.4 Hz), 7.80 (d, 2H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 17.7, 28.3, 33.9, 34.4, 74.5, 128.0, 129.3, 133.3, 138.2, 140.2, 143.5. Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.78; H, 6.32.

2.1.5. (1*R,2*S**,3*S**,4*R**,6*R**)-1-(Phenylsulfonyl)-2,4-dimethyl-7-oxabicyclo[4.1.0]heptan-3-ol (9).** A solution containing *t*-BuOOH (0.10 mL, 0.77 mmol) in 1.5 mL of THF was cooled to −78°C. *n*-BuLi (0.48 mL, 0.77 mmol) was added dropwise and the resulting solution was stirred for 15 min at the same temperature. Then, 103 mg (0.39 mmol) of **8** dissolved in 1.5 mL of THF were added, the reaction was warmed to rt and stirred overnight. The reaction mixture was quenched with brine, the organic layer was extracted with ether and dried over $MgSO_4$ and the solvent removed under reduced pressure. After purification by chromatography eluting with hexanes/ethyl acetate (1:1) 100 mg (92%) of **9** were obtained as a colorless oil: IR ($CHCl_3$) ν 3600–3300, 1460, 1330, 1160; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.55 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=5.9 Hz), 1.49–1.63 (m, 2H), 1.83–1.90 (m, 1H), 2.21 (q, 1H, J=11.0 Hz), 2.96 (quint, 1H, J=6.8 Hz), 3.31–3.39 (m, 1H), 3.76 (s, 1H), 7.55 (t, 2H, J=7.7 Hz), 7.67 (t, 1H, J=7.3 Hz), 7.88 (d, 2H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.7, 16.9, 25.7, 31.4, 32.0, 56.8, 73.6, 75.1, 129.2, 129.3, 134.4, 136.1. Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.57; H, 6.38. Found: C, 59.48; H, 6.30.

2.1.6. (1*R,2*S**,3*S**,4*R**,6*R**)-3-(Benzyloxy)-1-(phenylsulfonyl)-2,4-dimethyl-7-oxa bicyclo[4.1.0]heptane (10).** To a solution of **9** (94 mg, 0.33 mmol) in 3.5 mL of THF cooled at 0°C, were added 20 mg (0.50 mmol, 60% mineral dispersion) of NaH, 0.08 mL (0.67 mmol) of BnBr and 12.3 mg (0.03 mmol) of tetrabutylammonium iodide. The reaction mixture was allowed to warm to rt and stirred overnight. Then, quenched with water, extracted with AcOEt and dried over $MgSO_4$. The residue was chromatographed eluting with hexanes/ethyl acetate (5:1) to give 119 mg (96%) of **10** as a white solid: mp 95–96°C; IR (KBr) ν 2830, 1580, 1340, 1270; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (d, 3H, J=6.9 Hz), 0.93 (d, 3H, J=6.3 Hz), 1.53–1.68 (m, 2H), 2.23 (dd, 1H, J=11.0, 4.0 Hz), 3.08–3.22 (m, 2H), 3.78 (s, 1H), 4.48 (syst AB, 2H, J_{AB}=11.4 Hz), 7.29–7.34 (m, 5H), 7.60 (tt, 2H, J=7.0, 1.5 Hz), 7.72 (tt, 1H, J=7.0, 1.5 Hz), 7.92 (d, 2H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.9, 17.3, 25.0, 28.3, 32.7, 57.1, 71.3, 75.2, 80.6, 127.7, 128.4, 129.2, 129.5, 134.4, 136.2, 136.7, 137.9. Anal. Calcd for $C_{21}H_{23}O_4S$: C, 67.92; H, 6.20. Found: C, 68.03; H, 6.36.

2.1.7. (2*S,3*S**,4*R**,6*S**)-3-(Benzyloxy)-6-bromo-2,4-dimethylcyclohexan-1-one (11), and (2*S**,3*S**,4*R**,6*R**)-3-(benzyloxy)-6-bromo-2,4-dimethylcyclohexan-1-one (12).** To a suspension of $MgBr_2{\cdot}OEt_2$ (73 mg, 0.28 mmol) in 1.2 mL of ether, 70 mg (0.19 mmol) of **10** dissolved in 1.5 mL of ether were added and the mixture was stirred for 6 h. The reaction was quenched with brine, extracted with ether and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed eluting with hexanes/ethyl acetate (4:1) to afford 35 mg (59%) of **11** and 16 mg (26%) of **12**, both as colorless oils.

Compound **11**: IR ($CHCl_3$) ν 3020, 1730, 1570, 1100; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, 3H, J=6.9 Hz), 1.16 (d, 3H, J=7.0 Hz), 1.77 (dd, 1H, J=13.9, 10.2 Hz), 2.24 (quintd, 1H, J=7.0, 1.8 Hz), 2.54 (dd, 1H, J=13.9, 5.6 Hz), 3.21 (qd, 1H, J=6.9, 4.0 Hz), 3.35 (dd, 1H, J=7.0, 4.0 Hz), 4.44 (syst AB, 2H, J_{AB}=11.8 Hz), 4.67 (dd, 1H, J=10.3, 5.7 Hz), 7.25–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 18.1, 32.2, 39.2, 44.7, 50.4, 71.1, 83.9, 127.5, 127.8, 128.4, 137.7, 203.7. Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.11. Found: C, 57.96; H, 6.06.

Compound **12**: IR ($CHCl_3$) ν 2840, 1730, 1580, 1380; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, 3H, J=6.6 Hz), 1.20 (d, 3H, J=7.7 Hz), 2.25–2.40 (m, 2H), 2.62 (td, 1H, J=12.8, 4.8 Hz), 2.82 (qt, 1H, J=6.6, 2.8 Hz), 3.62 (td, 1H, J=2.9, 1.1 Hz), 4.50 (syst AB, 2H, J_{AB}=11.9 Hz), 4.73 (dd, 1H, J=12.8, 5.9 Hz), 7.26–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 15.9, 31.7, 40.0, 44.8, 52.8, 71.2, 86.1, 127.5, 128.3, 136.5, 137.9, 200.9. Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.11. Found: C, 57.96; H, 6.06.

2.1.8. (4*R,5*S**,6*S**)-5-(Benzyloxy)-4,6-dimethylcyclohex-2-en-1-one (13).** *Method A:* $CaCO_3$ (312 mg, 3.12 mmol) was suspended in 13 mL of DMF and the mixture was heated to 150°C. 194 mg (0.62 mmol) of a mixture of compounds **11** and **12** dissolved in 4 mL of DMF were added dropwise and stirring was maintained for 45 min at the same temperature. After cooling to rt, the reaction was quenched with water, extracted with ether and dried over $MgSO_4$. Concentration in vacuo and purification by

chromatography (hexanes/ethyl acetate 10:1) afforded 46 mg (32%) of **13** as a colorless oil.

Method B: A solution containing diisopropylamine (0.09 mL, 0.63 mmol) in 1 mL of ether was cooled to −78°C. Then, 0.40 mL of *n*-BuLi (0.64 mmol, 1.6 M solution in hexane) was added dropwise and after being stirred for 20 min, 47 mg (0.13 mmol) of **10** dissolved in 1.3 mL of ether were added dropwise. The reaction was warmed gradually to rt and refluxed for an additional 3 h. The reaction was quenched with water, extracted with ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by purification as described above afforded 19 mg (65%) of **13**. IR ($CHCl_3$) ν 3040, 1670, 1470, 1140; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, 3H, J=7.1 Hz), 1.22 (d, 3H, J=7.0 Hz), 2.71 (m, 1H), 2.85 (qd, 1H, J=7.1, 4.0 Hz), 3.56 (dd, 1H, J=6.9, 4.0 Hz), 4.52 (syst AB, 2H, J_{AB}=11.4 Hz), 5.93 (dd, 1H, J=10.1, 2.1 Hz), 6.66 (dd, 1H, J=10.1, 3.1 Hz), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 17.0, 33.5, 43.3, 71.1, 82.3, 127.4, 127.9, 128.3, 128.5, 137.9, 151.9, 202.1. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.26; H, 7.83. Found: C, 78.14; H, 7.74.

2.1.9. (1*R,4*R**,5*S**,6*R**)-5-(Benzyloxy)-4,6-dimethylcyclohex-2-en-1-ol (14).** A solution of $CeCl_3{\cdot}7H_2O$ (566 mg, 1.49 mmol) dissolved in 3 mL of MeOH was cooled to −78°C and $NaBH_4$ (42.6 mg, 1.12 mmol) was added. After 30 min, 172 mg (0.75 mmol) of **13** dissolved in 4.5 mL of MeOH were added at the same temperature, and the reaction was warmed gradually to rt. After being stirred for 3 h, the reaction mixture was diluted with a 0.5N HCl solution, extracted with ether and dried over $MgSO_4$. Concentration in vacuo followed by purification by chromatography eluting with hexanes/ethyl acetate (10:1) afforded 140.5 mg of **14** (81%) as a colorless oil: IR ($CHCl_3$) ν 3600–3300, 1650, 1380, 1150; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (d, 3H, J=7.3 Hz), 1.17 (d, 3H, J=7.0 Hz), 2.03 (m, 1H), 2.54 (m, 1H), 2.65 (d, 1H, J=10.2 Hz), 3.39 (s, 1H), 3.87 (dt, 1H, J=10.3, 5.1 Hz), 4.50 (syst AB, 2H, J_{AB}=11.4 Hz), 5.63 (dd, 1H, J=10.0, 5.0 Hz), 5.88 (ddd, 1H, J=10.0, 4.5, 1.5 Hz), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.9, 18.3, 32.8, 33.2, 67.9, 71.8, 83.8, 127.6, 127.7, 128.4, 128.9, 130.9, 137.3. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.40; H, 8.56.

2.1.10. (3*S,4*R**,5*S**,6*S**)-4-(Benzyloxy)-3,5-dimethyl-(benzoyloxy)-6-formyl-tetrahydropyran-2-one (2).** To a solution of **14** (23 mg, 0.1 mmol) in 20 mL of CH_2Cl_2, 46 mg (0.54 mmol) of $NaHCO_3$ were added and the mixture was cooled to −78°C. O_3 was bubbled during 50 min and then the mixture was diluted with benzene, filtered and concentrated in vacuo. The residue was dissolved in 2 mL of CH_2Cl_2 and 0.03 mL (0.40 mmol) of pyridine and 0.05 mL (0.49 mmol) of Ac_2O were added. After being stirred for 24 h, the mixture reaction was concentrated under reduced pressure and chromatographed eluting with hexanes/ethyl acetate (6:1) to afford 16 mg of **2** as a colorless oil (61%): IR ($CHCl_3$) ν 2780, 1730, 1580, 1200; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, 3H, J=6.9 Hz), 1.13 (d, 3H, J=7.1 Hz), 2.35–2.51 (m, 1H), 2.73–2.90 (m, 1H), 3.93 (dd, 1H, J=7.6, 2.1 Hz), 4.59 (syst AB, 2H, J_{AB}=11.2 Hz), 5.06 (m, 1H), 7.49–7.62 (m, 5H), 9.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 19.9, 30.7, 39.5, 55.5, 71.0, 80.1, 127.7, 129.6, 135.7, 136.2, 174.1, 201.5. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.51; H, 6.69.

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References

1. (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. (b) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1991**, *56*, 1346.
2. Schiff, P. B.; Frant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
3. (a) Balachandran, R. J.; ter Haar, E.; Welsh, M. J.; Grant, S. G.; Day, B. W. *Anti-Cancer Drugs* **1998**, *9*, 67. (b) Kalesse, M. *Chembiochem* **2000**, *1*, 171. (c) Martello, L. A.; Mc Daid, H. M.; Regl, D. L.; Yang, C. P. H.; Meng, D. F.; Pettus, T. R. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, III, A. B.; Horwitz, S. B. *Clin. Cancer Res.* **2000**, *6*, 1978.
4. (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Smith, III, A. B.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (c) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054. (d) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098. (e) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (f) Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823. (g) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 377. (h) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935. (i) Smith, III, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.
5. Although the synthetic sequence was performed using the racemic material, the optical resolution of **3** with (+)- and (−)-α-methylbenzylamine has been described, see: Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 903.
6. For a review on synthetic uses of 7-oxanorbornene derivatives, see: Vogel, P.; Cossy, J.; Plumet, P.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521.
7. Aceña, J. L.; Arjona, O.; León, M.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 8957.
8. Arjona, O.; de la Pradilla, R. F.; de Dios, A.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906.
9. Clark, C.; Hermans, P.; Meth-Cohn, O.; Moore, C.; Taljaard, H. C.; van Vuuren, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1378.
10. Durst, T.; Tin, K.-C.; de Reinach-Hirtzbach, F.; Decesare, J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258.
11. Stereochemical assignment and evaluation of the mixture **11**:**12** was performed using ^{1}H NMR techniques. See Section 2.

12. Arjona, O.; Aceña, J. L.; Plumet, J. *J. Org. Chem.* **1997**, *62*, 3360.
13. For some selected references on the reaction of epoxides with lithium amides, see: (a) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345. (b) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.
14. The reaction of bicyclic epoxysulfones with different lithium amides have also been studied, see: Arjona, O.; Menchaca, R.; Plumet, J. *Tetrahedron* **2000**, *56*, 3901.
15. Gemal, A.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
16. For a preliminary account on the synthesis of **14** described herein, see: Arjona, R.; Menchaca, R.; Plumet, J. *Tetrahedron Lett.* **1998**, *39*, 6753.
17. (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150.
18. The structural assignment of compound **2** was performed on the basis of its ^{1}H and ^{13}C NMR spectra (see Section 2), as well as by comparison with discodermolide fragments containing a related δ-lactone subunit (see, for instance, Ref. 4i).