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Synthesis of (*R*)-(-)-Phoracantholide I Based on Stereocontrolled Cleavage of Internal Acetal

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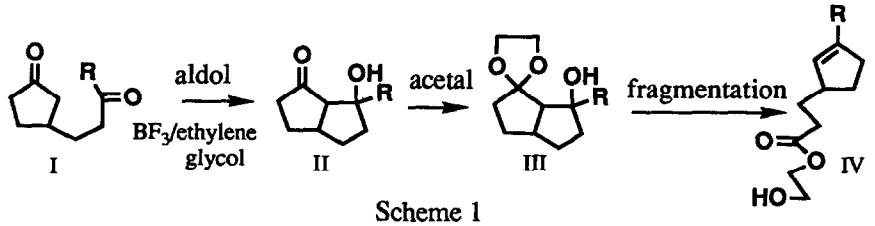
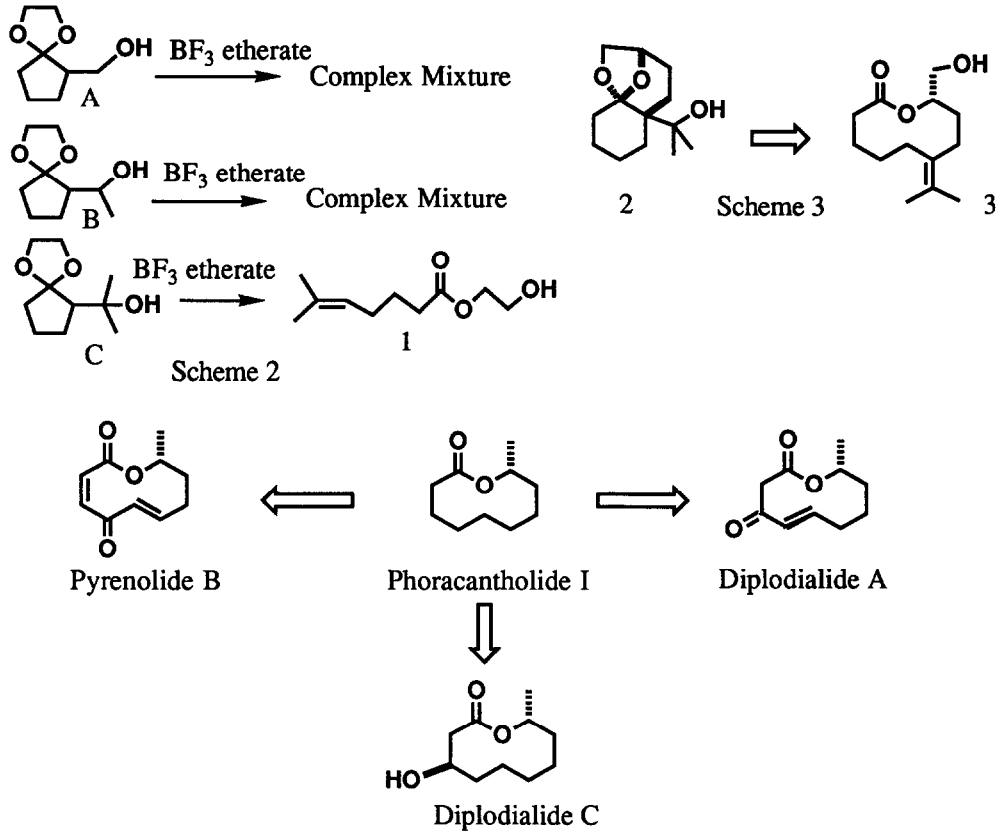
Abstract: *Oxidation of (S)-2-butenyl-2-ethoxycarbonylcyclohexanone (6) with MCPBA afforded directly two chiral internal acetals, 1S,6S,9R-(8) and 1R,6S,9S-(9), instead of the epoxide. By treatment with BF_3 etherate, the tertiary alcohol (12) obtained from 9 yielded an unexpected product (14) via the retro-aldol reaction and reconstruction of the internal acetal, and the expected fragmentation product (3) was not obtained. The mesylate of secondary alcohol (15b) prepared from 9 underwent silica-gel catalyzed, facile ring cleavage in a stereocontrolled fashion to afford the ring-enlarged 9-nonanolide derivatives (18). This methodology was applied for the synthesis of (R)-(-)-phoracantholide I. Examination using the Dreiding stereomodel provides a rationalized explanation for the stereocontrolled cleavage.*

Fragmentation reactions can elicit the ring transformations which provide new strategies involving ring contraction, ring retention, and ring expansion for the synthesis of a complex molecule. For example, Grob fragmentation[1] of 1,3-diol monotosylates to yield the ring-enlarged products is frequently used as a basic strategy for the synthesis of natural products. The de Mayo retro-aldolization[2] is analogous to the Grob fragmentation, and the characteristic of this reaction is that the β-ketol function in the molecule undergoes retro-aldol reaction to afford the ring-enlarged cyclic diketone derivatives; this methodology was applied for the synthesis of natural products by Oppolzer.[3] Previously, we reported[4] that cyclic ketones with one carbonyl function at an appropriate



Scheme 1

position in the side chain underwent a facile ring cleavage to reconstruct the new ring by treatment with BF_3/ethylene glycol.[6] This novel ring transformation involving the three steps: aldol condensation, acetalization reaction, and Grob fragmentation, could be widely applied for the synthesis of natural products.[5] The proposed mechanism for this novel ring transformation, as shown in Scheme 1, prompted us to examine the fragmentation of primary, secondary, and tertiary alcohol with the acetal function in the molecule, using BF_3 etherate (Scheme 2).[6] Compound **A**,**B** afforded a complex mixture, but the tertiary alcohol (**C**) underwent the expected fragmentation to give the ring cleavage product (**1**). The success of this preliminary experiment led to our study on fragmentation of compound **2** with an internal acetal and a tertiary alcohol, in expectation that the ten-membered lactone (9-nonanolide) may be formed (Scheme 3). This reaction seems to be an effective strategy for

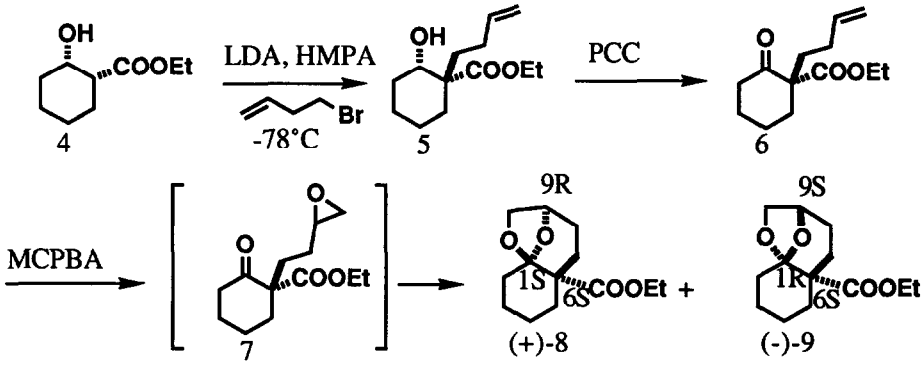


Scheme 4

the synthesis of natural products having the lactone moiety in the molecule. It is well known that several natural products with ten-membered lactone exist in nature. For example, pyrenolide A, B, and C from the culture broth of a phytopathogenic fungus *Pyrenophorateres,*[7] diplodialide A, B, C, and D from the fungus culture *Diplodia pinea,*[8] and phoracantholide I and J from the metasternal gland of the eucarypt longicorn *Phoracantha synonyma,*[9]respectively, have been isolated. Synthesis of phoracantholide I[5d,10] having the simplest ten-

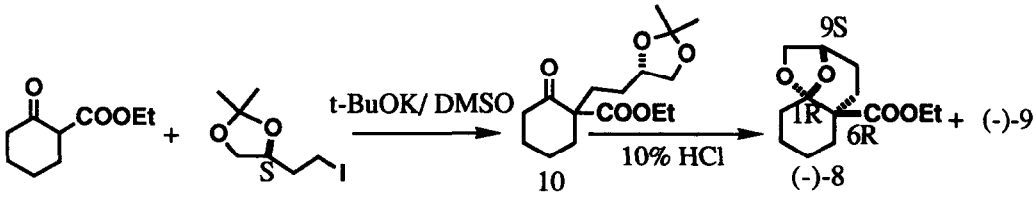
membered lactone structure seems to be significant, because this compound was already chemically transformed into three ten-membered lactone compounds (diplodialide A, C, and pyrenolide B) by two independent groups.[11, 12] Conversion of the ring-enlarged lactone (**3**) to phoracantholide I was thought to be possible (Scheme 4).

Observation using the Dreiding stereomodel suggests that (1*R*,2*S*)-1-ethoxycarbonyl-2-hydroxycyclohexane (**4**) readily prepared by enzymatic procedure[13] is suitable as a chiral building block (Scheme 7). Alkylation[14] of **4** with 4-bromo-1-butene/LDA (2 eq.) proceeded in a stereocontrolled fashion (57% yield), and subsequent oxidation with PCC in CH_2Cl_2 afforded the ketone (**6**) in 92% yield. Fortunately, 1,3-dioxolane ring (intramolecular acetal) required for the fragmentation could be directly formed in the epoxidation process using MCPBA in CH_2Cl_2. Treatment of **6** with MCPBA in CH_2Cl_2 at room temperature for 24 h afforded two diastereoisomeric acetals ((+)-**8**; $[\alpha]_D^{23}$ +9.95°) and ((-)-**9**; $[\alpha]_D^{23}$ -67.9°),[15] which could be separated easily by column chromatography. Both acetals should retain the *S*-configuration at C_6, but the configuration at C_9 remains unclear.



Scheme 5

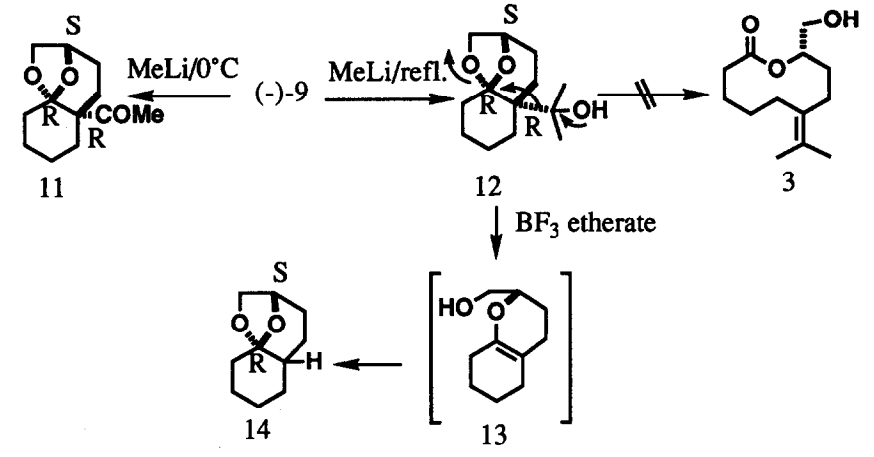
To clarify the stereochemical problem of (+)-**8** and (-)-**9**, the configurationally known alcohol was used for the synthesis of the acetal (Scheme 6). Alkylation of 2-ethoxycarbonylcyclohexanone with (*S*)-1-iodo-3,4-isopropylidenedioxybutane[16]/t-BuOK/DMSO gave the acetonide (**10**), in 60% yield, as an inseparable diastereoisomeric mixture with the *S*-configuration at the side chain. Deprotection of **10** with 10% HCl for 0.5 h at room temperature yielded two acetals, which could be separated by silica-gel column chromatography. The structure of each acetal was determined by comparison of the sign of optical rotation and the examination of ^{1}H-NMR spectroscopic data. In conclusion, a less polar product, (-)-**8** ($[\alpha]_D^{23}$ -10.8 °) should be the enantiomer of previous (+)-**8**, and a more polar product ($[\alpha]_D^{23}$ -62.0°) was identical with the previous (-)-**9**. These results



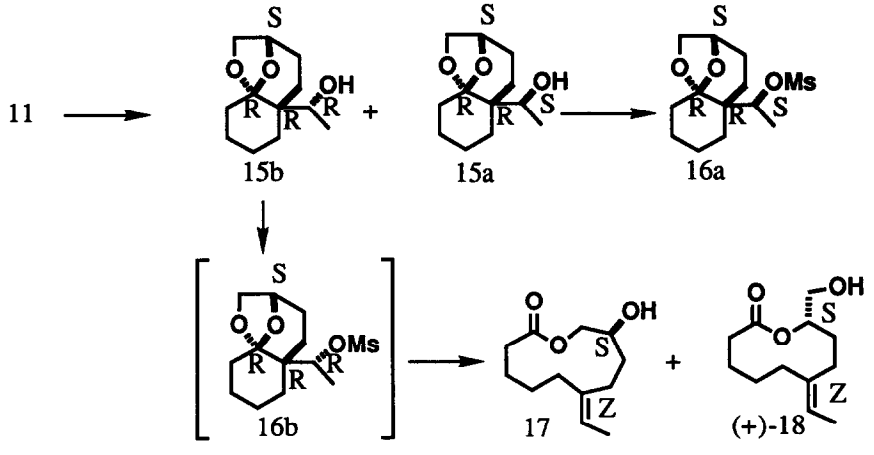
Scheme 6

allow us to conclude that the absolute configuration of (+)-**8** can be assigned as (1*S*,6*S*,9*R*), (-)-**8** as (1*R*,6*R*,9*S*), and (-)-**9** as (1*R*,6*S*,9*S*).

Treatment of (-)-**9**, which has the requisite *S*-configuration at the C_9 for the synthesis of (*R*)-(-)-phoracantholide I, with MeLi at 0°C for 10 min afforded only the ketone (**11**) in 84% yield, and the tertiary alcohol (**12**) was not obtained. Compound **12** could be prepared, in 80% yield, by alkylation under reflux conditions using MeLi/ether. However, treatment of **12** with BF_3 etherate under the same conditions as in the case of compound C did not afford the expected fragmentation product (**3**), but an unexpected product (**14**) was obtained as an epimeric mixture at C_6 in 75% yield. This compound seems to be formed *via* the retro-aldol reaction and subsequent reconstruction of the internal acetal (Scheme 7).



Scheme 7



Scheme 8

To overcome this unusual cleavage, the mesylate of **15** was synthesized with the expectation of forming the ring-enlarged lactone. Reduction of **11** with $LiAlH_4$ gave a mixture of C_{13}-epimeric alcohol (**15a**; 36%, mp 86°C) and (**15b**; 60%, mp 60°C), which could be readily separated by silica-gel column chromatography. The configuration of the alcohol at C_{13} in **15a,b** was determined on the basis of the ^{1}H-NMR spectral data. The OH proton in **15a** was observed at a lower field (δ 4.3) than that of **15b** (δ 1.7), indicating the presence of a hydrogen bond.[17] The presence of a hydrogen bond was also supported by the finding that the C_{13}-H in **15a** was observed as a sharp quartet signal (δ 4.36, J=6.27 Hz), in contrast to the broad quartet in **15b** (δ 4.20). The absence of an intramolecule hydrogen bond in **15b** is rationalized by the observation using the stereomodel. That is to say, as shown in Fig. 1 (unfavorable form of **15b**), the steric repulsion between C_{13}-Me and 1,3-diaxial hydrogen in the cyclohexane ring may hinder the formation of a hydrogen bond. The validity of the above observation was supported by the result of silica-gel catalyzed Grob type fragmentation.

Mesylation of **15a** with methanesulfonyl chloride / pyridine / CH_2Cl_2 at room temperature required for 24 h, and purification by column chromatography on silica gel afforded the mesylate (**16a**) in 90% yield. Compound **16a** was quite stable under various conditions to induce the Grob type fragmentation. This may be attributable to the steric repulsion (Fig. I, **16a**) between C_{13}-Me and 1,3-diaxial hydrogen in cyclohexane which hinders the antiperiplanar orientation of the leaving group and oxygen required for fragmentation. Mesylation of **15b** proceeded much faster (30 min) than in the case of **15a** under the same conditions. This also indicates the absence of an internal hydrogen bond in **15b**. In accordance with our expectation, **15b** with the stereochemically desired antiperiplanar orientation for fragmentation underwent facile ring cleavage during silica-gel column chromatography, and a mixture (80% yield) of two lactones (**17** and **18**) was obtained. The two lactones could be readily separated into **17** and **18** in the ratio of 1 to 10 by column chromatography on silica gel. The geometry of the double bond (*Z*) in each lactone was deduced on the basis of antiperiplanar mechanism, as depicted in Fig. 1.

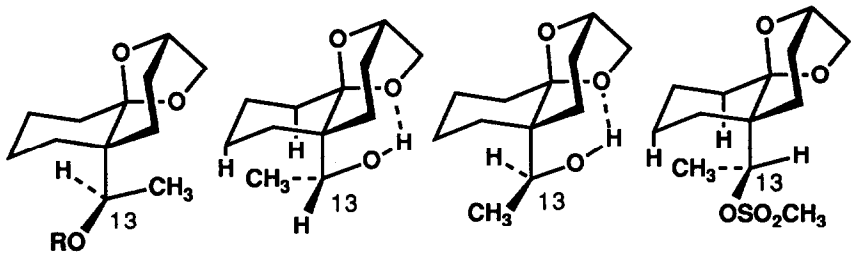
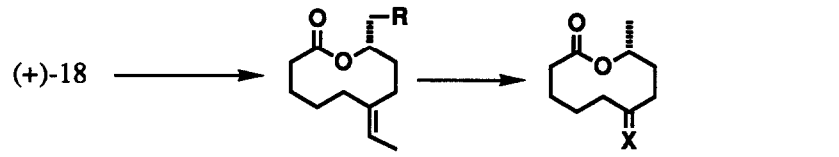


Fig. 1

The optical purity of **18** was determined by comparison of the ^{1}H-NMR spectra of each MTPA ester derived from the racemic (**18**) and the optically active (**18**); the optical purity of synthetic (+)-**18** was >99%ee., indicating that no racemization occurred in this fragmentation.

In the conversion of (+)-**18** to phoracantholide I, removal of the ethylidene and hydroxy functions is required (Scheme 9). This conversion was accomplished by the conventional method. Tosylation of the hydroxy group in (+)-**18** followed by reduction by Ueno's method[18] provided the methyl lactone (**20**) in 71% yield. Ozonolysis of **20** followed by thioacetalization using ethanedithiol / BF_3 at room temperature afforded in 73%

yield the thioacetal (22), which, upon treatment with Raney-Ni in refluxing methanol, afforded in 90% yield phoracantholide I [$[\alpha]_D^{23}$ -32.1° (*c* 0.56, $CHCl_3$)]. Spectroscopic data of the synthetic material were in good agreement with those reported.[10]



19 R=OTs
20 R=H

21 X=O
22 X=-SCH_2CH_2S-
phoracantholide I X=H_2

Scheme 9

Experimental

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. ^1H- and ^{13}C-NMR spectra were measured on JEOL JNM-PS-100 and GX-270 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer.Optical rotations were measured using JASCO DIP-360 polarimeter. Each reaction was carried out under an Ar atmosphere and monitored by TLC (Merck, silica gel 60F-254 plates). For gravity column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used, and for flash column chromatography, 230-400 mesh silica gel was used. All organic solvent extracts were washed with brine, and dried over $MgSO_4$, unless otherwise stated.

Ethyl *(1S,2S)*-(-)-1-(3-butenyl)-2-hydroxycyclohexanecarboxylate (5).

To a stirred solution of diisopropylamine (8.40 g) (83 mmol) in THF (30 ml) and BuLi (1.6M hexane solution, 52 ml) at -70 °C was added ethyl (+)-(1*R*, 2*S*)-2-hydroxycyclohexanecarboxylate (6.0 g) (34.8 mmol) in THF (20 ml). After 10 min, a solution of 4-bromo-1-butene (5.94 g) (44 mmol) in HMPA (25 ml) was added at -15 °C. The whole was stirred at room temperature for 30 min, poured into cold 10% aqueous NH_4Cl (100 ml), and extracted with ether. The ether extract was washed, dried, and concentrated *in vacuo* to afford an oily residue. The crude product was purified by column chromatography on silica gel to yield **5** (4.51 g, 57%) as a colorless oil. $[\alpha]_D^{22}$ -2.86° ($CHCl_3$, c = 2.11); IR (neat, cm^{-1}) 3510, 1700, 1640, 1200, 1130, 1070, 990; ^1H-NMR ($CDCl_3$) δ 5.78 (1 H, m), 5.06-4.91 (2 H, m), 4.21 (2 H, q, *J* = 6.9 Hz), 3.60-3.41 (2 H, m), 2.22-1.15 (12 H, m), 1.29 (3 H, t, *J* = 6.9 Hz); ^{13}C-NMR (270 MHz, $CDCl_3$) δ 177.06 (s), 138.32 (d), 114.66 (d), 74.80 (d), 60.53 (t), 51.34 (s), 36.29 (t), 32.35 (t), 31.58 (t), 28.53 (t), 23.85 (t), 22.61 (t), 14.25 (q); MS *m/z* (relative intensity) 226 (M^+, 4), 208 (3), 185 (58), 170 (16), 154 (38), 139 (100), 93 (75), 81 (65).

(-)-*(2S)*-2-(3-Butenyl)-2-ethoxycarbonylcyclohexanone (6).

To a stirred solution of **5** (1.12 g)(4.96 mmol) in CH_2Cl_2 (20 ml) was added PCC (1.28 g) (5.94 mmol) in CH_2Cl_2 (10 ml). After the whole was stirred for 3 h at room temperature, isopropanol (1 ml) and ether (200 ml) was added, stirred for 30 min, then reaction mixture was passed through Frorisil column (50 g). The filtrate was concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel to afford **6** (1.02 g, 92%) as a colorless oil. $[\alpha]_D^{22}$ -96.3° ($CHCl_3$, c = 2.24); IR (neat, cm^{-1}) 1740, 1710, 1640, 1100, 1060, 990; ^1H-NMR ($CDCl_3$) δ 5.80 (1 H, m), 5.12-4.88 (2 H, m), 4.21 (2 H, q, *J* = 7.1 Hz), 2.66-1.13 (12 H, m), 1.27 (3 H, t, *J* = 7.1 Hz); MS *m/z* (relative intensity) 224 (M^+, 1), 183 (2), 179 (6), 170 (100), 141 (20), 124 (95), 109 (15), 81 (25), 68 (19).

(+)-(*1S,6S,9R*)-6-Ethoxycarbonyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (+)-(8) and (-)-(*1R,6S,9S*)-6-Ethoxycarbonyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (-)-(9).
To a stirred solution of **6** (969 mg) (4.32 mmol) in CH_2Cl_2 (30 ml) was added MCPBA (1.12 g) (6.49 mmol) in CH_2Cl_2 (10 ml) at room temperature. The whole was stirred for 1 day at room temperature, diluted with CH_2Cl_2 (100 ml), washed with 10% aqueous $NaHSO_3$ (40 ml), then 10% aqueous Na_2CO_3, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel. Compound (+)-**8** (367 mg, 35%) and (-)-**9** (441 mg, 42%) were obtained, respectively, as a colorless oil.
(+)-**8**: $[\alpha]_D^{22}$ +9.95° ($CHCl_3$, c = 1.9); IR (neat, cm^{-1}) 1730, 1150, 1085, 1005; ^{1}H-NMR ($CDCl_3$) δ 4.55 (1 H, m), 4.18 (2 H, m), 3.87 (1 H, d, *J* = 6.6 Hz), 3.81 (1 H, ddd, *J* = 6.6, 4.6, 1.6 Hz), 2.52 (1 H, m), 2.07 (1 H, m), 1.96-1.32 (12 H, m), 1.27 (3 H, d, *J* = 6.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.75 (s), 107.98 (s), 75.22 (d), 68.12 (t), 60.26 (t), 51.96 (s), 34.91 (t), 31.81 (t), 28.77 (t), 27.75 (t) 23.51 (t), 21.80 (t), 14.26 (q); MS *m/z* (relative intensity) 240 (M^+, 100), 212 (43), 195 (16), 167 (50), 108 (30), 81 (34); HRMS m/z: calcd. for $C_{13}H_{20}O_4$: 240.1361; found 240.1358.
(-)-**9**: $[\alpha]_D^{22}$ -67.9° ($CHCl_3$, c = 1.89); IR (neat, cm^{-1}) 1730, 1160, 1140, 1060, 1040; ^{1}H-NMR ($CDCl_3$) δ 4.51 (1 H, m), 4.15 (2 H, t, *J* = 7.2 Hz), 3.93 (1 H, d, *J* = 6.9 Hz), 3.88 (1 H, dd, *J* = 6.9, 1.6 Hz), 2.47 (1 H, m), 2.11-1.19 (11 H, m), 1.25 (3 H, t, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.51 (s), 108.17 (s), 73.42 (d), 68.62 (t), 60.02 (t), 51.07 (s), 32.18 (t), 27.50 (t), 26.91 (t), 25.74 (t), 23.58 (t), 22.41 (t), 14.16 (q); MS *m/z* (relative intensity) 240 (M^+, 100), 212 (49), 195 (24), 167 (55), 108 (33), 81 (49), 67 (28); HRMS m/z: calcd. for $C_{13}H_{20}O_4$: 240.1361; found 240.1377.

(-)-(*1R,6R,9S*)-6-Acetyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (11).
To a stirred solution of **(-)-(9)** (3.02 g) (12.5 mmol) in ether (30 ml) was added 1.5 M MeLi (17 ml) in ether at 0°C over 10 min. After being stirred at room temperature for 10 min, 10% aqueous NH_4Cl (20 ml) was added, and the mixture was extracted with ether. The organic layer was washed, dried, and concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel to afford **11** (2.21 g, 84%) as a colorless oil. $[\alpha]_D^{23}$ -28.5° ($CHCl_3$, c = 1.96); IR (neat, cm^{-1}) 1690, 1240, 1050, 1010, 990, 950; ^{1}H-NMR ($CDCl_3$) δ 4.53 (1 H, m), 3.95-3.88 (2 H, m), 2.19 (3 H, s), 2.30-1.01 (12 H, m); MS *m/z* (relative intensity) 210 (M^+, 40), 167 (19), 150 (8), 123 (13), 109 (16), 43 (100); HRMS m/z: calcd. for $C_{12}H_{18}O_3$: 210.1256; found 210.1245.

(-)-(*1R,6R,9S*)-6-(1'-Hydroxy-1'-methyl)ethyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (12).
To a stirred solution of **(-)-(9)** (350 mg) (1.46 mmol) in ether (5 ml) was added 1.5 M MeLi (2.4 ml) in ether , and the mixture was heated at reflux for 30 min. The reaction mixture was diluted with 10% aqueous NH_4Cl (5 ml), and extracted with ether. The organic layer was washed, and dried, then concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel to afford **12** (264 mg, 80%) as a colorless oil. $[\alpha]_D^{26}$ -62.6° ($CHCl_3$, c = 1.74); IR (neat, cm^{-1}) 3510, 2910, 2850, 1455, 1010; ^{1}H-NMR ($CDCl_3$) δ 4.48 (1 H, m), 3.97-3.80 (2 H, m), 3.40 (1 H, s), 1.43 (3 H, s), 1.22 (3 H, s), 2.40-1.01 (12 H, m); ^{13}C-NMR ($CDCl_3$) δ 111.92 (s), 76.11 (s), 72.37 (d), 68.33 (t), 46.63 (s), 33.17 (t), 32.18 (q), 31.47 (t), 27.15 (q), 26.27 (t), 25.80 (t), 22.93 (t), 21.35 (t); MS *m/z* (relative intensity) 226 (M^+, 2), 208 (5), 168 (100); HRMS m/z: calcd. for $C_{13}H_{22}O_3$: 226.1569; found 226.1548.

(*1R,6RS,9S*)-11,12-Dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (14).
To a stirred solution of **12** (75 mg, 0.332 mmol) in CH_2Cl_2 (3 ml) was added BF_3 etherate (0.05 ml, 0.398 mmol) at 0°C. The mixture was stirred at room temperature for 30 min, diluted with 5% aqueous $NaHCO_3$ (5 ml), and extracted with CH_2Cl_2. The organic layer was dried, and concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel to afford **14** (41.8 mg, 75%) as a colorless oil. Compound **14** is inseparable mixture of C-6- epimers. IR (neat, cm^{-1}) 1440, 1265, 1195, 1100, 1045, 990, 920; ^{1}H-NMR ($CDCl_3$) δ 4.50 (1 H, m), 3.89-3.81 (2 H, m), 2.13-1.13 (13 H, m); ^{13}C-NMR ($CDCl_3$) for one epimer δ 108.11 (s), 74.12 (d), 68.56 (t), 42.53 (d), 34.46 (t), 30.95 (t), 29.31 (t), 25.39 (t), 24.10 (t), 23.93 (t), for another epimer δ 108.16 (s), 75.06 (d), 67.86 (t), 41.01 (d), 35.16 (t), 30.93 (t), 29.78 (t), 25.02 (t), 24.08 (t), 22.70 (t); MS *m/z* (relative intensity) 168 (M^+, 96), 138 (45), 81 (77), 67 (63), 55 (100).

(-)-*(1R,6R,9S)*-6-[(*1'S*)-1'-Hydroxy]ethyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (15a), and (-)-*(1R,6R,9S)*-6-[(*1'R*)-1'-Hydroxy]ethyl-11,12-dioxatricyclo[7,2,1,$0^{1,6}$]dodecane (15b).

To a suspended solution of $LiAlH_4$ (305 mg)(8.03 mmol) in ether (30 ml) was added dropwise with stirring a solution of **11** (2.55 g) (12.0 mmol) in ether (20 ml) at 0 °C. The mixture was stirred for 20 min at room temperature, then poured into 5% HCl (50 ml), and filtered. The separated organic layer was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel to afford the less polar **15a** (916 mg, 36%) and the more polar **15b** (1.53 g, 60%).

15a: colorless needles, mp 85.5-86 °C (from petroleum ether); $[\alpha]_D^{26}$ -70.6° ($CHCl_3$, c = 1.47); IR (neat, cm^{-1}) 3440, 2930, 2870, 1450, 1050, 1010; ^{1}H-NMR ($CDCl_3$) δ 4.54 (1 H, m), 4.36 (1 H, q, *J* = 6.3 Hz), 4.30 (1 H, s), 3.90-3.83 (2 H, m), 2.23-1.08 (12 H, m), 1.03 (3 H, d, *J* = 6.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 111.89 (s), 74.04 (d), 67.98 (t), 67.79 (d), 43.09 (s), 31.46 (t), 30.44 (t), 25.42 (t), 23.67 (t), 19.70 (t), 19.61 (t), 15.66 (q); MS *m/z* (relative intensity) 212 (M^+, 1), 194 (2), 168 (100), 111 (43), 98 (47), 81 (39); HRMS m/z: calcd. for $C_{12}H_{20}O_3$: 212.1412; found 212.1429.

15b: colorless needles, mp 60-60.5 °C (from petroleum ether); $[\alpha]_D^{22}$ -56.8° ($CHCl_3$, c = 1.65); IR (neat, cm^{-1}) 3460, 2940, 2870, 1450, 1050, 1020; ^{1}H-NMR ($CDCl_3$) δ 4.49 (1 H, m), 4.21 (1 H, m), 3.88-3.80 (2 H, m), 2.18-1.15 (13 H, m), 1.29 (3 H, d, *J* = 6.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 109.75 (s), 73.24 (d), 68.62 (d), 68.21 (t), 44.99 (s), 31.47 (t), 29.78 (t), 25.62 (t), 23.58 (t), 21.24 (t), 19.77 (t), 19.19 (q); MS *m/z* (relative intensity) 212 (M^+, 1), 194 (2), 168 (100), 111 (38), 98 (43), 81 (40); HRMS m/z: calcd. for $C_{12}H_{20}O_3$: 212.1412; found 212.1399.

***(6Z,9S)*-6-Ethylidene-9-hydroxy-10-decanolide (17), and *(6Z,9S)*-6-Ethylidene-9-hydroxymethyl-9-nonanolide (18).**

To a stirred solution of (-)- **15b** (950 mg)(4.48 mmol) in CH_2Cl_2 (20 ml) and pyridine (2 ml) was added dropwise methanesulfonyl chloride (770 mg)(6.72 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred at room temperature for 30 min, then diluted with 5% HCl (10 ml), and extracted with ether. The ether extract was washed, dried, and concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel to afford the less polar **17** (67 mg, 7%) and the more polar **18** (684 mg, 73%) as a colorless oil.

17: ^{1}H-NMR ($CDCl_3$) δ 5.25 (1 H, q, *J* = 6.9 Hz), 4.39 (1 H, dd, *J* = 10.6, 3.0 Hz), 4.02-3.91 (2 H, m), 2.58-1.40 (13 H, m), 1.60 (3 H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 174.21 (s), 138.77 (s), 120.04 (d), 68.68 (d), 67.12 (t), 33.99 (t), 33.76 (t), 32.70 (t), 25.91 (t), 23.66 (t), 23.29 (t), 13.38 (q); HRMS m/z: calcd. for $C_{12}H_{20}O_3$: 212.1412; found 212.1430.

18: $[\alpha]_D^{26}$ +3.00° ($CHCl_3$, c = 0.92); IR (neat, cm^{-1}) 3430, 1730, 1230, 1150, 1070, 1030; ^{1}H-NMR ($CDCl_3$) δ 5.24 (1 H, q, *J* = 6.9 Hz), 4.93 (1 H, m), 3.69 (1 H, dd, *J* = 11.9, 4.1 Hz), 3.63 (1 H, dd , *J* = 11.9, 6.3 Hz), 2.59-2.51 (2 H, m), 2.26-1.42 (11 H, m), 1.65 (3 H, dd, *J* = 6.9, 2.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.06 (s), 137.37 (s), 116.75 (d), 77.44 (d), 65.41 (t), 35.42 (t), 32.88 (t), 29.92 (t), 29.19 (t), 25.18 (t), 20.22 (t), 13.26 (q); MS *m/z* (relative intensity) 212 (M^+, 15), 194 (26), 181 (15), 93 (100), 81 (79), 67 (76); HRMS m/z: calcd. for $C_{12}H_{20}O_3$: 212.1412; found 212.1410.

***(6Z,9S)*-6-Ethylidene-9-*p*-toluenesulfonyloxymethyl-9-nonanolide (19).**

To a stirred solution of **18** (91 mg) (0.428 mmol) in pyridine (0.5 ml) and CH_2Cl_2 (3 ml) was added p-toluenesulfonyl chloride (122 mg) (0.640 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was diluted with 3% HCl (3 ml), and extracted with ether. The ether extract was washed, and dried, and concentrated *in vacuo* to afford an oily residue. The crude product was purified by column chromatography on silica gel to give **19** (149 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ -8.31°($CHCl_3$, c = 0.82); IR (neat, cm^{-1}) 1730, 1660, 1450, 1360, 1240, 1180; ^{1}H-NMR ($CDCl_3$) δ 7.78 (2 H, d, *J* = 8.3 Hz), 7.34 (2 H, d, *J* = 8.3 Hz), 5.22-4.86 (2 H, m), 4.18-3.94 (2 H, m), 2.45 (3 H, s), 2.69-1.18 (15 H, m).

***6(Z)*-6-Ethylidene-9-methyl-9-nonanolide (20).**

To a refluxing solution of **19** (183 mg, 0.363 mmol), NaI (117mg, 0.778 mmol), and a catalytic amount of azobisisobutyronitrile (AIBN) in DME (5 ml) was added dropwise tri-n-butyltin hydride (141 mg, 0.488 mmol).

The mixture was refluxed for 30 min, then cooled to 0 °C, diluted with 10% aqueous NH_4Cl (5 ml), and extracted with ether. The ether extract was washed, dried, and concentrated *in vacuo* to leave an oily residue. The crude product was purified by column chromatography on silica gel to give **20** (53 mg, 75%) as a colorless oil. $[\alpha]_D^{23}$ -1.84° ($CHCl_3$, c = 0.9) ; IR (neat, cm^{-1}) 1720, 1650, 1250, 1230, 1150, 1060; ^{1}H-NMR ($CDCl_3$) δ 5.21 (1 H, q, *J* = 6.6 Hz), 4.94 (1 H, m), 2.58-2.41 (2 H, m), 1.66 (3 H, d, *J* = 6.6 Hz), 2.19-1.25 (10 H, m), 1.22 (3 H, d, 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 173.84 (s), 137.82 (s), 116.13 (d), 72.54 (d), 35.57 (t), 34.41 (t), 32.76 (t), 30.06 (t), 25.27 (t), 20.58 (q), 20.04 (q), 13.24 (q); MS *m/z* (relative intensity) 196 (M^+, 41), 167 (21), 149 (20), 95 (100), 81 (66); HRMS *m/z*: calcd. for $C_{12}H_{20}O_2$: 196.1463; found 196.1481.

9(*R*)-6,6-Ethylenedithio-9-methyl-9-nonanolide (22).
According to standard manner, ozone was bubbled through a solution of **20** (46 mg, 0.215 mmol) in CH_2Cl_2 (5 ml) at -78°C. Zinc powder (150 mg) and acetic acid (1 ml) were added to the solution. It was allowed to warm to room temperature for 2 h. The zinc powder was filtered off, and the filtrate was evaporated *in vacuo* to afford an oily residure, which was subjected to flash silica-gel column chromatography to yield **21** (33.7 mg) as a colorless. To a solution of **21** (33.7 mg) and ethanedithiol (26 mg, 0.277 mmol) in CH_2Cl_2 (3 ml), was added BF_3 etherate (0.012 ml, 0.098 mmol) at 0°C. The mixture was stirred at room temperature for 4 h, diluted with H_2O (5 ml), and extracted with ether. The ether extract was washed with 5% $NaHCO_3$, and brine, then dried, and evaporated. The crude product was purified by column chromatography on silica gel to give **22** (41 mg, 73%). $[\alpha]_D^{24}$ -7.68° ($CHCl_3$, c = 1.08) ; IR (neat, cm^{-1}) 2900, 1720, 1150, 1100, 1060; ^{1}H-NMR ($CDCl_3$) δ 4.98 (1 H, m), 3.28 (4 H, s), 2.44-1.28 (12 H, m), 1.23 (3 H, d, *J* = 6.6 Hz); MS *m/z* (relative intensity) 260 (M^+, 86), 203 (66), 159 (75), 131 (100), 111 (55), 55 (48).

Phoracantholide I
To a stirred solution of **22** (16 mg, 0.061 mmol) in MeOH (2 ml) was added Raney Ni (W-2, 0.5 ml). The mixture was heated at reflux for 2 h, then filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residure, which was subjected to flash silica-gel column chromatography. The fraction eluted with 5% AcOEt in hexane (v/v) gave **phoracantholide I** (10 mg; 23% yield from 11) as a colorless oil. $[\alpha]_D^{23}$ -32.1° ($CHCl_3$, c = 0.56)[lit.[10a] $[\alpha]_D$ -35.1° ($CHCl_3$, c = 1.15)]; IR (neat, cm^{-1}) 2930, 1710, 1250; ^{1}H-NMR ($CDCl_3$) δ 5.24 (1 H, m), 2.53-1.18 (14 H, m), 1.27 (3 H, d, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 173.99 (s), 72.61 (d), 35.22 (t), 31.42 (t), 27.13 (t), 24.27 (t), 24.03 (t), 23.44 (t), 20.69 (t), 19.48 (q); MS *m/z* (relative intensity) 170 (M^+, 7), 155 (4), 98 (100), 84 (66), 69 (37), 55 (74); HRMS *m/z*: calcd. for $C_{10}H_{18}O_2$: 170.1307; found 170.1325.

References and notes

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