Tetrahedron Letters, Vol.32, No 40, pp 5585-5588, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

Synthesis of Phoracantholide I Based on Stereospecific Fragmentation Reactions

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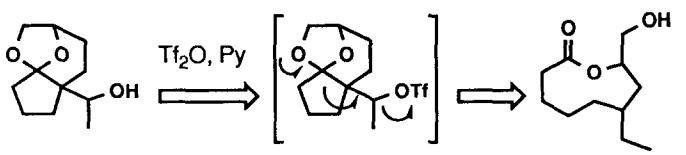
Key words R-(-)-Phoracantholide I; fragmentation, epoxidation, hydrogen bond, silica gel, acetal

Abstract: Phoracantholide I was synthesized on the basis of silica gel-catalyzed fragmentation to the ring- enlarged lactones

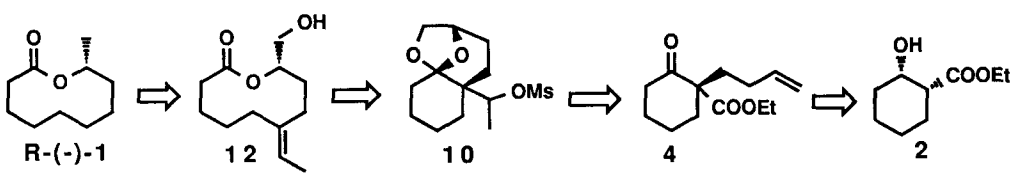
Fragmentation reactions seem to be one of the fundamental reactions to elicit the ring transformations which provide a variety of strategies for the synthesis of a complex molecule.[1] During studies on the novel ring transformation[2] developed in this laboratory, we found the fragmentation reaction to the ring-enlarged lactone rings,[3] as shown in Scheme I. This reaction, coupled with the ready preparation of the intramolecule acetal, seems to be widely applied for the synthesis of natural products having the lactone moiety in the molecule.

We wish to report here an asymmetric synthesis of (R)-(-)-Phoracantholide I, on the basis of facile ring cleavage of an intramolecule acetal to the ring-enlarged lactone. Phoracantholide I (**1**),[4] possessing a ten-membered lactone ring, has been isolated as defensive secretion from the metasternal gland of the eucarypt longicorn, *Pholacantha synonyma*.

Scheme I



Scheme II



The retrosynthetic analysis of (R)-(-)-**1** as shown in Scheme II allows us to select the tricyclic mesylate (**10**) as a key intermediate. The acetal moiety in compound **10** may be prepared from **4** *via* the epoxidation process with MCPBA, because a preliminary experiment[5a] suggests that the epoxidation of the α-butenyl cyclic ketone does not afford the epoxide, but the internal acetal.[5b]

In a synthesis of the chiral **4**, (1R,2S)-1-ethoxycarbonyl-2-hydroxycyclohexane (**2**) is suitable for chiral synthon, and can be readily prepared by a biological method.[6] Alkylation [LDA (2eq.), butenyl bromide, HMPA, THF, -78°C, 3 h] of **2**, according to Fráter's method,[7] proceeded in a stereocontrolled fashion, and subsequent oxidation with PCC in CH_2Cl_2 afforded (S)-**4** in 35% yield. Epoxidation of (S)-**4** with MCPBA in CH_2Cl_2 at room temperature for 24 h gave two diastereomeric acetals, (+)-**5** $[\alpha]_D^{23}$ +9.95° (c 1.9, $CHCl_3$) (35%) and (-)-**6** $[\alpha]_D^{23}$ -67.9° (c 1.89, $CHCl_3$) (42%), which could be separated easily by column chromatography on

Scheme III

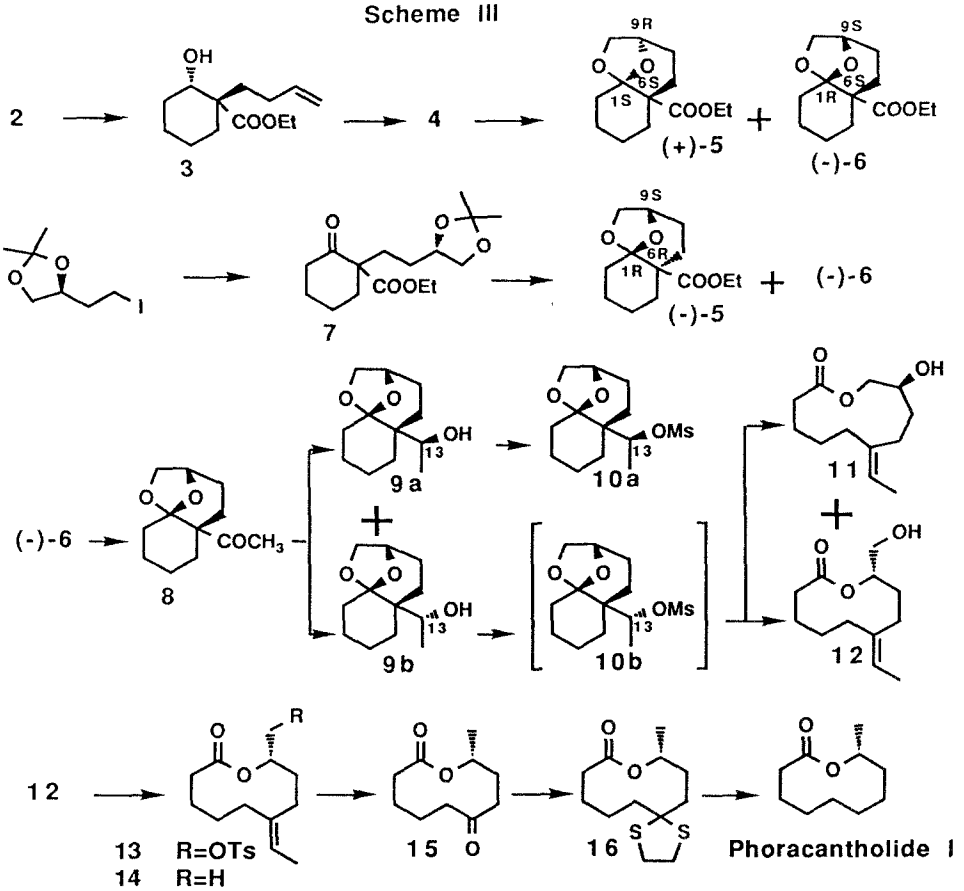
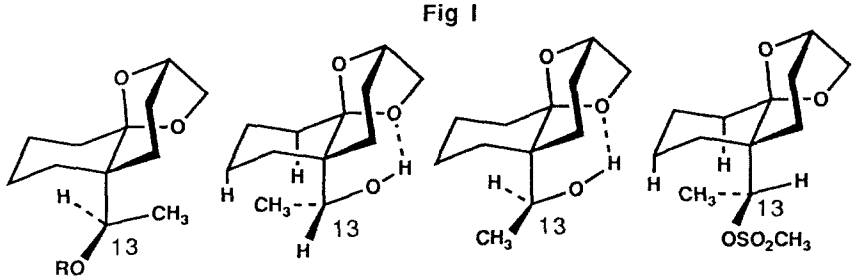


Fig I



silica gel. As described above, the epoxide was not obtained under the employed reaction conditions. In both acetals, the S configuration at C_6 should be retained, but the configuration at C_9 remains unclear.

To solve this stereochemical problem in (+)-**5** and (-)-**6**, we attempted to synthesize **5** and **6** using the configurationally known alcohol. Alkylation of 2-ethoxycarbonylcyclohexanone with (S)-1-iodo-3,4-isopropylidenedioxybutane[8] [t-BuOK, DMSO, room temp 3 h] gave the acetonide (**7**) in 60% yield. The S-configuration of the side chain in **7** should be retained, although this compound is an inseparable diastereomeric mixture.

Exposure (30 min) of **7** with 10%-HCl afforded two acetals, which could be separated by silica-gel column chromatography. One is the enantiomer of above (+)-**5**, (-)-**5** ($[\alpha]_D^{23}$ -10.8° (c 2.06, $CHCl_3$) (45%)) and the other is identical with (-)-**6** ($[\alpha]_D^{23}$ -62.0° (c 1.95, $CHCl_3$) (40%)). These results allow us to conclude that the absolute configuration of (-)-**5** can be assigned as (1R,6R,9S), (+)-**5** as (1S,6S,9R), and (-)-**6** as (1R,6S,9S), as depicted in Scheme III.

Treatment (ether, 0°C, 10 min) of (-)-**6**, which bears the desired S configuration at C_9 for synthesis of (R)-(-)-phoracantholide I, with MeLi afforded the ketone (**8**) in 84% yield. Reduction (LAH, ether, 5 min) of **8** gave, in 96% yield, a mixture (1:1.7) of the alcohols, which could be readily separated into **9a** (mp 86°C) and **9b** (mp 60 °C) by silica-gel column chromatography. The configuration of the alcohol at C_{13} in **9a,b** was determined on the basis of the ^{1}H-NMR spectral data. The OH proton in **9a** was observed at a lower field (δ 4.3) than that of **9b** (δ 1.7), indicating the presence of a hydrogen bond.[9] The presence of a hydrogen bond was also supported by the findings that the C_{13}-H in **9a** was observed as a sharp quartet signal (δ 4.36, J=6.27 Hz), in contrast to the broad quartet in **9b** (δ 4.20). The absence of an intramolecule hydrogen bond in **9b** is rationalized, as shown in Fig. I (unfavorable form of **9b**), by the steric repulsion between C_{13}-Me and 1,3-diaxial hydrogen in the cyclohexane ring which hinders the formation of a hydrogen bond. The validity of the above observation was supported by the result of silica-gel catalyzed-Grob type fragmentation.[10]

Treatment of **9a** with methanesulfonyl chloride (DMAP, pyridine, CH_2Cl_2, room temp., 24 h) and subsequent purification by column chromatography on silica gel afforded the mesylate (**10a**) in 90% yield. No Grob type fragmentation of **10a** under various conditions was observed. This may be attributable to the steric repulsion (Fig. I, **10a**) 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 **9b** proceeded much faster (30 min) than in the case of **9a** under the same conditions. This also indicates the absence of an internal hydrogen bond in **9b**. In accordance with our expectation, **9b** with the stereochemically desired antiperiplanar orientation for fragmentation underwent facile ring cleavage to afford a mixture (80% yield) of two lactones (**11** and **12**) during silica-gel column chromatography. The two lactones could be readily separated into **11** and **12** in the ratio of 1 to 10 by column chromatography on silica gel. The geometry of the double bond in each lactone was deduced on the basis of antiperiplaner mechanism, as depicted in Fig. 1.

Conversion of the hydroxy lactone (**12**) to phoracantholide I necessitates removal of the ethylidene and hydroxy functions. Tosylation [TsCl, pyridine, CH_2Cl_2, 3 h] of the hydroxy group in **12** followed by reduction by Ueno's method[11] [NaI, Bu_3SnH, AIBN, DME, reflux, 1 h] provided the methyl lactone (**14**) in 71% yield. Ozonolysis of **14** followed by thioacetalization [ethanedithiol, BF_3-Et_2O, CH_2Cl_2, room temp, 10h] afforded in 73% yield the thioacetal (**16**), which, upon treatment with Raney-Ni in refluxing methanol,[12] afforded in 90% yield phoracantholide I (**1**) [$[\alpha]_D^{23}$ -32.1° (c 0.56, $CHCl_3$)]. Spectroscopic data of the synthetic material were in good agreement with those reported.[4]

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Selected spectroscopic data of main products.

(+)-**5**. $[\alpha]_D^{23}$ ($CHCl_3$, c = 1.9) +9.95°; IR (neat, cm^{-1}) 2940, 1730, 1450, 1225, 1195, 1175, 1150, 1085, 1005; ^1H 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 ($CDCl_3$) 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 (EI, relative intensity) 240 (M^+, 100), 212 (43), 195 (16), 167 (50), 108 (30), 81 (34), 67 (18), 55 (34).

(-)-**6**· $[\alpha]_D^{23}$ ($CHCl_3$, c = 1.89) -67.9°; IR (neat, cm^{-1}) 2940, 1730, 1450, 1230, 1160, 1140, 1060, 1040; ^1H 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 ($CDCl_3$) 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 (EI, relative intensity) 240 (M^+, 100), 212 (49), 195 (24), 167 (55), 108 (33), 81 (49), 67 (28), 55 (45).

9a: colorless crystalline solid, mp 85.5-86°C (from petroleum ether), $[\alpha]_D^{26}$ ($CHCl_3$, c = 1.47) -70.6°, IR (neat, cm^{-1}) 3440, 2930, 2870, 1450, 1050, 1010; ^1H 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 (EI, relative intensity) 212 (M^+, 0.8), 194 (1.5), 168 (100), 111 (43), 98 (47), 81 (39), 67 (35), 55 (61), 41 (39).

9b· colorless crystalline solid, mp 60-60.5°C (from petroleum ether); $[\alpha]_D^{22}$ ($CHCl_3$, c = 1.65) -56.8°, IR (neat, cm^{-1}) 3460, 2940, 2870, 1450, 1050, 1020; ^1H 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 ($CDCl_3$) 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 (EI, relative intensity) 212 (M^+, 0.8), 194 (1.2), 168 (100), 111 (38), 98 (43), 81 (40), 67 (41), 55 (57).

12: $[\alpha]_D^{26}$ ($CHCl_3$, c = 0.92) +3.00°, IR (neat, cm^{-1}) 3430, 3030, 2930, 2860, 1730, 1450, 1260, 1230, 1150, 1070, 1030, 950; ^1H 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 (EI, relative intensity) 212 (M^+, 15), 194 (26), 181 (15), 93 (100), 81 (79), 67 (76), 55 (98), 41 (71).

(Received in Japan 5 June 1991)