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# Stereostructures of Unique 13-Membered Carbocyclic Cembranolides from the Soft Coral *Lobophytum pauciflorum*

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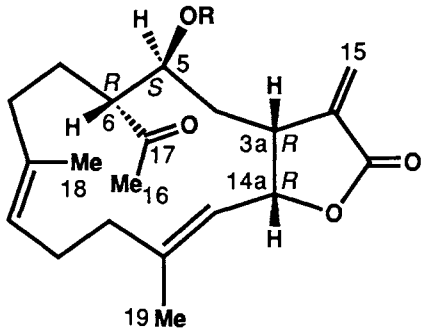
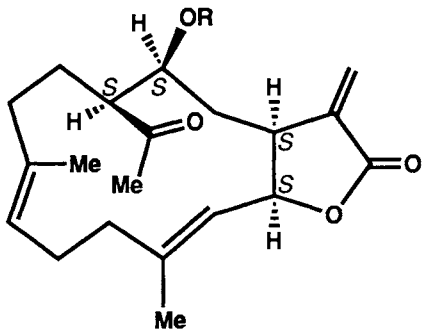
The relative and absolute configurations of the 13-membered carbocyclic cembranolides (lobophytol and lobophytol acetate) isolated from the soft coral *Lobophytum pauciflorum* were established on the basis of detailed spectroscopic analysis and chemical transformations.

In the previous paper[1] we reported the isolation and structures of lobophytol and lobophytol acetate,[2] marine cembranolides having a unique 13-membered carbocyclic skeleton from the soft coral *Lobophytum pauciflorum* . The stereochemistry was deduced as **1** by spectroscopic analysis.[3] However, some recent reports[4] on related cembranolide diterpenes having different absolute configurations at the angular positions from that of **1** prompted us to reinvestigate the stereostructures of lobophytol and lobophytol acetate. This paper describes our result that the relative and absolute configurations should be revised from **1** to **2** on the basis of detailed spectroscopic analysis and chemical transformations.

Most of the carbon and proton signals of lobophytol (**2a**) were assigned[5] by means of H,H COSY and decoupling difference spectra. Then its relative stereochemistry and conformation were reinvestigated by considering the coupling patterns of the protons and NOEs observed in the phase-sensitive NOESY spectrum (500 MHz, $CDCl_3$). Appearance of NOE between two angular protons [H-3a (δ 3.50) and H-14a (δ 5.29)] confirmed the *cis*-juncture of the lactonic ring. H-3a was coupled with methylene protons ($H_2$-4). The large coupling constant (11.3 Hz) between H-3a and one of the methylene protons (H-4α, δ 1.66) suggested that H-3a and H-4α were either in an eclipse (dihedral angle θ = 0°) or anticoplanar (θ = 180°) relationship. The latter turn-

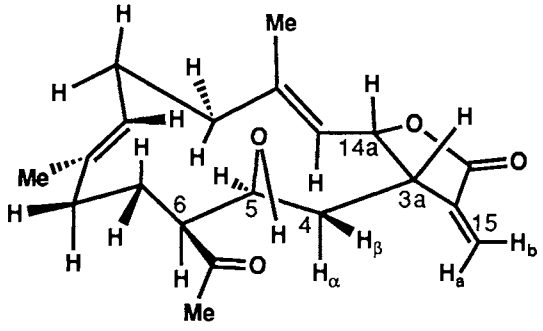


**1a; R = H 1b; R = Ac**



**2a; R = H 2b; R = Ac**

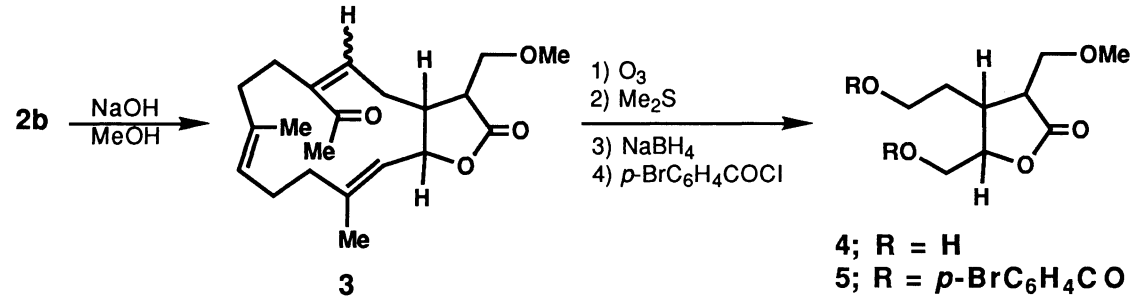
ed out to be true because H-3a showed NOE to another methylene proton (H-4β, δ 1.57; $J_{3a,4\beta}$ = 3.0 Hz). This proton also exhibited NOE to one (δ 5.50) of the exomethylene protons (H-15a). Thus, equatorial and axial natures of H-4β and H-4α, respectively, were established. These protons were coupled with a deshielded proton (H-5, δ 3.70) on the carbon bearing OH group. The coupling constants between H-4α, 4β and H-5 ($J_{4\beta,5}$ = 11.0 Hz, $J_{4\alpha,5}$ = 2.1 Hz) revealed that the OH was in an axial position. The '1,3-diaxial' relation of the OH and H-3a (see **2c**) is in good agreement with the finding that acylation of the OH resulted in the remarkable upfield shift of H-3a.[1] Interestingly, H-5 is strongly coupled ($J$ = 11.0 Hz) with the OH proton (δ 3.37). Assuming the equatorial orientation of the acetyl group as shown in **2c**, we were able to interpret the large coupling constant, because $\theta_{OH,5}$ became 180° by hydrogen bonding of the OH proton to the acetyl carbonyl. The small $J$ (2.1 Hz) between H-6 and H-5 as well as the existence of NOE between H-6 and H-4α supported the axial nature of H-6. These facts led us to revision of the relative stereochemistry of lobophytol and its acetate as shown in **2a** and **2b**. The analysis of the coupling constants and NOEs[6] observed for other protons suggested the conformation **2c** for lobophytol.

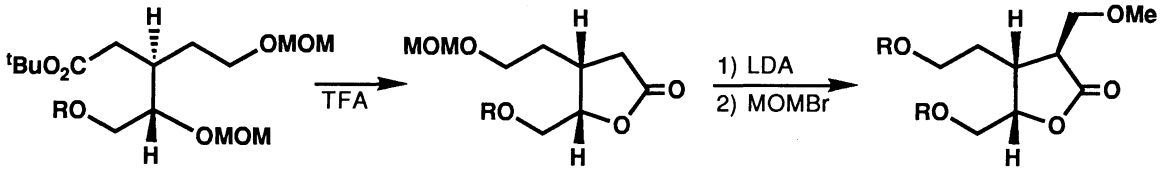


**2c**

The absolute configurations at 3a and 14a positions were established by the following chemical transformations. The enone **3**[1] obtained from the natural product (**2b**) on treatment with methanolic NaOH, was subjected to ozonolysis followed by $NaBH_4$ reduction, to give a diol **4**, which was transformed to a dibenzoate **5**.[7] The absolute configuration of **5** was elucidated by transforming the alcohol **6**, which was derived from *D*-mannitol,[4b] into **13**. The corresponding acetate **7** of **6** was treated with trifluoroacetic acid in $CH_2Cl_2$ to give a γ-lactone **8**[8] in 49 % yield. Methanolysis of **8** followed by protection of hydroxy group gave **10**. Treatment of **10** with LDA followed by addition of $CH_3OCH_2Cl$ at -78 °C gave an α-methoxymethyl γ-lactone **11** in 57 % yield. The compound **11** was then transformed into a dibenzoate **13**,[9,10] whose physical data were identical with those of **5** except for the chiroptical properties; **5** $[\alpha]_D$ +38.1°, CD $\lambda_{ext}$ 243 nm (Δε +0.20, EtOH), **13** $[\alpha]_D$ -36.6°, CD $\lambda_{ext}$ 246 nm (Δε -0.69, EtOH).

These chemical transformations clarified the absolute configurations (3a*S*, 14a*S*): therefore 5*S* and 6*S* configurations were also elucidated when coupled with the above-mentioned result for relative stereochemistries.




**6; R = H**
**7; R = Ac**

**8; R = Ac**
**9; R = H**
**10; R = MOM**

**11; R = MOM**
**12; R = H**
**13; R = *p*-BrC$_6$H$_4$CO**

References

1) Y. Yamada, S. Suzuki, K. Iguchi, K, Hosaka, H. Kikuchi, Y. Tsukitani, H. Horiai, and F. Shibayama, *Chem. Pharm. Bull.*, **27**, 2394 (1979).

2) We named lobophytol and lobophytol acetate for **2a** and **2b**, respectively.

3) Y. Yamada, S. Suzuki, K. Iguchi, H. Kikuchi, Y. Tsukitani, H. Horiai, and F. Shibayama, *Tetrahedron Lett.*, **21**, 3911 (1980).

4) a) M. Kobayashi, *Chem. Pharm. Bull.*, **36**, 488 (1988); b) H. Nagaoka, M. Iwashima, H. Abe, and Y. Yamada, *Tetrahedron Lett.*, **30**, 5911 (1989); c) T. Kusumi, I. Ohtani, Y. Inouye, and H. Kakisawa, *ibid.*, **29**, 4731 (1988).

5) $^1$H NMR data of **2a** ($CDCl_3$): δ 6.18 (1H, d, *J* = 3.0 Hz; H-15b), 5.50 (1H, d, *J* = 3.0 Hz; H-15a), 5.29 (1H, dd, *J* = 10.5, 7.8 Hz; H-14a), 5.08 (1H, bd, *J* = 10.5 Hz; H-14), 5.03 (1H, bt, *J* = 7.8 Hz; H-10), 3.70 (1H, tt, *J* = 11.0, 2.1 Hz; H-5), 3.50 (1H, ddq, *J* = 11.3, 7.8, 3.0 Hz; H-3a), 3.37 (1H, d, *J* = 11.0 Hz; OH), 2.34 (1H, ddd, *J* = 8.8, 2.5, 2.1 Hz; H-6), 2.34 (1H, m, H-11), 2.27 (1H, m, H-8), 2.25 (1H, m, H-12), 2.17 (3H, s; $H_3$-16), 2.10 (1H, m, H-11), 2.07 (1H, m, H-8), 2.05 (1H, m, H-12), 2.00 (1H, ddt, *J* = 14.0, 2.5, 8.8 Hz, H-7), 1.74 (3H, bs; $H_3$-19), 1.66 (1H, ddd, *J* = 14.2, 11.3, 2.1 Hz; H-4α), 1.60 (3H, bs; $H_3$-18), 1.57 (1H, ddd, *J* = 14.2, 11.0, 3 Hz; H-4β), 1.53 (1H, ddt, *J* = 14.0, 8.0, 2.5 Hz, H-7). $^{13}$C NMR data of **2a** ($CDCl_3$): δ 215.39 (s; C-17), 170.35 (s; C-2), 144.27 (s), 140.59 (s), 134.44 (s), 126.30 (d), 121.45 (t; C-15), 119.74 (d), 76.41 (d; C-14a), 68.93 (d; C-5), 56.31 (d; C-6), 40.18 (t), 40.03 (t), 38.51 (d), 38.17 (t), 30.97 (q; C-17), 25.09 (t), 23.57 (t), 15.79 (q), 14.90 (q).6) NOEs observed for **2a** in the phase-sensitive NOESY (500 MHz): H-15a ↔ H-4β; H-14a ↔ H-5; H-14a ↔ H-3a; H-14 ↔ H-5; H-14 ↔ H-4α; H-10 ↔ H-5; H-5 ↔ H-3a; H-5 ↔ H-6; H-6 ↔ H-4α.

7) **5**: $[\alpha]_D$ +38.1° (c 1.00, $CHCl_3$); UV $\lambda_{max}$ 245 nm (ε 39500, EtOH); $^1$H NMR (400 MHz, $CDCl_3$): δ 2.07 (2H, q, *J* = 6.8 Hz), 2.67 (1H, ddd, *J* = 3.4, 4.4, 10.3 Hz), 3.01 (1H, qd, *J* = 7.9, 10.3 Hz), 3.33 (3H, s), 3.67 (1H, dd, *J* = 3.4, 9.7 Hz), 3.75 (1H, dd, *J* = 4.4, 9.7 Hz), 4.44 (2H, m), 4.55 (1H, dd, *J* = 4.5, 12.5 Hz), 4.63 (1H, dd, *J* = 3.2, 12.5 Hz), 4.89 (1H, ddd, *J* = 3.2, 4.5, 7.9 Hz), 7.60 (2H, d, *J* = 8.6 Hz), 7.62 (2H, d, *J* = 8.6 Hz), 7.82 (2H, d, *J* = 8.6 Hz), 7.86 (2H, d, *J* = 8.6 Hz).

8) **8**: $[\alpha]_D$ +9.1° (c 1.24, $CHCl_3$); IR $\nu_{max}$ 1781, 1746 cm$^{-1}$ (film); $^1$H NMR (400 MHz, $CDCl_3$): δ 2.13 (3H,s), 2.43 (1H, dd, *J* = 10.5, 17.3 Hz), 2.61 (1H, dd, *J* = 8.8, 17.3 Hz), 2.87 (1H, m), 3.36 (3H, s), 3.55 (1H, m), 3.62 (1H, m), 4.21 (1H, dd, *J* = 4.7, 12.4 Hz), 4.41 (1H, dd, *J* = 3.2, 12.4 Hz), 4.60 (2H, s), 4.72 (1H, ddd, *J* = 3.2, 4.7, 7.8 Hz).

9) **11**→**12**; MeOH-HCl (10 : 1), 40 °C: **12**→**13**; *p*-$BrC_6H_4COCl$-pyridine.

10) **13**: $[\alpha]_D$ -36.6° (c 1.53, $CHCl_3$); UV $\lambda_{max}$ 245 nm (ε 40000, EtOH).

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