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First total synthesis and absolute configuration of marine cembrane diterpenoid (+)-11,12-epoxysarcophytol A

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Abstract

A concise and efficient total synthesis of (+)-11,12-epoxysarcophytol A (**1**), an epoxy cembrane diterpenoid from marine soft coral *Lobophytum*, is described, which allows the assignment of an absolute configuration (11*S*,12*S*) of the epoxide function unambiguously.

Cembranoids, a family of 14-membered cyclic diterpenoid natural products existing in terrestrial, and especially in marine organisms,[1] are of great interest to synthetic organic chemists and biologists because of their unique structure and wide range of biological activities.[2] (+)-11,12-Epoxysarcophytol A (**1**), an epoxy cembrane diterpene, was first isolated by Bowden and co-workers[3] in 1983 from an Australian marine soft coral *Lobophytum* sp. and characterized spectroscopically and chemically as (1*Z*,3*E*,7*E*)-14-hydroxyl-11,12-epoxycembra-1,3,7-triene. The configuration of 14-hydroxyl was confirmed as (*S*) by a zinc–copper couple-mediated reductive elimination of the epoxide moiety leading to the formation of a known cembrane diterpenoid sarcophytol A (**2**),[4] a possible biosynthesis precursor of **1**. Sarcophytol A (**2**) has shown therapeutic potential for cancer prevention and have been studied[5] extensively both synthetically and biologically. However, the *absolute configuration* of the epoxide function of **1** remains undetermined and was merely assumed as (11*S*,12*S*) by the authors.[3]

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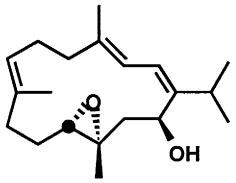
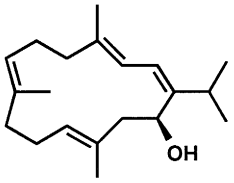


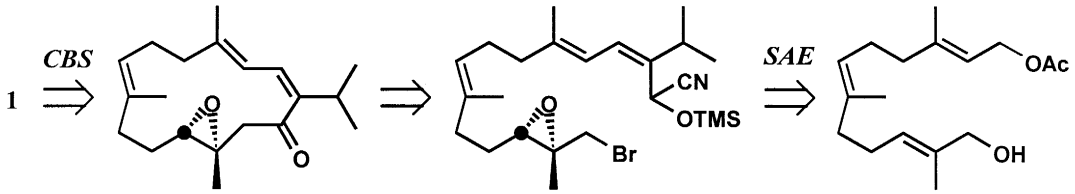
(+)-(11, 12)-Epoxysarcophytol-A (1)



Sarcophytol-A (2)

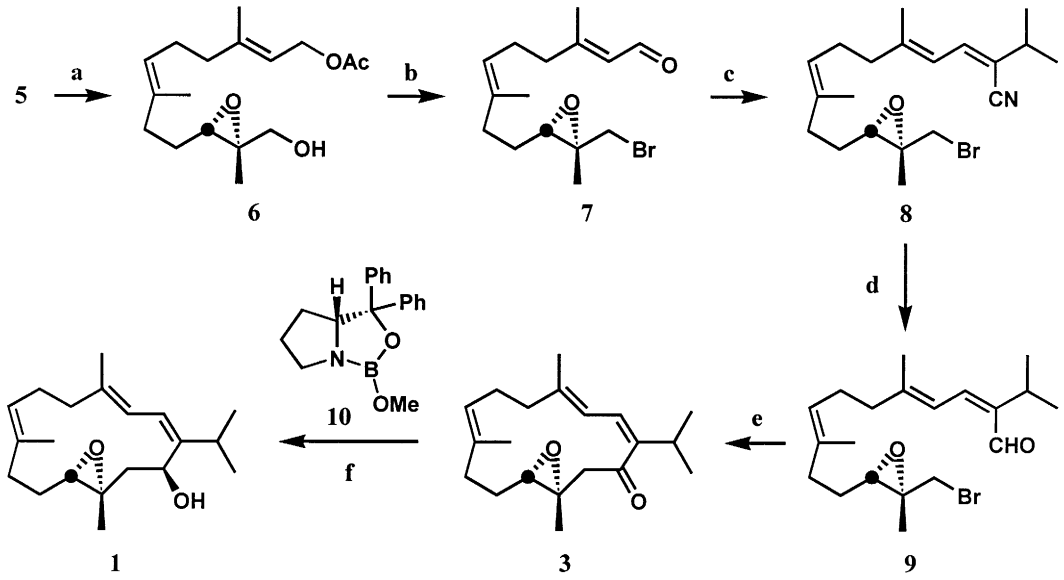
In continuation of our on-going project on the asymmetric synthesis of cembrane diterpenoids, we report herein the completion of the first total synthesis of **1** and its absolute configuration assignment.

The synthetic strategy which adopted the Takayanagi's synthesis[6] of **2**, as shown retrosynthetically in Scheme 1, involves: (1) chemoselective and enantioselective CBS reduction of the ketonic carbonyl of the epoxy cyclic derivative **3**; (2) macrocyclization of precursor **4** by an intramolecular alkylation process of cyanohydrin silyl ether-derived carbanion; and (3) Sharpless epoxidation of **5** to construct the epoxide function enantioselectively.



Scheme 1. SAE=Sharpless asymmetric epoxidation

Total synthesis of **1** is outlined in Scheme 2. The key intermediate **8** was prepared as reported previously[7] with optimized conditions. Enantioselective Sharpless epoxidation[8] of **5** mediated by the Ti(O-*i*-Pr)$_4$/L-(+)-DET system furnished the epoxide **6** in 95% yield with an enantiomeric excess of 98% as measured by means of ^{1}H NMR spectrometry of the ester derivative of (*R*)-(−)-acetylmandelic acid. The epoxy alcohol **6** was converted to the epoxy bromide **7** by the following sequence: (1) mesylation of **6**; (2) S_N2 substitution of the mesylate to give the corresponding bromide; (3) saponification of the acetyl group; and (4) MnO_2 oxidation. Bromo aldehyde **7** was condensed with 3-methyl-2-(diethylphosphono)butanenitrile[9] [$(CH_3)_2CHCH(CN)P(O)(OEt)_2$] under modified Horner–Emmons conditions[10] to afford the desired *Z*-form α,β-unsaturated nitrile **8** in 90% yield. Reduction of nitrile **8** with diisobutylaluminum hydride (Dibal-H) was conducted in *n*-hexane at −78°C and followed by treatment of the resulting imine intermediate with 10% aqueous oxalic acid to give the desired aldehyde **9**[11] in 88% isolated yield after flash chromatography on silica gel. Aldehyde **9** was transformed by treatment with Me_3SiCN catalyzed[12] by a complex of KCN–18-C-6 into cyanohydrin trimethylsilyl ether **4**, the macrocyclization precursor, which was used *immediately* without further purification according to a reported procedure by Takayanagi.[6] Thus, a solution of the cyanohydrin derivative **4** in THF was added slowly (over 1.5 h) to a refluxing mixture of $LiN(SiMe_3)_2$ in THF (~1.0 M). Subsequent treatment of the crude cyclization product with a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF) in 10% aqueous THF at 20°C for 24 h afforded the desired epoxy ketone **3**[11] in 85% overall yield from aldehyde **9** after flash silica gel chromatography. CBS reduction[13] of the ketonic carbonyl of **3** was carried out with $BH_3 \cdot Me_2S$ in toluene at 0°C in the presence of a 10 mol% of chiral complex **10** derived[14] in situ from D-(+)-proline and trimethyl borate to give the title compound **1**[11] in 88% yield with an *S:R* stereoselectivity of 95:5 at C-14.



Scheme 2. Enantioselective total synthesis of **1**. (a) Ti(O-*i*-Pr)$_4$, L-(+)-DET, *tert*-BuO_2H, CH_2Cl_2, −40°C, 95%, 98% ee; (b) (1) CH_3SO_2Cl, Et_3N, CH_2Cl_2, −10–0°C; then LiBr, acetone, 50°C, 82%; (2) K_2CO_3, MeOH, 23°C; then MnO_2, hexane, 23°C, 91%; (c) $LiN(SiMe_3)_2/(CH_3)_2CHCH(CN)P(O)(OEt)_2$, toluene, −78°C; then **7**, 90%; (d) Dibal-H, hexane, −78°C; then 10% aq. oxalic acid, 0°C, 88%; (e) (1) Me_3SiCN, cat. KCN/18-C-6, THF; (2) $LiN(SiMe_3)_2$, THF, reflux; then *n*-$Bu_4N^+F^-$, 10% aq. THF, 85% from **9**; (f) $BH_3 \cdot Me_2S$, **10** (10 mol%), toluene, 0°C, 88%. (DET=diethyl tartrate; Dibal-H=diisobutylaluminum hydride)

The synthetic **1** was identical[15] spectroscopically with those of natural products reported in the literature[3] as well as the specific rotation {$[\alpha]_D^{20}$ +218 (*c* 0.35, $CHCl_3$), lit.[3] $[\alpha]_D$ +229 (*c* 0.95, $CHCl_3$)}. The corresponding acetate of synthetic **1** was obtained by direct acetylation (Ac_2O, Py, cat. 4-DMAP) and showed identical[15] spectroscopic properties with those of natural products[3] as well as the optical character {$[\alpha]_D^{20}$ +290 (*c* 0.62, $CHCl_3$), lit.[3] $[\alpha]_D$ +296 (*c* 0.36, $CHCl_3$)}. Therefore, we were able to conclude that the absolute configuration of (11,12)-epoxy of **1** was (11*S*,12*S*).

In summary, a concise and efficient enantioselective synthesis of (+)-(11*S*,12*S*)-epoxysarcophytol-A (**1**) was accomplished for the first time in six simple operations from readily available *trans*, *trans*-farnesol derivative **5** with an overall yield of ca. 42%, by which the absolute stereochemistry of the natural product **1** was assigned unambiguously. The synthesis presented here features a combination of the well-known highly enantioselective Sharpless epoxidation and CBS reduction for the assembly of three chiral centers and the macrocyclization of cyanohydrin silyl ether-derived carbanion alkylation leading to the 14-membered cembrane cyclic skeleton.

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References

1. Tursch, B.; Braeckamn, J. C.; Dolaze, D.; Kaisin, M. In *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2, pp. 286–387.
2. (a) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719–732; (b) Cox, N. J. G.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1313–1321, and references cited therein.
3. Bowden, B. F.; Coll, J. C.; Tapiolas, D. M. *Aust. J. Chem.* **1983**, *36*, 2289–2295.
4. (a) Kobayashi, M.; Nakagawa, T.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2382–2387; (b) Blackman, A. J.; Bowden, B. F.; Coll, J. C.; Frick, B.; Mahendran, M.; Mitchell, S. J. *Aust. J. Chem.* **1982**, *35*, 1873–1880.
5. Li, W.-D. Z.; Li, Y.; Li, Y.-L. *Tetrahedron Lett.* **1999**, *40*, 965–968.
6. (a) Takayanagi, H.; Kitano, Y.; Morinaka, Y. *J. Org. Chem.* **1994**, *59*, 2700–2706; (b) idem, *Tetrahedron Lett.* **1990**, *31*, 3317–3320.
7. (a) Yue, X.-J.; Li, Y.-L.; Sun, Y.-J. *Bull. Soc. Chim. Belgium* **1995**, *104*, 509; (b) Yue, X.-J.; Li, T.-H.; Li, Y.-L. *Chinese Chem. Lett.* **1995**, *6*, 189–192.
8. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; (b) Wang, Z.-M.; Zhou, W.-S. *Tetrahedron* **1987**, *43*, 2935–2944; for applications in natural product synthesis, see: Pfenninger, A. *Synthesis* **1986**, 89–116.
9. (a) Raggio, M. L.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 1873–1875; (b) Freerksen, R. W.; Selikon, S. J.; Wroble, R. R.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 4087–4096, and references cited therein.
10. Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581–1584.
11. Selected spectral data. Compound **9**: colorless oil, $[\alpha]_D^{20}$ −26.7 (*c* 1.2, $CHCl_3$); IR (film): ν_{max}=2962, 1667, 1627 cm^{-1} (CH=O); ^1H NMR (400 MHz, $CDCl_3$): δ=1.04 (d, *J*=6.8 Hz, 6H, $2CH_3$), 1.40 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.40–2.40 (m, 8H, $4CH_2$), 2.82–2.86 (m, 2H, H-11 and C*H*$(CH_3)_2$), 3.20 and 3.36 (each d, *J*=10.3 Hz, each 1H, CH_2Br), 5.16 (m, 1H, CH=), 6.82 (d, *J*=12.3 Hz, 1H, CH=), 7.09 (d, *J*=12.3 Hz, 1H, CH=), 10.26 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.0, 15.9, 16.6, 22.0, 26.2, 27.1. 33.1, 36.0, 39.6, 40.5, 59.5, 64.5, 117.9, 124.2, 134.4, 137.8, 142.2, 148.0, 190.4; LR-MS (EI): *m/z* 384 ($[M+2]^+$, 2%), 382 (M^+, 2), 369 (20), 367 (20), 233 (80), 231 (80), 137 (100); compound **3**: colorless oil, $[\alpha]_D^{20}$ +60.2 (*c* 0.65, $CHCl_3$); IR (film): ν_{max}=1690 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ=1.11 (d, *J*=6.8 Hz, 6H, $2CH_3$), 1.42 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.40–2.30 (m, 8H, $4CH_2$), 2.66 (sept, *J*=6.8 Hz, 1H, CH), 2.69 (t, *J*=5.6 Hz, 1H, H-11), 2.79 and 2.92 (each d, *J*=15.0 Hz, each 1H, CH_2Br), 5.10 (t, *J*=6.2 Hz, 1H, CH=), 5.95 (d, *J*=11.6 Hz, 1H, CH=), 6.17 (d, *J*=11.6 Hz, 1H, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1, 17.0, 19.7, 21.2, 22.2, 24.6, 25.1, 30.5, 36.2, 38.9, 48.9, 59.1, 60.2, 121.0, 123.3, 126.6, 133.5, 142.1, 147.4, 205.6; HR-MS (EI): *m/z* calcd for $[M^+]$: 302.2240; found: 302.2238; compound **1**: colorless oil, $[\alpha]_D^{20}$ +218 (*c* 0.35, $CHCl_3$); IR (film): ν_{max}=3365 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$): δ=1.08 (d, *J*=6.6 Hz, 6H, $2CH_3$), 1.26 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.20–2.40 (m, 10H, $4CH_2$), 2.68 (sept, *J*=6.6 Hz, 1H, CH), 3.07 (t, *J*=6.8 Hz, 1H, H-11), 4.59 (t, *J*=5.6 Hz, 1H, CH_2O), 5.09 (m, 1H, CH=), 5.73 (d, *J*=10.6 Hz, 1H, CH=), 5.92 (d, *J*=10.6 Hz, 1H, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7, 16.6, 19.2, 23.0, 24.7, 24.8, 27.3, 36.4, 38.7, 41.6, 58.1, 59.2, 64.0, 118.2, 12.1, 126.3, 131.0, 135.6, 148.3; HR-MS (EI): *m/z* calcd for $[M^+]$: 304.2397; found: 304.2392.
12. Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822–5823.
13. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012, and references cited therein.
14. Masui, M.; Shioiri, T. *Synlett* **1997**, 273–274.
15. Authentic samples of natural product **1** and its acetate were not available for direct comparisons.