Tetrahedron Letters, Vol. 34, No. 17, pp. 2799-2800, 1993
Printed in Great Britain

0040-4039/93 \$6.00 + .00
Pergamon Press Ltd

TOTAL SYNTHESIS OF (±)-SARCOPHYTOL-M

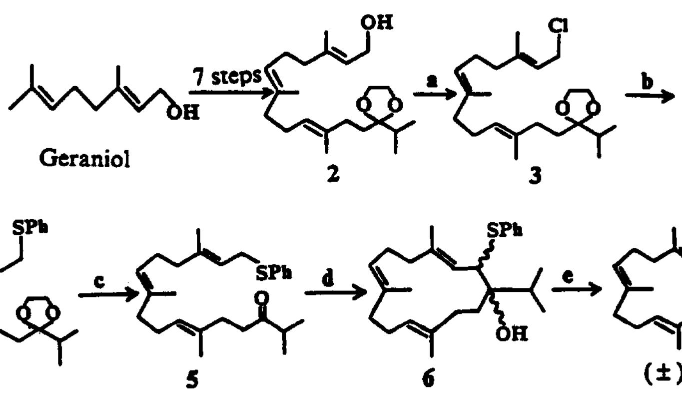
Yulin LI* Xiangjun YUE Yacheng XING

State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. CHINA

Abstract: *The total synthesis of (±)-sarcophytol-M, a marine cembranol, was first achieved from geraniol through twelve steps by using intramolecular nucleophilic addition of sulfur-stabilized carbanion to ketone as the key step.*

(+)-Sarcophytol-M(1), a cembrane-type diterpenoid was first isolated from a soft coral (*Sarcophyton glaucum*) in 1989, and its structure was established as (3*E*,7*E*,11*E*, 1*R*)-cembra-3,7,11-trien-1-ol[1]. As far as we know, the total synthesis of 1 has not been reported yet. Herein we wish to describe the total synthesis of (±)-sarcophytol-M.

In a previous work[2], intermediate 2 has been prepared from geraniol *via* 7 steps from which the total syntheis of cembrene -C has been succeeded. With alcohol 2 in hand, the synthetic route of (±)-Sarcophytol-M from 2 was outlined below:



a) CCl_4, Ph_3P, reflux, 78%; b) PhSNa, MeOH, 80%; c) TsOH, acetone, 98%;
d) LDA-THF, -78℃, 58%; e) Li-$EtNH_2$, -78℃, 78%.

Ketal alcohol 2 was converted into its chloride 3 by chlorination usiny Ph_3P / CCl_4. 3 was subjected to nuclephilic substitution to give the corresponding sulfuride 4[3]. After removal of the ketal protective group, the cyclized precursor 5 was obtained in 62% overall yield from 2 *via* 3 steps.

Precursor 5 was cyclized using LDA in anhydrous THF at -78℃ under argon atmosphere to give 6 in 58% yield. 6 was reduced with Li-$EtNH_2$[4] at -78℃ to afford (±)-1 in 70% yield.

The intermediates **3–6** were first prepared and their structures were established by the spectral data of IR, MS and ^{1}HNMR[5]. The spectral data of (±)–**1** coincide with those of literature[1]. Thus, the total synthesis of (±)–sarcophytol–M was accomplished in twelve steps and in 8.9% overall yield from geraniol. The bioactive test is in progress.

Acknowledgement

This work was supported by the National Natural Science Foundation of China and by the Special Research Grant for Doctoral Sites in Chinese Universities.

References and notes

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5. The spectral data

   3 δ(80MHz):0.96(*d*, 6H, *J*=6.9Hz, CH_3),1.52(*s*, 3H, CH_3), 1.56(*s*, 3H, CH_3), 1.64(*s*, 3H, CH_3), 1.20–2.40(*m*, 13H, CH, CH_2), 3.96(*d*, 2H, *J*=7.9Hz, CH_2), 3.90(*s*, 4H, OCH_2CH_2O), 4.80~5.60(*m*, 3H, CH=); *m / z*(EI):368(M^+, 1%), 243(10), 135(17), 153(47), 93(30), 81(65), 71(100). Anal. Calcd. for $C_{22}H_{37}O_2Cl$: C, 71.61; H, 10.11; Cl, 9.61. Found: C, 71.71; H, 10.08; Cl, 9.34.

   4 v_{max}:740, 651(SPh)cm^{-1};δ(80MHz):1.00(d, 6H, *J*=6.9Hz, CH_3), 1.46(s, 3H, CH_3),1.52(s, 3H, CH_3), 1.54(s, 3H, CH_3), 1.60–2.42(m, 13H, CH, CH_2), 3.46(d, 2H, *J*=7.6Hz, CH_2SPh),3.90(s, 4H, $-OCH_2CH_2O-$), 5.00–5.40(m, 3H, CH=), 7.20–7.50(m, 5H, ArH)ppm; *m / z*(EI):442(M^+, 15%), 389(20), 289(100), 261(15), 93(40), 81(60), 71(100). Anal. Calcd. for $C_{28}H_{42}O_2S$: C, 75.97; H, 9.56; S, 7.24. Found: C, 75.68; H, 9.60; S, 7.42.

   5 v_{max}:1711(s, C=O), 739, 651(–SPh)cm^{-1}; δ(80MHz): 1.01(d, 6H, *J*=6.8Hz, CH_3), 1.48(s, 3H, CH_3), 1.54(s, 3H, CH_3),1.56(s, 3H, CH_3), 1.60–2.40(m, 13H, CH, CH_2), 3.46(d, 2H, *J*=7.6Hz, CH_2SPh), 5.00–5.40(m, 3H, CH=), 7.2–7.5(m, 5H, ArH)ppm; *m / z*(EI):398(M^+, 10%), 313(10), 289(100), 275(40), 153(50), 81(65), 71(100). Anal. Calcd. for $C_{26}H_{38}OS$: C, 78.34; H, 9.61; S, 8.04. Found: C, 78.56; H, 9.62; S, 8.28.

   6 v_{max}:3390(s, OH), 750, 690(–SPh)cm^{-1}; δ(80MHz): 1.04(d, 6H, *J*=6.9, CH_3), 1.50(s, 3H, CH_3), 1.54(s, 3H, CH_3), 1.58(s, 3H, CH_3), 1.10–2.30(m, 14H, CH, CH_2, OH), 3.50(d, 1H, *J*=7.6Hz, CHSPh), 4.80–5.40(m, 3H, CH=), 7.2–7.50(m, 5H, ArH)ppm; *m / z*(EI):398(M^+, 0.4%), 305(20), 261(10), 153(50), 93(40), 81(65), 71(100). Aanl. Calcd. for $C_{26}H_{38}OS$: C, 78.34; H, 9.61; S, 8.04. Found: C, 78.29; H, 9.58; S, 8.07.

(Received in China 20 November 1992)