Tetrahedron Letters,Vol.23,No.51,pp 5413-5414,1982 0040-4039/82/515413-02$03.00/0
Printed in Creat Britain

(10R, 11R)-(+)-SQUALENE-10, 11-EPOXIDE: ISOLATION FROM LAURENCIA OKAMURAI AND THE ASYMMETRIC SYNTHESIS

Hideo Kigoshi, Makoto Ojika, Yoshikazu Shizuri, Haruki Niwa, and Kiyoyuki Yamada*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464 Japan

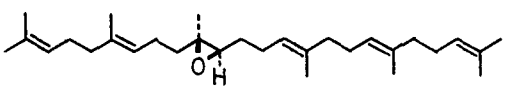
Abstract. *From a red alga Laurencia okamurai, (10R, 11R)-(+)-squalene-10, 11-epoxide 1 was isolated and its asymmetric synthesis has been achieved starting from trans, trans-farnesol.*

As part of our chemical studies on marine algae, we have examined the constituents of a red alga Laurencia okamurai collected off the coast of Goza, Mie Prefecture, Japan in July and isolated an epoxy compound, (10R, 11R)-(+)-squalene-10, 11-epoxide 1, whose structural proof and asymmetric synthesis are described in the present paper.

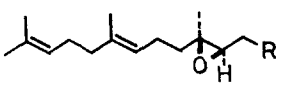
Isolation of 1 would be interesting in view of its possible biogenetic significance in connection with the structurally related squalene-2, 3-epoxide,[1] the important role of which in the biosynthesis of terpenoids is well-known. Natural occurrence of squalene-10, 11-epoxide was first reported in 1976 by Katayama and Marumo,[2] who isolated it as a fungal metabolite from the mycelia of Sclerotinia fructicola; stereochemistry of the metabolite was unsettled. Very recently Fattorusso and coworkers isolated (10S, 11S)-(-)-squalene-10, 11-epoxide from a marine green alga Caulerpa prolifera.[3] It is worthy of note that the (10S, 11S)-enantiomer of squalene-10, 11-epoxide was isolated from the green alga,[3] while the (10R, 11R)-enantiomer 1 was obtained from the red alga.

The ethyl acetate-soluble fraction of acetone extracts of fresh L. okamurai was chromatographed on silica gel with hexane-benzene, benzene, and benzene-ethyl acetate, successively. The fraction eluted with benzene was further separated by preparative TLC on silica gel with hexane-ether (85:15), giving an epoxy compound 1,[4,5] $[\alpha]_D^{25}$ +10.4° (c 0.80, $CHCl_3$) (0.0003%) as colorless oil. Based on the spectral (^{1}H-NMR, ^{13}C-NMR, and MS) properties, the epoxide 1 was deduced to be squalene-10, 11-epoxide. This inference was verified by comparison of the spectral data of the epoxide 1 with those of (±)-squalene-10, 11-epoxide prepared from squalene with m-chloroperbenzoic acid according to the procedure of Katayama and Marumo.[2]

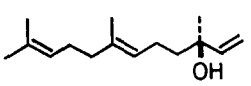
Asymmetric synthesis of 1 was executed as follows, which established unambiguously the



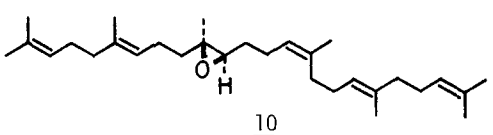
1



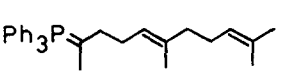
2 R = OH
3 R = OAc
4 R = OTs
5 R = I
6 R = CH_2COO^tBu
7 R = CH_2CHO



8



10



9

absolute stereochemistry of the epoxy moiety in 1. Sharpless asymmetric epoxidation reaction[6] of trans, trans-farnesol using (-)-diethyl tartrate [t-BuOOH/(-)-DET/Ti(i-PrO)$_4$, CH_2Cl_2, -50 ~ -45 °C, 1 h] afforded (2R, 3R)-epoxyfarnesol 2,[4,7] $[\alpha]_D^{26}$ +6.53° (c 4.21, $CHCl_3$) (colorless oil, 84% after purification[8a]). ^{1}H-NMR spectral analysis of the derived acetate 3[7,9] in the presence of a chiral shift reagent Eu(hfc)$_3$ gave an enantiomeric excess (ee) of 96%. Based on the observations reported by Sharpless,[6] absolute stereochemistry of 2R and 3R was assigned to the product 2 as depicted, which was confirmed by converting the epoxide 2 to R-(-)-nerolidol 8[10] by the following sequence: the epoxide 2 was transformed (TsCl, Py, 0 °C, 5 h) into the tosylate 4,[4,7] $[\alpha]_D^{27}$ +21.4° (c 5.67, $CHCl_3$) (colorless oil, 96% after purification[8b]) and the tosylate 4 on reaction with sodium iodide (acetone, room temp., 10 h) yielded the iodide 5[4,7] $[\alpha]_D^{22}$ -27.2° (c 4.45, $CHCl_3$) (colorless oil, ~100% after purification[8d]), reduction of which with zinc (AcOH-ether, room temp., 1 h) afforded R-(-)-nerolidol 8[7] $[\alpha]_D^{20}$ -17.9° (c 1.15, EtOH) [lit.[10] $[\alpha]_D^{22}$ +15.1° for S-(+)-nerolidol] (colorless oil, 97% after purification[8c]). Bishomologation of the C_{15}-skeleton of the iodide 5 was carried out by reacting the iodide 5 with t-butyl lithioacetate[11] (THF-HMPA, -78 °C, 1 h) giving the ester 6[4,7] $[\alpha]_D^{22}$ +8.44 (c 3.78, $CHCl_3$) (colorless oil, 84% after purification[8d]). Reduction of the ester 6 (DIBAL, toluene, -110 ~ -100 °C, 2 h) yielded the aldehyde 7[4,7] $[\alpha]_D^{21}$ +11.3° (c 4.41, $CHCl_3$) (colorless oil, 81% after purification[12]). The Wittig reaction of the aldehyde 7 with the phosphorane 9[13] (THF/-78 °C, 40 min. → room temp., 5 h) afforded a 4:3 mixture[14] of 1 and its isomer 10, which was separated by chromatography on silica gel impregnated with silver nitrate with benzene-ethyl acetate (20:1 → 10:1) yielding 1,[4,5] $[\alpha]_D^{22}$ +10.7° (c 1.19, $CHCl_3$) (colorless oil, 24%) and the isomer 10[4] (colorless oil, 16%), respectively. The spectral (IR, ^{1}H-NMR, ^{13}C-NMR, MS) properties including the specific rotation as well as chromatographic behaviors of synthetic 1 were in accord with those of natural 1.

Acknowledgment. Financial support from the Ministry of Education, Science, and Culture (Grant-in-Aid for Scientific Research No. 447025) is gratefully acknowledged.

REFERENCES AND NOTES

1. (a) E. J. Corey, W. E. Russey, and P. R. O. de Montellano, J. Am. Chem. Soc., 88, 4750 (1966); (b) E. E. van Tamelen, J. D. Willet, R. B. Clayton, and K. E. Lord, J. Am. Chem. Soc., 88, 4752 (1966).
2. M. Katayama and S. Marumo, Tetrahedron Lett., 1293 (1976).
3. L. De Napoli, E. Fattorusso, S. Magno, and L. Mayol, Phytochemistry, 21, 782 (1982).
4. Satisfactory exact mass spectral data were obtained.
5. 1: IR (CCl_4) 1660 cm^{-1}; ^{1}H-NMR (CCl_4, 90 MHz) δ 1.18 (3H, s), 1.50 (4H, m), 1.58 (3H x 5, s), 1.65 (3H x 2, s), 1.98 (16H, m), 2.53 (1H, t, J = 6.0 Hz), 5.04 (5H, m); ^{13}C-NMR (C_6D_6, 22.5 MHz) δ 16.1 (q, Me x 3), 16.9 (q), 17.8 (Me x 2, q), 24.2 (t), 25.4 (t), 25.9 (q, Me x 2), 27.0 (t), 27.1 (t), 27.2 (t), 29.5 (t), 39.3 (t), 40.1 (t, CH_2 x 3), 59.9 (s), 62.7 (d), 124.0 (d), 124.4 (d), 124.6 (d), 124.8 (d, CH x 2), 131.2 (s, C x 2), 135.1 (s), 135.2 (s), 135.7 (s); MS (m/z) 426 (M^+), 411, 408.
6. T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).
7. The IR, ^{1}H-NMR, and mass spectral data for this compound were in accord with the structure assigned.
8. By chromatography on silica gel with hexane-EtOAc: (a) 4:1; (b) 6:1; (c) 10:1; (d) 20:1.
9. Obtained on acetylation of 2 with Ac_2O and pyridine (room temp., 1 h).
10. P. Vlad and M. Souček, Collect. Czech. Chem. Commun., 27, 1726 (1962).
11. (a) M. W. Rathke and A. Lindert, J. Am. Chem. Soc., 93, 2318 (1971); (b) W. Bos and H. J. J. Pabon, Rec. Trav. Chim. Pays-Bas, 99, 141 (1980).
12. By chromatography on silica gel with hexane-ether (3:1).
13. R. M. Coates and W. H. Robinson, J. Am. Chem. Soc., 93, 1785 (1971).
14. The ratio of two isomers, 1 and 10 was determined by HPLC analysis (Develosil ODS, MeCN).

(Received in Japan 14 August 1982)