Pergamon

Tetrahedron Letters 40 (1999) 1963–1966

TETRAHEDRON LETTERS

The First Total Synthesis of Preverecynarmin

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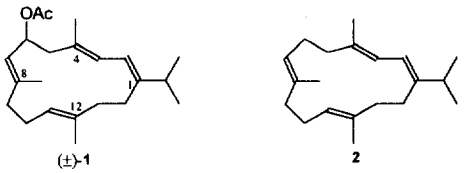
Received 30 September 1998; revised 4 January 1999; accepted 11 January 1999

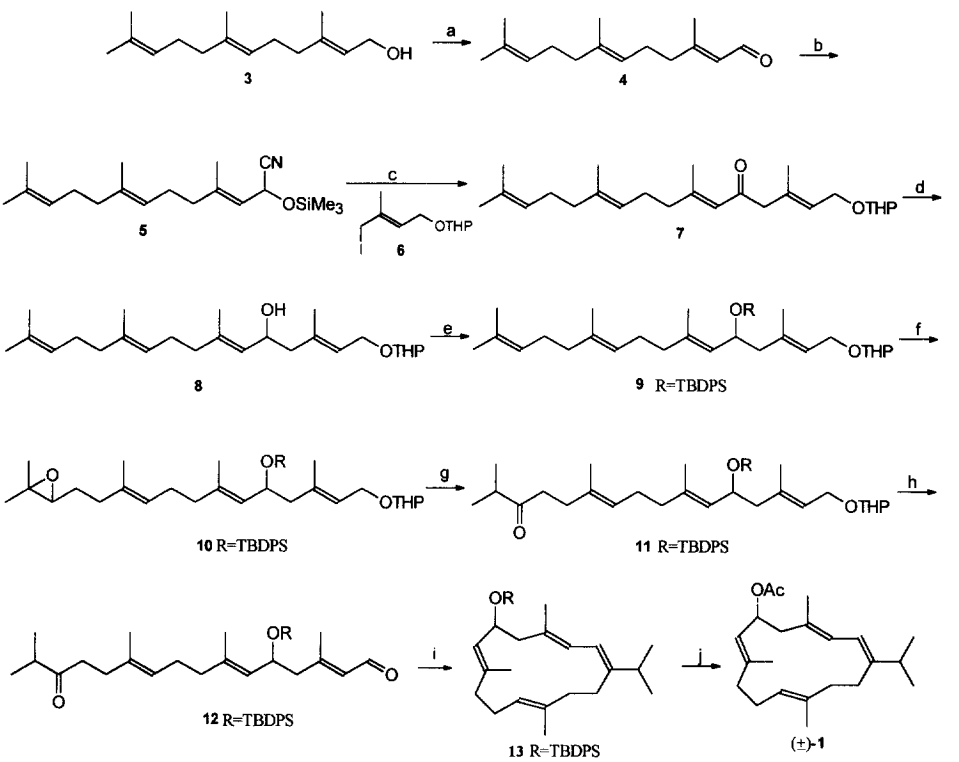
Abstract Preverecynaimin, isolated from a pennatulatean coral, has been synthesized from *E,E*-farnesol.

Preverecynarmin **1**, (+)-(1*E*,3*E*,7*E*,11*E*)-cembra-1,3,7,11-tetraen-6-yl acetate was first isolated in 1990 from both *Armina maculate* and its prey, the pennatulacean coral *veretillum cynomorium* along with three other briarane diterpenoids and cembrene-C **2** (1*E*,3*E*,7*E*,11*E*)-cembra-1,3,7,11-tetraene.[2] It is first time that cembranoids have been isolated from pennatulaceans. The co-occurrence of both the briarane and cembrane skeletons supports the theory that the cembranoid carbon skeleton is a biosynthetic precursor of the briaranes. This prompted our search for a practical synthesis of preverecynarmin. As far as we know, neither biological activity nor a total synthesis of **1** has been reported. Herein we wish to describe the first total synthesis of (±)-preverecynarmin (±)-**1**.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00124-0



Our synthetic route which started from *E,E*-farnesol involves three key steps: 1) alkylation of the cyanohydrin trimethylsilyl ether **5** with halide **6**; 2) the regioselective epoxidation of **9**; 3) the intramolecular macrocyclization of **12** induced by Ti(0).



a) MnO_2, *n*-hexane, r.t., 15h., 97%; b) Me_3SiCN, KCN/18-crown-6,0℃, 30min, 100%; c) 1.$LiN(SiMe_3)_2$, THF, 0℃, 20min then **6**, r.t., 4h, 23%; 2. 10% aq. n-$Bu_4N^+F^-$/THF, r.t., 4h, 95%; d) $NaBH_4$, MeOH, 89%; e) TBDPSiCl, imidazole, DMF, r.t., 4h, 89%; f) mCPBA(0.6eq), CH_2Cl_2, r.t., 30min, 56%; g) $HClO_4$, dry CH_2Cl_2, r.t., 5min, 75%; h) 1. *p*-TsOH, MeOH, r.t., 1h, 90%; 2. MnO_2, *n*-hexane, r.t., 8h, 94%; I) $Zn/TiCl_4$, Py, THF, reflux 24h. 66%; j) 1. 1M *n*-$Bu_4N^+F^-$ in THF, r.t., 20h; 2. AcO_2, Py, DMAP, r.t., 30min, 78%

The first stage of the synthesis is the construction of a 20-membered carbon chain possessing a carbonyl group at C-6. Although many papers have reported that sulfur-stabilized anions can be used as acyl carbonion equivalents in alkylation reactions,[3-6] we selected a cyanohydrin TMS ether as the acyl anion equivalent.[7] Farnesol was oxidized by MnO_2 in *n*-hexane to farnesal **4,** which was converted to the cyanohydrin trimethylsilyl ether **5** by an addition of Me_3SiCN in the presence of a catalytic amount of KCN/18-crown-6 complex.[8] The cyanohydrin **5** was treated with 1.25equiv of $LiN(SiMe_3)_2$ in THF and the lithiated cyanohydrin alkylated with **6**[9] to afford the alkylated cyanohydrin which was directly converted into the ketone by using a catalytic amount of n-$Bu_4N^+F^-$ in 10% aqueous THF without purification. After reduction with $NaBH_4$, the alcohol **8** so obtained was protected with TBDPSCl to afford the silyl ether **9**.

Another key step was the regioselective epoxidation of the silyl ether **9**. When 0.6eq mCPBA was used, the major product was the epoxide **10**. In order to obtain more of the epoxide **10**, this reaction was repeated three times. In anhydrous CH_2Cl_2, $HClO_4$ converted the epoxide **10** into the ketone **11**. Removal of the THP group from **11** with a catalytic amount of *p*-TsOH in MeOH followed by oxidation using 20 equiv. of MnO_2 in *n*-hexane resulted in formation of the cyclization precursor **12**. To effect cyclization, a highly diluted solution of **12** in 30 ml DME was syringed slowly over 24hrs to a mixture of $TiCl_4$/Zn-DME.[10a,b] The macrocyclization product **13** was then deprotected using 1M n-$Bu_4N^+F^-$ in THF and then acetylated by Ac_2O in pyridine in the presence of a catalytic amount of DMAP to give the title compound (±)-**1** as clear oil. The spectral data of (±)-**1** agreed with that of literature.[11]

Acknowledgment This work was financially supported by the National Nature Science Foundation of China (Grant NO.29672015)

Reference and Notes

1. Present address is Department of Chemistry, Qingdao University, Qingdao, 266071
2. Guerriero, M. Ambrosio, F. Pierra, *Helv. Chim. Acta.*, **1990**, 73(2), 277
3. Seebach, D., Corey, E.J., *J. Org., Chem.*, **1975**, 40, 231
4. Hoppmann, A., Weyerstahl, P., *Tetrahedron*, **1978**, 34, 1723
5. Lipshutz, B.H., Garcia, E., *Tetrahedron Lett.*, **1990**, 31, 7261
6. Nakata, M., Ohashi, J., Ohsawa, K., Nishimura, T., Kinoshita, M., Tatsuta, K., *Bull. Chem. Soc. Jpn.*, **1993**, 66, 3464
7. a). Takayanagi, H., Kitano, Y., Morinaka, Y., *J. Org. Chem.*, **1994**, 59, 2700
   b). Takayanagi, H., Kitano, Y., Morinaka, *Tetrahedron Lett.*, **1990**, 31, 3317
8. Theodora W. Greene, Protective Groups in Organic Synthesis; John Wiley & Sons, Inc. 1981, pp.47, pp.141
9. The iodide **6** was prepared from 3-methyl-2-buten-1-ol in three steps. First the alcohol was protected with DHP, then oxidised by TBHP in presence of 0.2 eq. SeO_2, and then the allylic alcohol was iodinated with I_2/PPh_3/imidazole.
10. a). McMurry, J. E., *Chem. Rev.*, **1989**, 89, 1513; b). The cyclization precursor **12** (120mg, 0.215mmol) was dissolved in 30 ml DME. This solution was added to a mixture of $TiCl_4$/Zn in 20 ml DME. The concentration of substrate is no more than 5×10^{-3}mol/l.
11. Spectral data of compound (±)-**1**: ν=2959, 2921, 2860, 1736, 1438, 1358, 1240; ^{1}H NMR: δ (400MHz, C_6D_6)=1.03 (d, 3H, J=7.0Hz, CH_3), 1.04 (d, 3H, J=7.0Hz, CH_3), 1.53 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.02 (s, 3H, CH_3CO), 2.10-2.60 (m, 11H, CH_2, CH), 5.05 (m, 1H, CH=), 5.23 (t, 1H, J=9.1Hz, CH=), 5.90 (m, 1H, CHO), 6.16 (m, 2H, CH=); ^{13}C NMR: δ (100MHz, C_6D_6)=16.4, 17.3, 18.2, 21.0, 21.7, 23.1, 24.8, 28.0, 32.9, 37.3, 39.5, 46.1, 70.2, 119.1, 124.1, 124.6, 126.3, 130.0, 134.3, 140.0, 147.0, 169.6; m/z (EI, 70ev): 330 (M^+, 20%), 270 (52), 255 (7), 227 (10), 202 (14), 187 (20), 159 (81), 136 (42), 121 (100);