Pergamon

Tetrahedron Letters 40 (1999) 1963–1966

TETRAHEDRON
LETTERS

The First Total Synthesis of Preverecynarmin

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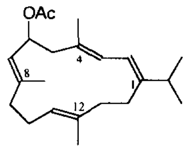
Received 30 September 1998; revised 4 January 1999; accepted 11 January 1999

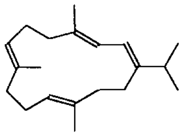
Abstract Preverecynaimin, isolated from a pennatulatean coral, has been synthesized from *E,E*-farnesol.

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**.

PII: S0040-4039(99)00124-0



(±)-1



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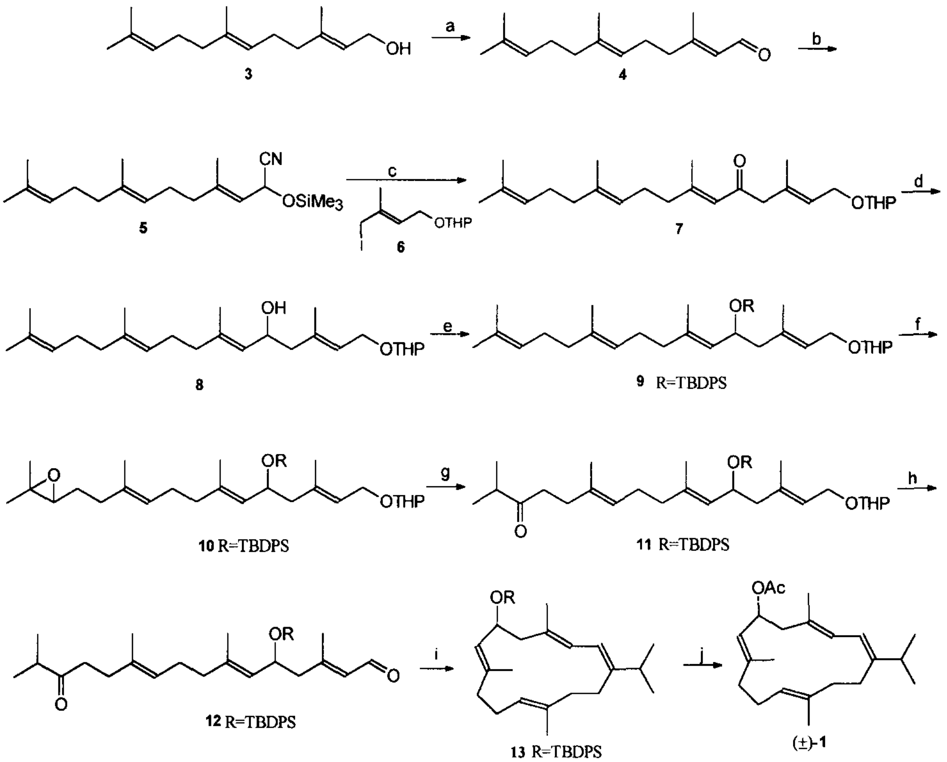
Our synthetic route which started from *E,E*-farnesol involves three key steps: 1) alkylation of the cyanohydrin trimethylsilyl ether **5** with halide **6**; 2) the regioselective epoxidation of **9**; 3) the intramolecular macrocyclization of **12** induced by Ti(0).



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. $n\text{-}Bu_4N^+F^-$/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 $n\text{-}Bu_4N^+F^-$ 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 $n\text{-}Bu_4N^+F^-$ 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

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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);