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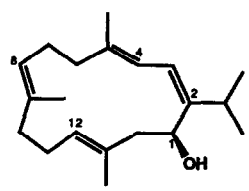
STEREO- AND ENANTIOSELECTIVE TOTAL SYNTHESIS OF SARCOPHYTOL-A

Hisao TAKAYANAGI,* Yasunori KITANO, Yasuhiro MORINAKA

Pharmaceuticals Laboratory, Research Center, Mitsubishi Kasei Corporation
1000, Kamoshida-cho, Midori-ku, Yokohama 227, Japan

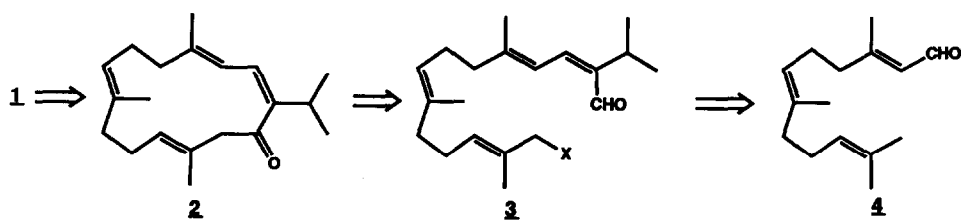
Summary: The first total synthesis of sarcophytol-A, a biologically important marine cembranoid, was achieved in a highly stereo- and enantioselective manner.

Sarcophytol-A (1),[1] a cembrane type diterpenoid isolated in 1979 from the soft coral Sarcophyton glaucum, has been shown to inhibit the activity of the powerful tumor-promoter teleocidin[2] and exhibit potent antitumor activity.[3] Recently, the geometrical structure of 1 has been finally confirmed to be 2Z, 4E, 8E, 12E and the absolute configuration has been determined as 1S.[4] Its intriguing bioactivities and challenging structural features prompted our search for a practical synthesis. In this communication we wish to report the first stereo- and enantioselective total synthesis of 1.



sarcophytol-A(1)

Our synthetic strategy starting from E,E-farnesal (4)[5] outlined in scheme-1 involves three key-steps: (1) stereoselective synthesis of the conjugated 2Z,4E-dienal 3, (2) macrocyclization of 3 using modified Takahashi's protected cyanohydrin procedure , and (3) eventual enantioselective reduction of the resulting large-ring ketone 2 to 1.

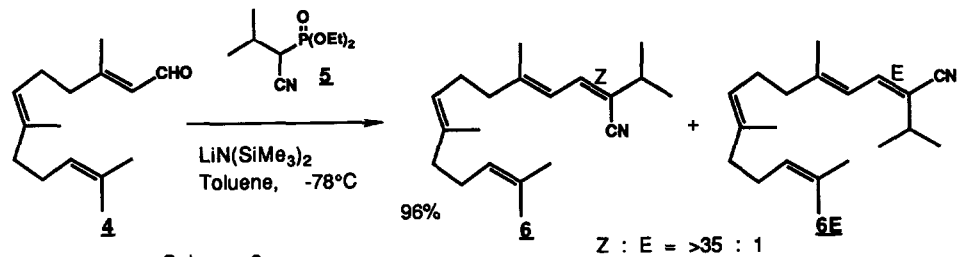


2 3 4

Scheme-1

On the first stage of the synthesis we had to construct stereoselectively the conjugated 2Z,4E-diene moiety possessing a functional group convertible into aldehyde.

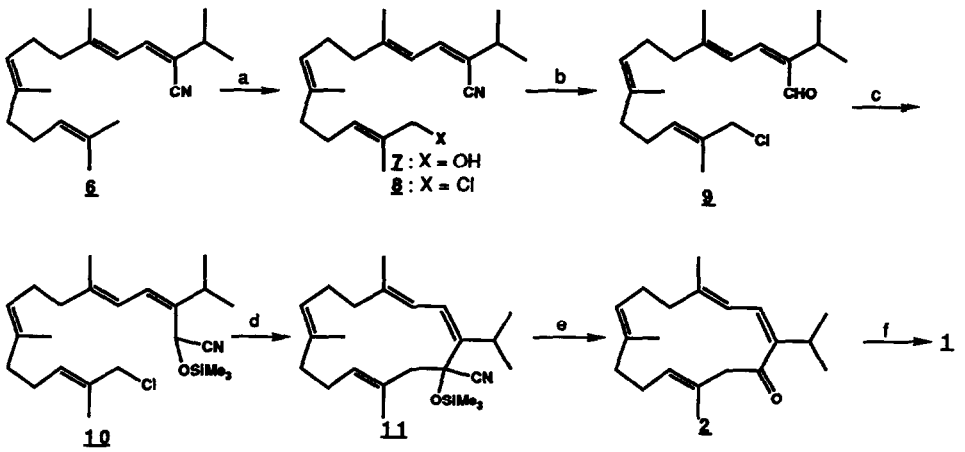
Although several procedures for stereoselective preparation of Z-alkene by Wittig type reaction have been developed, these methods seemed not to be suitable for the preparation of the alkene required in this synthsis, i.e., trisubstituted one attached by a bulky isopropyl group.[6] We found out that the Horner-Emmons reaction of 4 using phosphonate nitrile 5 under selected reaction condition[7] gave fairly good results. Thus, 1.3 equiv of 5 in toluene was deprotonated at -78 °C by means of 1 M $LiN(SiMe_3)_2$ n-hexane solution, and after 20 min the aldehyde 4 was added. The heterogeneous reaction mixture was allowed to warm to room temperature over 5 hr with well stirring. The desired diene nitrile 6 was obtained along with its geometrical isomer 6E in a ratio of >35:1[8] in 96% yield (scheme-2). By using the corresponding phosphonate ester[5] of 5, such a stereoselctivity could not be realized under various reaction conditions.



Scheme-2

The next task was to functionalize the terminal E methyl group of 6 prior to the reduction of nitrile to aldehyde. Oxidation of 6 with 80% t-BuOOH in the presence of catalytic amount of SeO_2[9] in CH_2Cl_2 at 25 °C gave hydroxy nitrile 7 in 52% yield (based on the consumed starting material), which was then converted to the corresponding chloride 8 with PPh_3 (1.3 equiv) in refluxing CCl_4 for 1hr in 93% yield. Reduction of the nitrile group in 8 (DIBAL in n-hexane at -78 °C, 2 hr), and mild hydrolysis[10] of the resulting imine with acid (15% acetic acid aqueous solution, 0 °C, 5 hr, under argon atmosphere) gave the desired dienal 9 in 79% yield (scheme-3).

The unstable conjugated dienal 9 thus obtained was converted to the cyanohydrin trimethylsilyl ether 10 (Me_3SiCN, catalytic amount of 18-crown-6/KCN complex, 0 °C, 2 hr). The macrocyclization reaction of 10 was immediately carried out without purification substantially according to Takahashi's method,[11] except for the use of trimethylsilyl (TMS) ether instead of ethoxyethyl (EE) ether for the protection of the cyanohydrin group. Thus, a 0.06 M solution of 10 in THF was added over 50 min at 55 °C under argon atmosphere to the same volume of THF solution of $LiN(SiMe_3)_2$ (3.5 equiv). The desired cyclized product 11 was obtained in 77% yield along with 15% of unexpected cyclic ketone 2 whose spectral data (NMR, IR, MS) were identical with those reported[12] for 2 derived from natural 1. When the crude cyclization product was dissolved in 10% aqueous THF containing 0.02 equiv of $n\text{-}Bu_4N^+F^-$ at 25 °C for 2 days under argon atmosphere, 2 was again formed in 89% overall yield from 9 after chromatographic purification.



Scheme-3 : a) SeO_2, t-BuOOH (52%) ; PPh_3, CCl_4 (93%) ; b) DIBAL, -78°C ; then aq. AcOH (79%) ; c) Me_3SiCN, KCN / 16-crown-8 ether complex ; d) $LiN(SiMe_3)_2$, THF, 55°C ; e) 10% aq. THF, n-$Bu_4N^+F^-$ (89% from 9) ; f) chiral $LiAlH_4$ reagent, Et_2O, -78°C (88%)

It is noteworthy that the intramolecular alkylation of cyanohydrin TMS ether[13] proceeded regioselectively at α-position in high yield without geometrical isomerization of conjugated diene system in spite of the absence of the metal chelating effect[14] of EE group.

The final crucial step in the sequence involved an enantioselective reduction of 14-membered ketone 2. Treatment of 2 with 5 equiv of chiral reducing reagent, prepared by mixing $LiAlH_4$ in ether with (S)-2-(2,6-xylidinomethyl)pyrrolidine,[15] at -78 °C led to optically active 1 of 93% ee[16] in 88% yield. Upon a single recrystallization the crude 1 gave enantiomerically pure[16] (100% ee) 1 as white crystals in good yield (>70%). The melting point[17] and optical rotation[18] of the synthetic 1 thus obtained showed good agreement with those of natural sarcopytol-A[19] {synthetic: mp 56.5-57.5 °C, $[\alpha]_D$ +225° (c = 0.9, $CHCl_3$) ; natural: mp 55.5-56.5 °C,[17] $[\alpha]_D$ +228° (c = 1.2, $CHCl_3$)[18]}. In addition, the chromatographical (HPLC, chiral HPLC, GC, TLC) and spectral (NMR, IR, MS) data of the synthetic 1 were completely identical with those of naturally occurring material.

Thus, we succeeded in obtaining enantiomerically pure sarcophytol-A in eight steps and 19% overall yield from E,E-farnesal.

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7) Z,E-Ratios were dependent on the bases and solvents used: (n-BuLi,THF; 2.1:1), (NaN($SiMe_3$)$_2$,toluene; 8.8:1), (KN($SiMe_3$)$_2$,THF/HMPA; 1:1.5). Scope and limitations of this reaction including phophonate nitriles other than 5 will be reported elsewhere.

8) The ratio was determined by GC analysis.

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10) 2Z,4E-Dienal system was easily isomerized by long exposure to even if weak acid to afford a mixture of geometrical isomers.

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16) The enantiomeric exess was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD, n-hexane : i-PrOH = 100 : 1).

17) Melting point of natural 1 had not been reported in the literature.[1,19]

18) Specific rotation of +141° (c = 1.10, $CHCl_3$) had been recorded[1,19] for natural sarcophytol-A.

19) A pure crystalline authentic sample of natural 1, recently obtained by Dr. M. Kobayashi, Hokkaido University, was kindly provided for comparison with synthetic material.

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