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Synthesis and Stereochemistry of Sarcophytol B: An Anticancer Cembranoid

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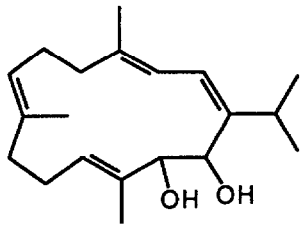
Abstract: A short (5 step), efficient synthesis of sarcophytol B (**1**) from farnesal is reported using a low-temperature, titanium-induced pinacol coupling reaction of 1,14-dialdehyde **5** as the key step. An X-ray structure determination showed that sarcophytol B has trans diol stereochemistry.

The cembrane sesquiterpenes[1] are a large group of natural products distinguished by the presence of a 14-membered carbocyclic ring. Though a number of cembranoids have been shown to have pronounced biological activity, relatively little synthetic work has been reported in the area.[2] We now report a brief and efficient synthesis of sarcophytol B (**1**),[3] a simple cembranoid glycol that has been claimed to have potent anticancer activity.[4]

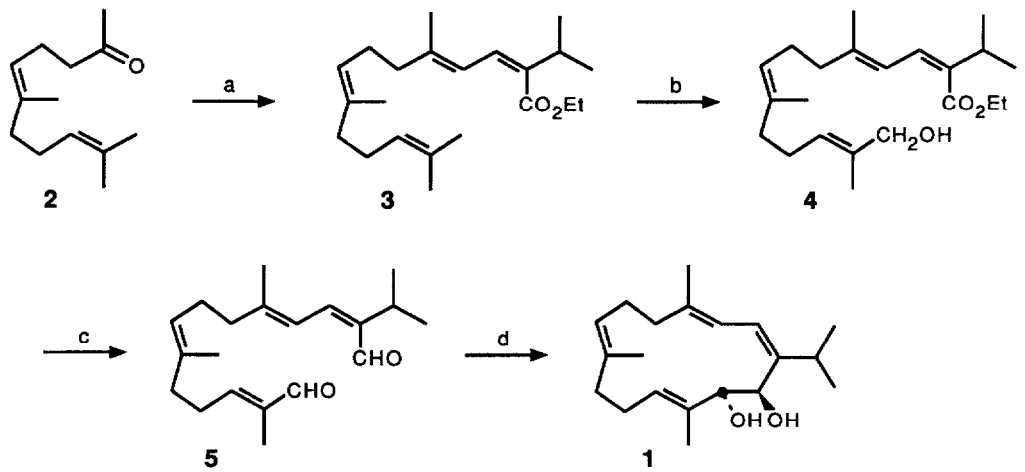
Sarcophytol B



We have found in numerous studies over the past decade that the titanium-induced cyclization of dicarbonyl compounds is an extraordinarily general and effective means of preparing carbocyclic rings of all sizes.[5] Although the reaction is usually carried out at an elevated temperature such that deoxygenation occurs and a cycloalkene is produced, we have also found that the intermediate 1,2-diols (pinacols) can be isolated if the cyclization is carried out at or below room temperature.[6] Cis diols predominate when six-membered rings are formed, but trans diols predominate when ten-membered and larger rings are prepared. The applicability of this reaction to a synthesis of sarcophytol B is evident, except for the fact that the relative stereochemistry of the hydroxyl groups in the natural product is not known. We nevertheless thought it worthwhile to undertake a synthesis to see if we could determine the stereochemistry of the natural product.

Synthesis of sarcophytol B by titanium-induced pinacol coupling requires preparation of dialdehyde **5**, a requirement met in only four steps as outlined in the Scheme.[7] Thus, reaction of farnesal[8] (**2**) with ethyl 1-diethylphosphono-2-methylbutanoate led in 82% yield to a 2.7:1 mixture of *Z* and *E* unsaturated esters **3**, which could be readily separated by column chromatography. Oxidation of the *Z* isomer by treatment with SeO_2/*t*-BuOOH[9] gave hydroxy ester **4**,[10] which was reduced to the corresponding diol with $LiAlH_4$ and oxidized to the required dialdehyde **5** by reaction with $BaMnO_4$.[11]

Dialdehyde **5** in dimethoxyethane (DME) was added by syringe pump over 30 hours at -40° to a stirred slurry of a low-valent titanium reagent prepared by reduction of $TiCl_3(DME)_2$/Zn-Cu in DME. Hydrolysis of the product with aqueous K_2CO_3, followed by chromatography of the residue on silica gel, led in 46% yield to a white crystalline solid, mp 126-128°C. The stereochemical purity of the product was evident by ^{13}C NMR, and its spectroscopic properties[12] were identical to those reported[13] for natural sarcophytol B. Unfortunately, though, we were unable to obtain an authentic sample for direct comparison.

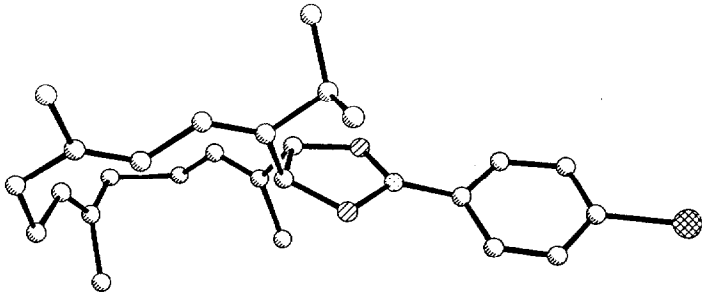


Scheme: Synthesis of Sarcophytol B

(a) *n*-BuLi, $(CH_3)_2CHCH[PO(OEt)_2]COOEt$, THF; then **2**; 60%; (b) SeO_2, *t*-BuOOH, CH_2Cl_2; 45%; (c) $LiAlH_4$, ether; then $BaMnO_4$, CH_2Cl_2; 70%; (d) $TiCl_3(DME)_2$/Zn-Cu, dimethoxyethane, -40°C; then H_2O, K_2CO_3; 46%.

Elucidation of the stereochemistry of our synthetic product was accomplished by single-crystal x-ray analysis of the *p*-bromophenylboronate derivative, crystallized from isopropyl ether. Preliminary x-ray photographs showed the crystal to have triclinic symmetry and gave accurate lattice constants of a = 10.750(3), b = 11.3021(15), c = 12.213 (2) Å, and α = 102.062(12)°, β = 114.593(15)°, γ = 100.466(16)°. These cell constants are consistent with space group P1bar with two molecules of composition $C_{26}H_{24}BO_2Br$ forming the racemic unit cell. All unique diffraction maxima with $2\theta \leq 112.0°$ were collected on a computer-controlled four-circle diffractometer using variable speed 1° ω-scans and graphite monochromated CuKα radiation (λ = 1.54184 Å). Block diagonal least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.97 (R_w = 5.53%) for the observed data.

As indicated by the computer-generated model reproduced below, our synthetic product has trans stereochemistry of the two hydroxyl groups. In view of the spectral identity of this material with the natural product, we therefore conclude that naturally occurring sarcophytol B also has trans stereochemistry.



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References

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7. Satisfactory analytical data were obtained on all synthetic intermediates.

8. Farnesal was prepared from commercially available farnesol by oxidation with $BaMnO_4$ in CH_2Cl_2.

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10. The hydroxy ester was usually contaminated with variable amounts of the further oxidized aldehyde ester, but this had no effect on the synthesis since both compounds were useful.

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12. ^{1}H NMR δ 1.05 (d, 3 H, J = 7 Hz), 1.11 (d, 3 H, J = 7 Hz), 1.45 (s, 3 H), 1.61 (d, 3 H, J = 0.7 Hz), 1.72 (d, 3 H, J = 1.1 Hz), 2.0-2.2 (m, 8 Hz), 2.37 (d, 1 H, J = 3.3 Hz), 2.41 (d, 1 H, J = 3.3 Hz), 2.55 (sept, 1 H, J = 7 Hz), 3.91 (dd, 1 H, J = 7.7, 3.3 Hz), 4.92 (t, 1 H, J = 5.2 Hz), 5.4 (t, 1 H, J = 6.0 Hz), 5.89 (d, 1 H, J = 11.5 Hz), 6.16 (d, 1 H, 11.5 Hz); ^{13}C NMR δ 15.86, 16.40, 16.49, 23.66, 24.44, 25.37, 25.95, 28.00, 38.19, 39.70, 73.34, 77.49, 121.32, 121.95, 124.00, 127.37, 134.39 (2C), 136.39, 143.94.

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