Stereochemical Course of the Transannular Cyclization, in Chloroform, of Epoxycembranoids Derived from the Geometrical Isomers of (14*S*)-14-Hydroxy-1,3,7,11-cembratetraenes

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A new cembranoid sarcophytol T (**5a**) was isolated from the soft coral *Sarcophyton glaucum*, and the structure was shown to be (14*S*)-14-hydroxy-1(*E*),3(*Z*),7(*E*),11(*E*)-cembratetraene, a geometrical isomer of the potent antitumor promoter sarcophytol A (**1**). Compound **5a** and its geometrical isomers, sarcophytol N (**6**, 1*Z*,3*Z*) and sarcophytol F (**7**, 1*E*,3*E*), were found to be converted by autoxidation to bicyclo[9.3.0]tetradecene derivatives when kept in $CHCl_3$ solution at room temperature, in the same way as **1** (1*Z*,3*E*). The stereochemistry of each product (**4** from **1** and **5a**, **12** from **6**, and **16** from **7**) was derived by NOE analyses and by conversion of **12** and **16** to the enantiomeric ketones **17** and **18**, respectively. 4-Hydroxy-1,14-epoxy 2-ene derivatives were shown to be the immediate precursors in the transannular cyclization, while cembrene C (**23**), the parent hydrocarbon of **1**, also reacted in $CHCl_3$, giving the bicyclic derivatives **25**.

Introduction

Sarcophytol A (**1**) (Chart I), a simple monohydroxycembratetraene isolated from the soft coral *Sarcophyton glaucum*,[1,2] has recently been shown to be active as a potent antitumor promoter in a two-stage mouse skin carcinogenesis model as well as having an inhibitory effect on the hyperplasia of mouse skin; thus, the possibility exists of the compound inhibiting chemical carcinogenesis.[3] Another interesting feature of **1** and its monooxy derivatives was its degradation process. When left in $CHCl_3$ at room temperature, compound **1** gave several autoxidation products, of which the bicyclic derivative **4** was the major component (42% from **1**).[4a] The reaction was triggered by autoxidation[5] of the reactive 1,3-diene giving the 3,4-epoxide **2**. This epoxide and its isomer 1,14-epoxide **3** were obtained by exposing **1** directly to the air. On further storage in $CHCl_3$, the epoxide **2** was found to be converted to the 1,14-epoxide **3** and eventually to the bicyclic product **4**.[4a] Possibly, the residual hydrochloric acid in $CHCl_3$ assisted the opening of the 3,4- and 1,14-epoxy rings. Indeed **1** was stable and did not afford any of these epoxides and cyclized products when it was dissolved in $CHCl_3$ and stirred with $NaHCO_3$ solution for 10 days.[4b] Although the transannular cyclization of 10- and 11-membered rings has been well documented,[6] particularly in the sesquiterpene field, examples of the reaction in the larger rings, such as the 14-membered cembranoids, were scarce due to difficulty in obtaining sufficient amounts of the starting material. Only formic and perchloric acid catalyzed cyclization of the natural product cembrene (or thunbergene, 2(*E*),4(*Z*),7(*E*),11(*E*)-cembratetraene)[7] and its derivative isocembrol[8] have been reported by Raldugin et al. and Dauben et al., but the yields were quite modest (less than 10%), and the reaction was not proved to be of synthetic value. However, the spontaneous cyclization of **1** in $CHCl_3$ occurred at room temperature, and the yield was much better.[4a] This suggested that transannular cyclization of epoxycembrenes in fact has potential synthetic utility.

During the reinvestigation of the lipids of *S. glaucum*, we obtained a small amount of a new cembranoid sarcophytol T (**5a**), which is the 1*E*,3*Z*-isomer of sarcophytol A (1*Z*,3*E*) and accordingly is the 13-deoxy derivative of a cembranoid of *S. glaucum* sarcophytol K.[9] Two other geometrical isomers, sarcophytol N (**6**, 1*Z*,3*Z*)[10] and sarcophytol F (**7**, 1*E*,3*E*),[9] have been obtained previously. Thus, with all three geometrical isomers of **1** at hand, we studied their reactivity and process in the transannular cyclization. Unfortunately, several attempts at the selective oxidation at the C-3 double bond by ordinary reagents, *m*-chloroperbenzoic acid, for instance, were unsuccessful and gave a mixture of 7,8- and 11,12-epoxides. Owing to the limited amounts available, the starting materials were directly left to react in $CHCl_3$, as in **1**.

Results and Discussion

Structure and Transannular Cyclization of Sarcophytol T (5a). Sarcophytol T showed common UV (251 nm, ϵ 23 000) and mass spectra (MS, M^+, m/z 288) with the other three isomers[1,8,9] and afforded a monoacetate **5b** on acetylation. The ^1H and ^{13}C NMR spectra (Experi-

(1) Kobayashi, M.; Nakagawa, T.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2382.
(2) Kobayashi, M.; Kondo, K.; Osabe, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1988**, *36*, 2331.
(3) Fujiki, H.; Suganuma, M.; Suguri, H.; Yoshizawa, S.; Takagi, K.; Kobayashi, M. *J. Cancer Res. Clin. Oncol.* **1989**, *115*, 25.
(4) (a) Kobayashi, M.; Osabe, K. *Chem. Pharm. Bull.* **1989**, *37*, 1192. (b) Kobayashi, M. Unpublished.
(5) Van Sickle, D. E.; Mayo, F. R.; Arluck, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 4824. Van Sickle, D. E.; Mayo, F. R.; Arluck, R. M. *J. Am. Chem. Soc.* **1965**, *87*, 4832. Mayo, F. R. *J. Am. Chem. Soc.* **1958**, *80*, 2497 and references cited therein.
(6) For summaries and examples of the transannular cyclization of 10- and 11-membered rings, see: Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651. Hikino, H.; Konno, C.; Nagashima, T.; Kohama, T.; Takemoto, T. *Chem. Pharm. Bull.* **1977**, *25*, 6. Niwa, M.; Iguchi, M.; Yamada, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3137. Niwa, M.; Iguch, M.; Yamada, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148. De Pascual, T. J.; Barrero, A. F. *An. Quim.* **1978**, *74*, 519. Namikawa, M.; Murae, T.; Takahashi, T. *Chem. Lett.* **1978**, *391*. Nishimura, H.; Hasegawa, H.; Seo, A.; Nakano, H.; Mizutani, J. *Agric. Biol. Chem.* **1979**, *43*, 2397. Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1979**, 4291. Tsankova, E.; Ognyakov, I.; Norin, T. *Tetrahedron* **1980**, *36*, 669. Tsankova, E.; Ognyakov, I.; Orakhovats, A. *Chem. Ind. (London)* **1980**, *87*. Kodama, M.; Matsuki, Y.; Ito, S. *Tetrahedron Lett.* **1981**, *22*, 4271. Toma, K.; Murae, T.; Takahashi, T. *Chem. Lett.* **1982**, 551. Yamamura, S.; Niwa, M.; Ito, M.; Saito, Y. *Chem. Lett.* **1982**, 1681. Baruah, R. N.; Baruah, N. C.; Sharma, R. P. *Indian J. Chem.* **1983**, *22B*, 597. Tsankova, E.; Cerrini, S.; Lamba, D. *Tetrahedron* **1983**, *39*, 3397. Shirahama, H.; Arora, G. S.; Osawa, E.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 2869. Susuki, Y.; Yoshihara, Y.; Yang, C.; Zheng, C.; Shibuya, H.; Yamamoto, Y.; Tanaka, N.; Kitagawa, I. *Chem. Pharm. Bull.* **1986**, *34*, 434.
(7) Raldugin, V. A.; Shewstov, S. A.; Pentagova, V. A. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1985**, 89.
(8) Dauben, W. G.; Hubbell, J. P.; Oberhansli, P.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 669.
(9) Kobayashi, M.; Iesaka, T.; Nakano, E. *Chem. Pharm. Bull.* **1989**, *37*, 2053.
(10) Kobayashi, M.; Osabe, K. *Chem. Pharm. Bull.* **1989**, *37*, 631.

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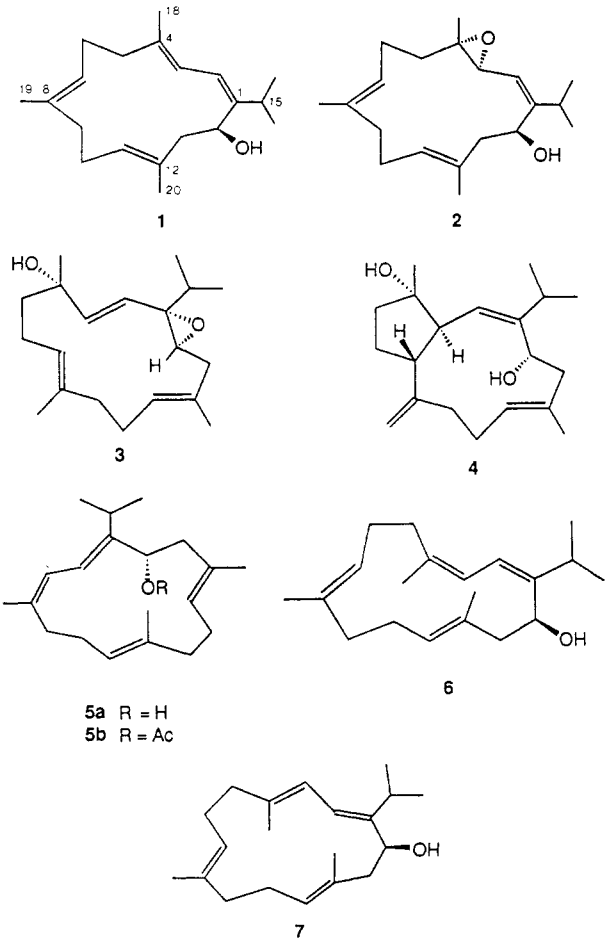
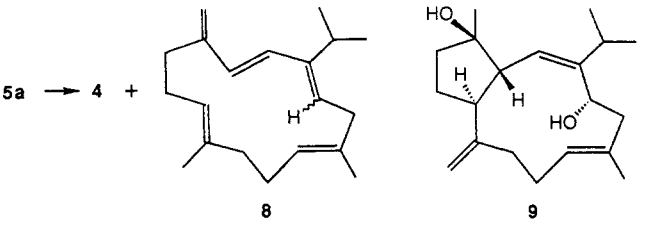
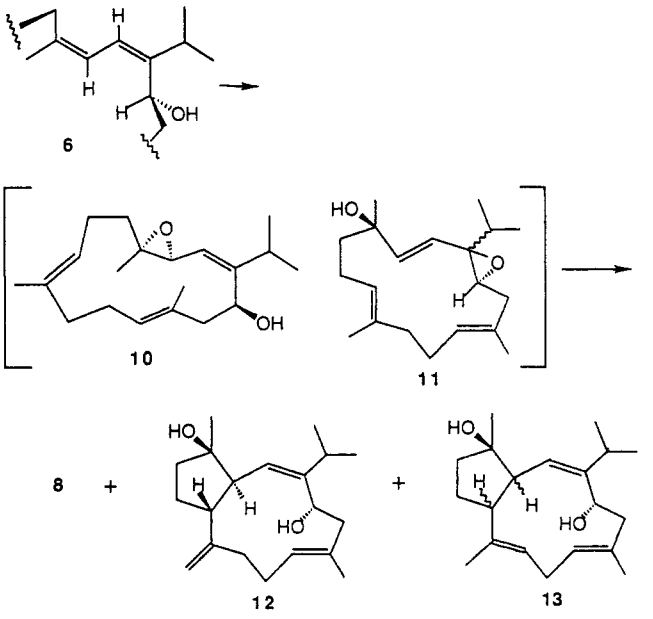
Chart I



Scheme I



Scheme II

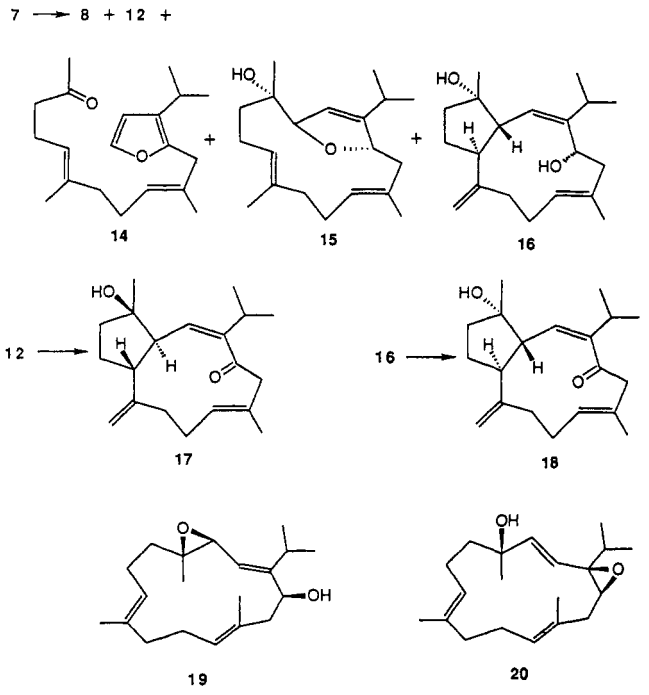


mental Section) of **5a** exhibited the signals of an isopropyl group, a tetrasubstituted conjugated diene, a hydroxymethine proton, three olefinic methyl groups, and two olefinic protons. The H-15 was deshielded by the 1,3-diene, and the ^{1}H NMR signal was shifted by ca. 0.4 ppm to lower field (δ 2.90) than that of the 1*Z*-isomers. The H-14 signal was unaffected by the diene and appeared at normal position (δ 4.37). These are the results of the 1*E* geometry of the diene,[9,10] as found in 1(*E*),3(*E*)-diene **7** (H-14, δ 4.31; H-15, δ 2.98), in contrast with those of 1*Z* isomers **1** (H-14, δ 4.98; H-15, δ 2.55) and **6** (H-14, δ 5.06; H-15, δ 2.52). The 1*E*,3*Z* geometry was also indicated by the presence of NOEs between H-3 (br d, J = 11.5 Hz) and H-15,18 (H-18, δ 1.83; ^{13}C NMR, C-18, δ 22.1 or 22.6 or 23.9). A weak NOE was observed between H-2 and H-14, and between H-2 and one of the H-13 (δ 2.45, dd, J = 14.5, 10.5 Hz) protons which is anti to H-14. This NOE revealed the existence of conformational movements about the 1,14 bond. On storage in $CHCl_3$ at room temperature for 3 days, compound **5a** was decomposed and afforded the pentaene **8** (15%),[9,10] a common product obtained from **1**, **6**, and **7**, and a bicyclic product **4** (10%), which was identical with that derived from 1[4a] (Scheme I). Hence, the absolute configuration at C-14 of **5a** is *S*, the same as in the other three isomers, and this was confirmed by the micro Horeau determination[11] using GC and HPLC. Compound **4** was the predominant bicyclic product, and its diastereomer **9**, which was expected from the results of the same treatment of **6** and **7** (vide infra), was not detected. Thus, sarcophytol T (**5a**) behaved in the same way as **1**, even though it is isomeric at C-1 and C-3.

Transannular Cyclization of Sarcophytol N (6) and F (7) and Cembrene C (23). Sarcophytol N (**6**) takes a common rigid spatial arrangement as in 1,[10] regarding C-1–C-4 and C-14–C-17, and the H-14 is markedly deshielded by the 1,3-diene. The large NOE found between H-2 and H-14 (17%) indicates the proximity of these two protons and limits the direction of autoxidation from the outward face of the diene, with respect to the cembrane ring (Scheme II). Compound **6** was more stable to autoxidation, as compared with **1**, but after prolonged storage in $CHCl_3$ (1 month), it gave bicyclic products **12** (17%) and **13** (5%), together with the pentaene **8**. The reaction should have occurred through either the 3(*S*),4(*R*)-epoxide intermediate **10** or its isomeric 1,14-epoxide **11**, as in the case of **1**,[4a] but these compounds were not detected in the product mixture. The ^{13}C and ^{1}H NMR of the major product **12** showed the formation of a methyl group, on a fully substituted carbon atom also carrying an oxygen atom, and an *exo*-methylene group. The H-2 signal appeared as a doublet (δ 5.14, J = 10.0 Hz) showing the coupling with H-3 (δ 2.14, t, J = 10.5 Hz), which was further coupled with H-7 (δ 2.80, dt, J = 10.5, 8.5 Hz). The NOE was observed between H-2 and H-7 and between H-2 and H-16 or H-17, but not between H-2 and H-3,18. A weak NOE was observed between H-3 and H-18. These results show that **12** bears a trans-fused bicyclic system as in **4** but is isomeric at C-4. The minor product **13** was an endo-olefin isomer and showed ^{1}H NMR signals of two olefinic methyl groups and a signal of one of the H-10 protons which is doubly allylic (δ 2.85). A NOE was observed between H-2 and H-16 or H-17, but not between H-2 and H-7 or H-2 and H-18, so that the stereochemistry at C-3 and C-7 is not clear.

(11) Brooks, C. J. W.; Gilbert, J. D. *J. Chem. Soc., Chem. Commun.* 1973, 194.

Scheme III



Sarcophytol F (**7**) was found to be markedly reactive when kept in $CHCl_3$, and within 3 days, most of the starting material was consumed. Column chromatography of the mixture gave the penaene **8** (14%), the furan **14** (5%), and the dihydrofuran **15** (9%) derivatives, which were previously obtained from **1**,[2,4a] and the bicyclic products **16** (18%) and **12** (1%) (Scheme III). It was shown that the geometry of **16** at C-1 is *Z* and the cyclopentane ring is trans fused, since NOEs were observed between H-2 and H-7, and between H-2 and H-16 or H-17, but not between H-2 and H-3,18. A weak NOE was observed between H-3 and H-18. The observed NOEs and the formation of **15** from **7** indicate that the initial intermediate is the 3(*S*),4(*S*)-epoxide **19** and the absolute configuration of **16** at C-4 is the same as in **4**; accordingly, the configurations at C-3 and C-7 are opposite. Thus, compound **16** bears the opposite absolute configurations at C-3,4,7 as compared with **12** which was derived from sarcophytol N (**6**). This was confirmed by the pyridinium chlorochromate (PCC) oxidation of **12** and **16**, which afforded the enantiomeric ketones **17** ($[\alpha]_D$ −430°) and **18** ($[\alpha]_D$ +410°), respectively, with identical UV and ^1H NMR properties. In another experiment, small amounts of two epoxides were isolated, and the ^1H NMR analyses showed them to be the expected 3,4-epoxide (**19**, H-2, δ 5.76, d, J = 10.5 Hz; H-3, δ 3.70, d, J = 10.5 Hz) and 1,14-epoxide (**20**, H-2,3, δ 5.58, 6.37, each d, J = 16.0 Hz). The spectral data of **20** were found to be identical with those of sarcophytol C, which we reported in an earlier work.[12] Sarcophytol C was thus shown to be an artifact derived from the labile sarcophytol F. The epoxide **20** was the C-1 diastereomer of the 1,14(*E*)-epoxide **3** derived from **1**,[4a] and the NOE, which was observed between H-14 and H-2 or H-3 in **3**, was absent. The 3,4-epoxide **19** was found to be gradually converted to the 1,14-epoxide **20**, when kept further in $CHCl_3$. On brief treatment with 0.05% H_2SO_4 in dioxane–H_2O, both **19** and **20** were converted to a mixture containing **15** and **16**.[13]

In contrast to the case of **1** and **6**, the lack of any NOE data concerning the direction of the cembrane ring with respect to the C-14 chiral center in **5a** and **7** makes their epoxidation step unpredictable. Theoretically, it is possible for both **5a** and **7** to afford any of the four bicyclic isomers **4**, **9**, **12**, and **16** according to the preference of either of two possible 3,4-epoxides (Scheme IV). The 1*Z* geometry of the products, **4** from **5a** and **16** from **7**, indicates that the direct attack of 3,4-epoxides, by the C-7 double bond, does not occur and their immediate precursors are 4-hydroxy-1,14-epoxy 2-enes. Four conformers (e.g., **20a–d** from **19**) could be derived from each 4-hydroxy-1,14-epoxy 2-ene having a crossed spatial arrangement of 2,3- and 7,8-double bonds, according to the upward or downward direction of C-19 with respect to the average plane of the ring, and according to the boat- or chair-like conformation regarding C-3–C-8. From the structure of the bicyclic product, it was evident that the 3,4-epoxide **19**, derived from **7**, was converted to the 1,14(*Z*)-epoxide **20** and underwent cyclization through the conformer **20a** or **20b**. Small amounts of 3(*R*),4(*R*)-epoxide **21** must have formed, which accounts for the formation of **12** as a minor product. The preferred conformer of its immediate precursor is **11a** or **11b**, but it is not clear whether it is the same as that derived from **6**, or its C-1 diastereomer. Also, formation of **4** from **5a** indicates that the initial autoxidation product is the 3-(*R*),4(*S*)-epoxide **22**. It was converted to **4**, via the 4-hydroxy-1,14(*E*)-epoxy 2(*E*)-ene (conformer **3a** or **3b**), since its 1,14*Z* isomer **20** affords the diastereomer **16**. It is noteworthy that the mode of the antipodal fusion of the cyclopentane ring in **4** and **16** was controlled by the chirality of the 1,14-epoxy rings.

The behavior of the four geometrical isomers **1**, **5a**, **6**, and **7** in the spontaneous autoxidation–cyclization in $CHCl_3$ seemed to indicate that the hydroxyl group at C-14 is a requisite functional group for the reaction. The acetate of 3,4-epoxide **2** was stable and was unchanged after 1 month in $CHCl_3$.[4a] However, the known compound cembrene C (**23**),[14] a 14-deoxy derivative of **1**, was found to be reactive, and on storage in $CHCl_3$ at room temperature for 10 days, it was converted to the bicyclic derivative **25** in higher yield (46%) than those from **1**, **5a**, **6**, and **7** (Scheme V). The ^1H and ^{13}C NMR data (Experimental Section) were consistent with the structure and showed chemical shifts that are analogous to those of **4**,[4a] except for the absence of the signal due to the H-14 hydroxymethine proton. The NOEs were observed between H-2 and H-7,18 and between H-2 and H-16 or H-17, but not between H-2 and H-3, and showed that the bicyclic ring is trans fused as in **4**, **12**, and **16**. Thus the 14-hydroxyl group is not neccessary for transannular cyclization of these systems. The reaction takes place via the 3,4-epoxy intermediate **24**, through the interaction of the epoxide ring and the C-7 double bond. The C-14 hydroxyl groups in compounds **1**, **5a**, **6**, and **7** merely participate in the 3,4-epoxy ring opening, giving 1,14-epoxy 2-enes which are also reactive, and causing the isomerization of the C-1 double bond in the case of **5a** and **7**.

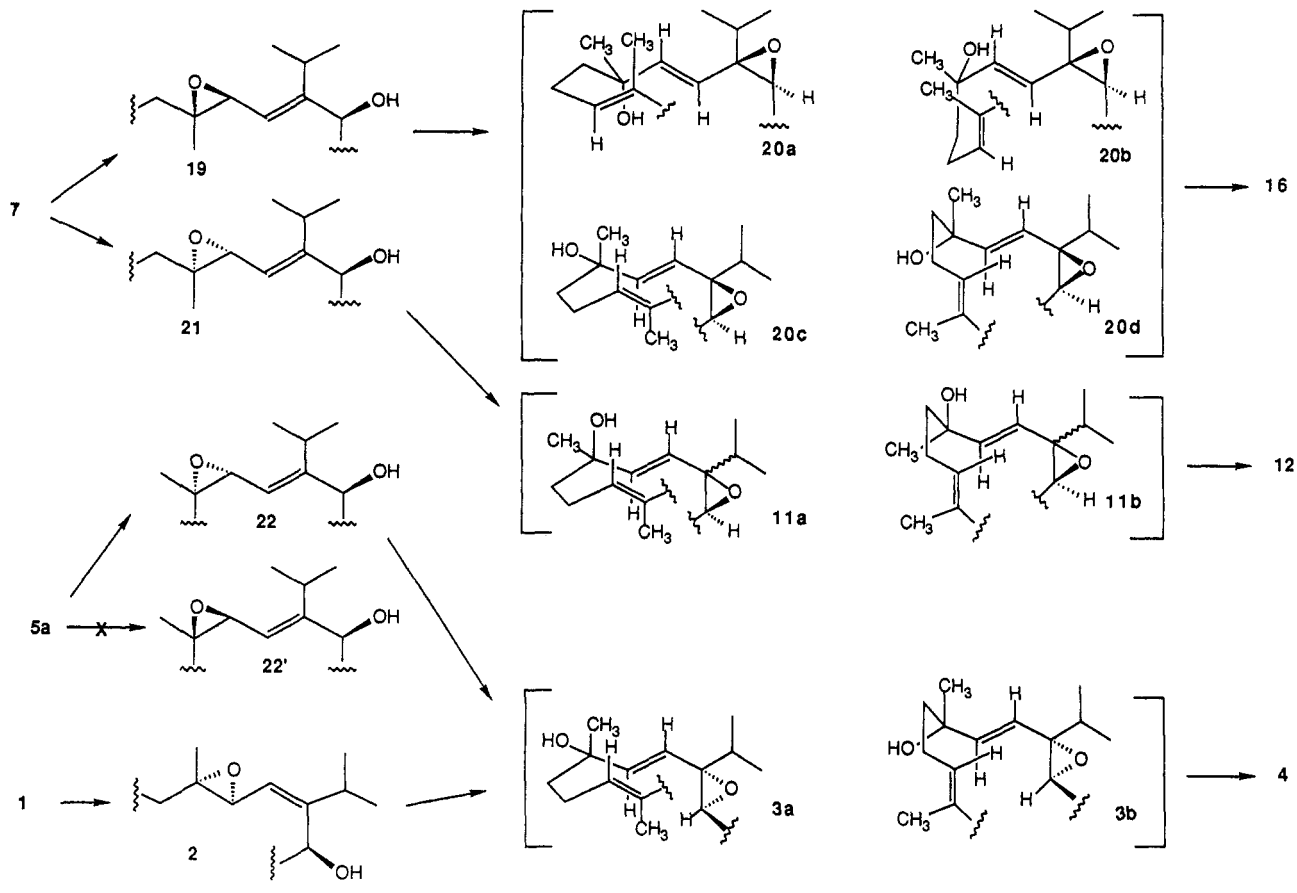
In summary, the 3,4-epoxy-3,7,11-cembratrienes were shown to be quite reactive in transannular cyclization as in 10- and 11-membered sesquiterpenes.[6] Although there are many studies of the transannular cyclization of sesquiterpene epoxides, examples using α,β-unsaturated epoxides are not known. The reactivity of the strained epoxide rings should be intensified by the conjugated double bond. Present results suggest the potential of such in-

(12) Nakagawa, T.; Kobayashi, M.; Hayashi, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1981**, *29*, 82.

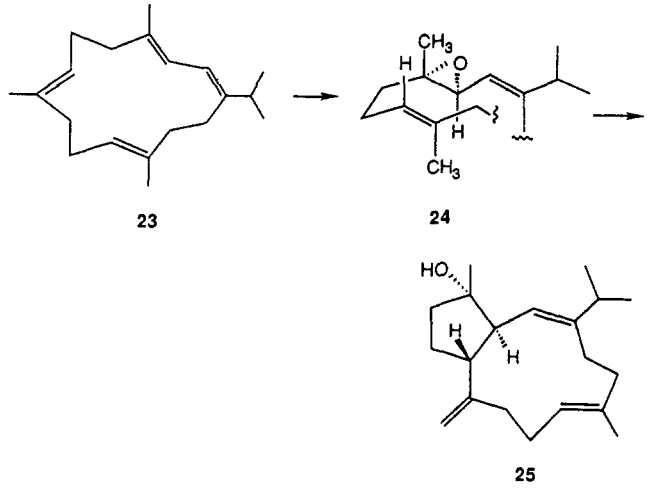
(13) This condition is not appropriate, and the products were complex.

(14) Vanderah, D. J.; Rutledge, N.; Schmitz, F. J.; Ciereszko, L. S. *J. Org. Chem.* **1978**, *43*, 1614.

Scheme IV



Scheme V



termediates for the synthesis of bicyclic diterpenes. The yield would be higher if the 3,4-epoxy derivatives were used directly as the starting materials. Favorable conformers for the transannular cyclization can be derived with the aid of molecular mechanics. The composition of the products is simple as compared with those of the smaller rings.[6] The reaction leads preferentially to the bicyclic product having an *exo*-methylene group at C-8, and other products such as isomeric olefins or 8-hydroxy derivatives are not detected. Compounds **4**, **12**, and **16** are stable enough to permit the existence of two double bonds in the nine-membered ring, and the carbonium ion intermediate is deprotonated to give exo olefins having less strain than the corresponding endo-olefin isomers.

Experimental Section

General. UV spectra were determined on a Shimadzu UV-220 spectrometer. Optical rotations were determined in $CHCl_3$ on a JASCO DIP-370 digital polarimeter. NMR spectra were determined in $CDCl_3$ on a JEOL JMS GX-270 spectrometer at 270 MHz (^1H) and on a JEOL JNM FX-90Q spectrometer at 22.5 MHz (^{13}C) with tetramethylsilane as an internal standard. ^{13}C NMR signals were assigned by using INEPT and by comparison of chemical shift data with those in the literature. MS were determined on a JEOL JMS D300 mass spectrometer. Chromatography was done by flash chromatography[15] using silica gel (Wako gel C-300, 200–300 mesh, Wako Pure Chemical Industries).

Sarcophytol A (1), Sarcophytol N (6), Sarcophytol F (7), Sarcophytol T (5a), and Cembrene C (23). The three geometrical isomers **1**, **6**, and **7** were purified in the same procedure as reported,[10] using a crude sarcophytol A fraction which was obtained previously and stored at −30 °C. Sarcophytol T (**5a**) was eluted immediately before **7**, by chromatography (ethyl acetate–hexane, 8:92), and was obtained as a mixture containing **6**, but further purification was unsuccessful. The mixture (400 mg) was acetylated in a usual way (Ac_2O–pyridine) and subjected to chromatography over a column of 8% $AgNO_3$–SiO_2 with ethyl acetate–hexane (4:96, then 6:94), giving the acetate of **6** (350 mg) and **5b** (65 mg). Hydrolysis of **5b** with 2.5% KOH in MeOH at room temperature for 1 h, followed by the usual workup, gave **5a** (58.2 mg). Cembrene C (**23**) was isolated by using the least polar fraction of the cembranoid mixture from *S. glaucum*,[10] by column chromatography eluting with hexane. It was identified with an authentic specimen previously obtained, by ^1H and ^{13}C NMR, UV, and mass spectra.

Sarcophytol T (5a): oil; $[\alpha]^{19}_D$ −12° (*c* 0.84); ^1H NMR δ 1.10, 1.19 (each 3 H, d, J = 7.3 Hz), 1.58, 1.60 (each 3 H, s), 1.83 (3 H, s, H-18), 2.35 (1 H, br dd, J = 14.5, 3.0 Hz, H-13), 2.45 (1 H, dd, J = 14.5, 10.5 Hz, H-13), 2.90 (1 H, sept, J = 7.3 Hz, H-15),

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

4.37 (1 H, m, H-14), 4.97 (1 H, br t, J = 8.0 Hz), 5.00 (1 H, br t, J = 7.5 Hz), 6.07 (1 H, d, J = 11.5 Hz, H-2), 6.25 (1 H, br d, J = 11.5 Hz, H-3); ^{13}C NMR δ C-1 (143.3), C-2,3 (122.4, 122.6), C-4 (138.0), C-5 (31.7), C-6,10 (24.6, 24.9), C-7,11 (124.3, 126.8), C-8 (133.1), C-9 (39.4), C-12 (130.5), C-13 (44.9), C-14 (72.4), C-15 (28.1), C-16,17,18 (22.1, 22.6, 23.9), C-19,20 (15.6, 16.9); UV (95% EtOH) 251 nm (ϵ 23 000); MS, m/z 288 (M^+), 273, 255, 245, 203, 177, 159, 152, 137, 109; high-resolution MS [found (calcd)] (m/z) $C_{20}H_{32}O$ (M^+), 288.2443 (288.2453).

Micro Horeau Determination of 5a. The absolute configuration at C-14 of **5a** was determined as S by the reported procedure,[11] using GC and HPLC. The increment of one of the two chiral amide peaks, relative to the peaks obtained from cyclohexanol, was the same as that of **1** (S) and opposite that of (−)-menthol (R).

Sarcophytol T Acetate (5b): oil; $[\alpha]^{19}_D$ −48° (c 1.12); ^{1}H NMR δ 1.080, 1.085 (each 3 H, d, J = 7.0 Hz), 1.58, 1.63 (each 3 H, br s), 1.83 (3 H, d, J = 0.5 Hz, H-18), 2.02 (OAc), 2.47 (1 H, dd, J = 14.5, 11.0 Hz, H-13), 2.90 (1 H, sept, J = 7.0 Hz), 4.95 (1 H, br t, J = 8.0 Hz), 5.01 (1 H, br t, J = 7.0 Hz), 5.52 (1 H, dd, J = 11.0, 3.5 Hz, H-14), 6.14 (1 H, d, J = 11.5 Hz, H-2), 6.25 (1 H, br d, J = 11.5 Hz, H-3); MS, m/z 330 (M^+), 288, 270, 255, 245, 227, 220, 202, 187, 177, 159, 152, 137, 109.

$CHCl_3$ Treatment of 5a. A solution of **5a** (50 mg) in $CHCl_3$ (1.5 mL) was kept at room temperature for 3 days. The evaporation residue was separated by column chromatography, first with hexane, giving 6.9 mg of **8**, and then with MeOH–$CHCl_3$ (3:200), giving 5.2 mg of **4**, $[\alpha]^{20}_D$ −60° (c 0.24, $CDCl_3$), which was identical with an authentic specimen, by comparisons of their ^{1}H NMR and mass spectra and TLC behavior.

$CHCl_3$ Treatment of Sarcophytol N (6). A solution of **6** (52.2 mg) in $CHCl_3$ (4 mL) was kept at room temperature for 27 days. The evaporation residue was separated by column chromatography with Et_2O–$CHCl_3$ (2:8 and 3:7), to give **13** (2.6 mg, 5%) and then **12** (9.3 mg, 17%).

12: oil; $[\alpha]^{21}_D$ +25° (c 1.40); ^{1}H NMR δ 1.10, 1.14 (each 3 H, d, J = 7.0 Hz), 1.25 (3 H, s, H-18), 1.64 (3 H, br s), 2.54 (1 H, sept, J = 7.0 Hz), 2.80 (1 H, dt, J = 10.5, 8.5 Hz, H-7), 4.47 (1 H, dd, J = 10.5, 3.5 Hz, H-14), 4.81 (1 H, t, J = 1.5 Hz, H-19), 4.92 (1 H, q, J = 1.5 Hz, H-19), 5.13 (1 H, br t, J = 7.5 Hz, H-11), 5.14 (1 H, d, J = 10.0 Hz, H-2); MS, m/z 304 (M^+), 289, 286, 271, 261, 243, 235, 217, 203, 193; high-resolution MS found (calcd)] (m/z) $C_{20}H_{32}O_2$ (M^+), 304.2400 (304.2402).

13: oil; $[\alpha]^{18}_D$ −127° (c 0.52); ^{1}H NMR δ 1.09, 1.11 (each 3 H, d, J = 7.0 Hz), 1.19 (3 H, s, H-18), 1.72, 1.77 (each 3 H, s), 2.40 (1 H, t, J = 11.5 Hz, H-3), 2.52 (1 H, sept, J = 7.0 Hz), 2.85 (1 H, m, H-10), 2.94 (1 H, dt, J = 11.5, 8.5 Hz, H-7), 4.60 (1 H, dd, J = 10.5, 4.0 Hz, H-14), 4.72 (1 H, br d, J = 10.5 Hz), 5.23 (1 H, d, J = 11.5 Hz, H-2), 5.52 (1 H, br t, J = 7.5 Hz); MS, m/z 304 (M^+), 286, 271, 243, 217, 203, 175; high-resolution MS [found (calcd)] (m/z) $C_{20}H_{32}O_2$ (M^+), 304.2409 (304.2402).

$CHCl_3$ Treatment of Sarcophytol F (7). A solution of **7** (640 mg) in $CHCl_3$ (40 mL) was kept at room temperature for 7 days. The product was a complex mixture containing **8**, **14**, **15**, and **16**, but **19** and **20** were lost. The evaporation residue was submitted to column chromatography. Elution with hexane gave a mixture mainly composed of **8** (84.3 mg). Elution with ethyl acetate–hexane (5:95 and 7:93) gave **14** (33.1 mg, 5%) and **15** (63.1 mg, 9%). Compounds **14** and **15** were identical with authentic specimens prepared previously, by comparison of their ^{1}H NMR spectra and their behavior in several TLC systems. Elution with ethyl acetate–hexane (15:85) gave **16** (126 mg, 18%) and **12** (7.1 mg). Compound **12** was identical with that obtained from **6**, by comparisons of their ^{1}H NMR and mass spectra. In another run, a $CHCl_3$ solution of **7** (15.4 mg) was kept similarly until **19** and **20** became major components of the mixture (ca. 3 days). Column chromatography of the evaporation residue with ethyl acetate–hexane (15:85) gave first 4.6 mg of **20** and then 1.9 mg of **19**.

16: oil; $[\alpha]^{21}_D$ +100° (c 0.72); ^{1}H NMR δ 1.06, 1.17 (each 3 H, d, J = 7.0 Hz), 1.26 (3 H, s, H-18), 1.98 (1 H, partly overlapped sept, J = 7.0 Hz), 1.71 (3 H, br s), 2.43 (1 H, dd, J = 13.5, 5.5 Hz, H-13), 2.68 (1 H, ddd, J = 10.0, 9.5, 8.5 Hz, H-7), 2.85 (1 H, t, J = 10.0, H-3), 4.52 (1 H, dd, J = 5.5, 2.5 Hz, H-14), 4.85 (1 H, t, J = 1.5 Hz, H-19), 4.93 (1 H, br s, H-19), 5.05 (1 H, d, J = 10.0 Hz, H-2), 5.23 (1 H, br t, J = 8.5 Hz, H-11); ^{13}C NMR δ C-1,8 (150.5, 150.7), C-2,11 (124.7, 127.6), C-3,7 (49.9, 57.1), C-4 (80.7), C-5,6,10 (27.5, 28.3, 29.4), C-9,13 (40.2, 42.6), C-12 (131.3), C-14 (75.9), C-15 (33.7), C-16,17 (22.3, 24.8), C-18 (28.0), C-19 (111.3), C-20 (20.0); MS, m/z 304 (M^+), 286, 271, 261, 258, 243, 203, 193; high-resolution MS [found (calcd)] (m/z) $C_{20}H_{32}O_2$ (M^+), 304.2428 (304.2402).

19: oil; $[\alpha]^{29}_D$ +105° (c 0.38); ^{1}H NMR (pyridine-d_5) δ 0.97, 1.23 (each 3 H, d, J = 7.0 Hz), 1.26 (3 H, s, H-18), 1.57, 1.67 (each 3 H, s), 3.17 (1 H, sept, J = 7.0 Hz), 3.70 (1 H, d, J = 10.5 Hz, H-3), 4.57 (1 H, br dd, J = 10.0, 6.0 Hz, H-14), 5.76 (1 H, d, J = 10.5 Hz, H-2); MS, m/z 304 (M^+), 286, 271, 261, 243, 178, 161, 151, 135, 122.

20: oil; $[\alpha]^{24}_D$ +113° (c 0.92); ^{1}H NMR δ 1.00, 1.05 (each 3 H, d, J = 7.0 Hz), 1.16 (3 H, s, H-18), 1.59, 1.61 (each 3 H, s), 3.05 (1 H, br dd, J = 10.0, 3.5 Hz, H-14), 4.98–5.13 (2 H, m), 5.58, 6.37 (each 1 H, d, J = 16.0 Hz, H-2,3); ^{13}C NMR δ C-1 (67.3), C-2 (117.5), C-3 (142.0), C-4 (73.4), C-5,9 (38.2, 40.2), C-6,10 (24.3, 25.2), C-7,11 (125.2, 127.1), C-8 (133.5), C-12 (131.8), C-13 (42.9), C-14 (62.1), C-15 (35.6), C-16,17 (18.4, 18.5), C-18 (26.8), C-19,20 (15.1, 17.7); MS, m/z 304 (M^+), 289, 286, 271, 243, 215, 203, 139, 121, 110.

H_2SO_4 Treatment of 19. A solution of **19** (1.9 mg) in 0.05% H_2SO_4 in dioxane–H_2O (4:1, 0.4 mL) was kept at room temperature for 30 min. The mixture was diluted with H_2O and extracted with Et_2O. After the usual workup, the solvent was evaporated. Column chromatography of the residue with ethyl acetate–hexane (1:9) gave **15** (0.31 mg) and **16** (0.40 mg). Compounds **15** and **16** were identical with authentic specimens, by comparison of their behavior in several TLC systems.

H_2SO_4 Treatment of 20. A solution of **20** (8.4 mg) was treated with H_2SO_4 in a similar way as had been done for **19**. Column chromatography of the product mixture with MeOH–$CHCl_3$ (5:95) gave a mixture (6.0 mg) of **15** and **16**. The identification was made by comparison with authentic specimens by several TLC systems.

PCC Oxidation of 12 and 16. (a) A solution of **16** (25.1 mg) in CH_2Cl_2 (1.5 mL) was stirred with PCC (45 mg) at room temperature for 30 min, and then the mixture was diluted with H_2O and extracted with Et_2O. The Et_2O solution was washed with H_2O and saturated NaCl solution, and then the solvent was evaporated. Column chromatography of the residue with $CHCl_3$ gave 19.4 mg of **18** as an oil: $[\alpha]^{22}_D$ +410° (c 0.96); ^{1}H NMR δ 1.02, 1.13 (each 3 H, d, J = 6.5 Hz), 1.29 (3 H, s, H-18), 1.67 (3 H, s), 1.81 (1 H, dd, J = 10.5, 10.0 Hz, H-3), 2.53 (1 H, d sept, J = 1.0, 7.0 Hz, H-15), 2.81, 3.21 (each 1 H, d, J = 11.5 Hz, H-13), 2.80 (1 H, dt, J = 10.5, 8.5 Hz, H-7), 4.84 (1 H, t, J = 1.5 Hz, H-19), 4.93 (1 H, q, J = 1.5 Hz, H-19), 5.15 (1 H, dd, J = 10.0, 1.0 Hz, H-2), 5.34 (1 H, br t, J = 8.0 Hz); MS, m/z 302 (M^+), 285, 259, 138; high-resolution MS [found (calcd)] (m/z) $C_{20}H_{30}O_2$ (M^+), 302.2225 (302.2246); UV (95% EtOH) 300 nm (ϵ 400), 232 nm (soulder, ϵ 4200). (b) Compound **12** (16.4 mg) was treated with PCC (28 mg) in the same way as done for **16**. Column chromatography of the product mixture gave 6.8 mg of **17** as an oil: $[\alpha]^{22}_D$ −430° (c 1.36). Its ^{1}H NMR and mass spectra were identical with those of **18**.

$CHCl_3$ Treatment of Cembrene C (23). A solution of **23** (100 mg) in $CHCl_3$ (4 mL) was kept at room temperature for 10 days. The evaporation residue was separated by column chromatography with $CHCl_3$ to give 58.5 mg (46%) of **25** as an oil: ^{1}H NMR δ 1.04, 1.05 (each 3 H, d, J = 7.0 Hz), 1.08 (3 H, s, H-18), 1.63 (3 H, s, H-20), 4.79, 4.87 (each 1 H, br s, H-19), 5.08 (1 H, br t, J = 7.5 Hz, H-11), 4.88 (1 H, d, overlapped with a signal at δ 4.87); ^{1}H NMR (pyridine-d_5) δ 1.03, 1.11 (each 3 H, d, J = 7.0 Hz, 1.32 (3 H, s, H-18), 1.69 (3 H, s, H-20), 2.51 (1 H, dt, J = 10.5, 8.5 Hz, H-7), 2.70 (1 H, dd, J = 10.5, 8.5 Hz, H-3), 2.91 (1 H, m), 4.92, 5.05 (each 1 H, br s, H-19), 5.06 (1 H, d, J = 9.5 Hz, H-2), 5.20 (1 H, br t, J = 8.0 Hz, H-11); ^{13}C NMR (C_6D_6) δ C-1,8 (146.8, 150.1), C-2,11 (124.3, 124.7), C-3,7 (51.2, 56.2), C-4 (81.2), C-5,6,10,14 (26.6, 27.7, 27.9, 29.1), C-9 (40.9), C-12 (134.1), C-13 (37.1), C-15 (33.6), C-16,17,18 (22.4, 24.2, 24.8), C-19 (111.2), C-20 (17.3); MS, m/z 288 (M^+), 273, 270, 255, 245, 227, 203, 187; high-resolution MS [found (calcd)] (m/z) $C_{20}H_{32}O$ (M^+), 288.2480 (288.2453).