Marine Terpenes and Terpenoids. X.[1] Acid-Catalyzed Transannular Cyclization of 11,12-Epoxycembranolide

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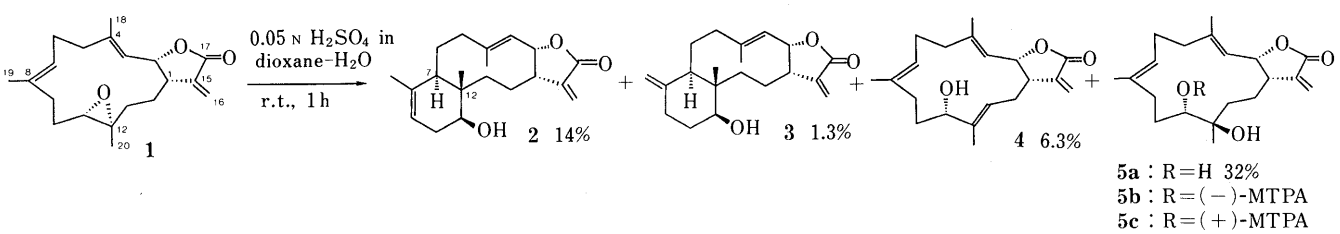
Acid-catalyzed transannular cyclization of 11,12-epoxycembranolide (1), isolated from the soft coral *Sinularia mayi*, was studied. The major product was the *trans*-fused bicyclo[8.4.0]tetradecene derivative 2, and the maximum yield was 89% with boron trifluoride in benzene at 0 °C. When treated with *p*-toluenesulfonic acid in benzene at 55 °C, 1 gave a bicyclo[9.3.0]tetradecene derivative 11 in 36% yield. Its immediate precursor was shown to be the allylic alcohol 4, which was converted to 11 on treatment with *p*-toluenesulfonic acid. The stereochemistries of the cyclization products indicated that the reaction takes place through a conformation in which the dispositions of 11,12- and 12,13-bonds are crossed, with respect to the 7,8- and 3,4-double bonds, respectively.

Keywords transannular cyclization; 11,12-epoxycembranolide; stereochemistry; bicyclo[8.4.0]tetradecene; bicyclo[9.3.0]-tetradecene; soft coral; *Sinularia mayi*; cembrane

Acid-catalyzed transannular cyclization of ten- and eleven-membered rings has been well documented, particularly in the sesquiterpene field.[2] In contrast, examples of its application to larger ring systems, such as the fourteen-membered cembranoids, are scarce due to the difficulty in obtaining sufficient amounts of the starting materials. Dauben *et al.* and Raldugin *et al.* reported the perchloric acid- and formic acid-catalyzed cyclization of the natural product cembrene (2*E*,4*Z*,7*E*,11*E*-cembratetraene),[3,4] and its derivative isocembrol. The yields were, however, quite modest (less than 10%), and the reaction was not proved to be of synthetic value. Earlier Manchand and Blount had shown that the cembranolide ovatolide, when refluxed in benzene with an equimolar amount of *p*-toluenesulfonic acid (TsOH), underwent cleavage of the lactone ring at C-2 and was converted to the 2,11-cyclo derivative in significant yield (59%).[5]

In a previous paper, we showed that the anti-tumor promoter sarcophytol A (14*S*-hydroxy-1,3,7,11-cembratetraene), the major cembranoid of the common soft coral *Sarcophyton glaucum*, underwent spontaneous transannular cyclization, through autoxidation at C-3, when kept in $CHCl_3$; it gave the bicyclo[9.3.0]tetradecene derivative in 42% overall yield.[6] This suggested that the transannular cyclization of cembranoids in fact has potential synthetic availability, if suitable epoxycembranoids were used directly as the starting materials. During the investigation of the chemical components of the soft coral *Sinularia mayi*, we obtained several cembranolide derivatives having an 11,12-epoxy group.[7,8] They are ideal starting materials for this type of cyclization reaction, considering that the biogenetically normal positions of unsaturation are C-3, C-7, and C-11 in the cembranoids derived from geranylgeraniol or geranyllinalol. The present paper describes the transannular reaction of 11,12-epoxycembranolide when treated with acids. It affords, at the same time, some information concerning the possible biosynthesis of as yet unknown cyclic diterpenes which might be derived from the cembranoid skeleton.

The simplest *S. mayi* cembranolide (**1**),[9,10] having an 11,12*E*-epoxy ring, was used as the starting material. Other major 11,12-epoxycembranoids of *S. mayi*, having a 13-acetoxy[7] or 13-oxo moiety,[7,11] were expected to give a more complex outcome. The absolute configuration of **1** at C-11 and C-12 had been left unsettled. It was shown to be 11*S*,12*S* from an analysis of one of the products derived from **1** (*vide infra*). Treatment of **1** with 0.5 N H_2SO_4 in dioxane–H_2O (4 : 1) at room temperature for 1 h gave four products, of which the minor products **2** (14%) and **3** (1.3%) were indeed found to be bicyclic compounds, and other two were an allylic alcohol **4** (6.3%), having a *trans* 12,13-double bond, and a glycol **5a** (32%). Attempted Horeau determination of the configuration at C-11, using these four compounds, was unsuccessful. No diagnostic optical rotation of the excess α-phenylbutyric acid,[12] and no reliable results from high-performance liquid chromatography (HPLC)[13] and gas chromatography (GC)[14] of the (+)-α-phenylethylamides were obtained. In contrast, proton nuclear magnetic resonance (^{1}H-NMR) analyses of the *R*-(+)- and *S*-(−)-α-methoxy-α-trifluoromethylphenylacetate (MTPA), which was proposed by Dale and Mosher in 1973,[15] and recently reevaluated by Kusumi *et al.*[16a] and Takano *et al.*,[16b] was effective. The ^{1}H-NMR spectra of the two enantiomeric esters of **5a** showed that the $\Delta\delta[\delta(-)\text{-MTPA}-\delta(+)\text{-MTPA}]$ of H-20, H-1, and H-19 were +0.074, +0.039 and −0.002 ppm, respectively. Hence, compound **1** has 11*S*,12*S* configuration, which is the same as those of the other two major cembranolides of *S. mayi*, having 13-acetoxy and 13-oxo moieties.[16a] This established the configuration at C-12 of



5a : R=H 32%
5b : R=(−)-MTPA
5c : R=(+)-MTPA

Chart 1

the products to be as shown in Chart 1, since the acid-catalyzed cleavage of epoxides is known to occur by an $SN2$ mechanism, with entire inversion of the configuration at the sites of cleavage. The ^{1}H-NMR and carbon-13 nuclear magnetic resonance (^{13}C-NMR) of the bicyclic compounds **2** and **3** indicated that their C-3 double bonds remained unchanged. They showed the formation of one quaternary methyl group (**2**, δ0.69; **3**, δ0.60) and one axial hydroxymethine proton (**2**, δ3.59, dd, J=9.9, 5.5 Hz; **3**, δ3.61, br dd, J=12.5, 4.4 Hz). Compound **2** possessed two olefinic methyl groups (δ1.69, 1.79) while **3** was the isomer having a terminal olefin (δ4.86, 4.91, each br s). The structure of **2** was confirmed by heteronuclear multiple bond correlation spectroscopy (HMBC) which enabled correlation of all of the carbons involved in the bicyclic system. The epoxy ring cleavage and the substitution are synchronous in the transannular cyclization,[2,17] and from the configurations at C-11 and C-12, compound **1** should lead to the bicyclic ring having the configuration at C-11 retained and that of C-12 inverted. Irradiation at H-20 of these compounds did not cause a nuclear Overhauser effect (NOE) at H-7, suggesting the ring-fusion of **2** and **3** to be *trans* (*vide infra*).

Reaction of **1** with TsOH in methanol was similarly unsatisfactory, giving **2** (1.5%) and its methanol adduct **6** (5.4%). The major products were the 11,12-glycol 12-monomethyl ether **7** (18.3%) and a ketone **8** (9.2%). ^{1}H-NMR of **8** showed the formation of a secondary methyl group (δ1.08, d, J=7.0 Hz). In this case the recombination of the 11*S*,12*S*-epoxide is also stereospecific,[18] and lead to the ketone **8** with 12*S* configuration. Further treatment of **8** under the same reaction conditions did not cause epimerization at C-12. The methyl ether derivative **6** afforded a clue to the stereochemistry at C-7 of the transannular cyclization products. NOEs were observed between H-19 and H-20, and between H-19 and the methoxy methyl group, but not between H-7 and H-19,20, and indicated the *trans*-fusion of the cyclohexane ring in **6**. Thus, the transannular cyclization of such a cembranoid system was shown to follow the normal course, which was established in epoxygermacrene derivatives.[17] Epoxide ring opening and carbon–carbon bond formation followed the Markonikoff rule, and the spatial arrangement of the 11,12-bond and C-7 double bond is not parallel but is crossed in the transition state of the reaction. The resultant carbonium ion intermediate is deprotonated giving **2** and **3**, or trapped by the solvent methanol, giving **6**. Such a conformation in the transition state may be analogous to that in the ground state of **1**. Serial ^{1}H-NMR experiments with **1** showed the presence of NOEs between H-2 and H-1,18, and between H-7 and H-11. Weak NOE was observed between H-3 and H-7. These observations indicate that **1** takes a major conformation in which its three methyl groups are directed to the same face, whereas H-3, H-7 and H-11 are opposite, with respect to the average plane of the fourteen-membered ring (Chart 2, A).

In contrast to the complexity and low yields of the products under these conditions, an improved result was obtained by the treatment of **1** with BF_3. When **1** was treated in benzene solution at 0 °C for 2 min, the bicyclic compound **2** was obtained in 89% yield. The by-product isolated was a 1,4-epoxycyclohexane derivative **9**. The mass spectrum (MS) and high-resolution MS revealed an unchanged molecular formula, and no hydroxyl bands were observed in the infrared (IR) spectrum. It showed the ^{1}H-NMR signals of two quaternary methyl groups at δ0.91 and 1.38, and NOEs were observed between H-20 and H-1,2,11,18. Characteristically deshielded bridgehead carbons were observed at δ86.6 (C-8) and 86.3 (C-11) in the ^{13}C-NMR spectrum. The same 1,2,3,3-tetrasubstituted 1,4-epoxycyclohexane moiety exists in a farnesylacetone derivative, isolated from the brown alga *Cystophora moniliformis*.[19] The corresponding ^{13}C-NMR chemical shifts are 86.6 (C-1) and 85.9 (C-4) ppm. Compound **9** is derived by the attack of the C-11 hydroxyl group on the cationic center at C-8 in the carbonium intermediate. Such a derivative was not seen in the transannular cyclizations of its germacrene counterparts reported in the past. The yield of **2** from **1** is the highest among the limited examples of the transannular cyclization of cembranoids so far known, and shows the potential of such an approach for the syntheses of bicyclic diterpenes.

The reaction of **1** with TsOH was much slower in benzene solution at room temperature. When kept at 55 °C for 30 min, it gave small amounts of **2** (26%) and its isomer **10** (7%, ^{1}H-NMR, H-19, δ1.69, 3H, s; ^{13}C-NMR, C-7,8, δ131.9, 132.7, s), and a novel bicyclo[9.3.0]tetradecene derivative (**11**, 36%). The ^{1}H- and ^{13}C-NMR of **11** showed

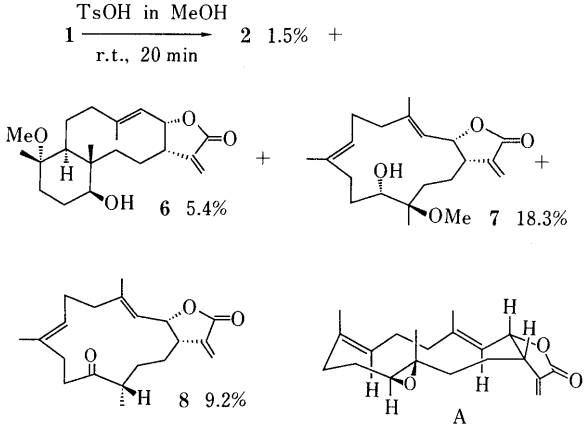


Chart 2

Chart 3

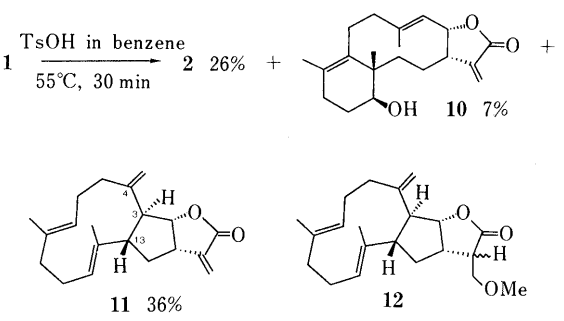


Chart 4

the signals of a terminal methylene group (^{1}H-NMR, δ 5.03, 5.08, br s; ^{13}C-NMR, δ 109.8, 149.2), and two olefinic methyl signals (δ 1.49, 6H, s). In contrast to the other cyclization products, **2**, **3** and **10**, the ^{1}H-NMR of **11** indicated that the C-7 double bond remained intact. Instead, the C-3 double bond participated in the ring closure. The H-2 signal appeared at δ 4.75 as dd (J=8.8, 7.0 Hz) but the H-3 signal was shifted to higher field and was masked in the other signals. The ^{1}H-NMR of the methanol adduct **12**, obtained by brief treatment of **11** in KOH–methanol solution, gave better resolution. The H-2 signal at δ 4.71 (dd, J=8.4, 6.0 Hz) was coupled with a methine proton at δ 2.29 (dd, J=12.0, 6.0 Hz), which was further coupled with a methine at δ 2.41 (td, J=12.0, 5.5 Hz). The two-dimensional ^{1}H-NMR of **12** indicated that the methine proton at δ 2.41 and H-1 (δ 2.81) are coupled concurrently with the C-14 protons at δ 1.51 and 2.1. The ^{13}C-NMR chemical shift of C-2 is unusually deshielded and appeared at δ 87.9 in **11** and δ 90.5 in **12**. The newly formed olefinic bond is due to dehydration at C-12, and the ^{13}C-NMR signal of C-20 appeared at 13.3 ppm, indicating that it is apparently linked to an *E*-double bond. These results exclude the possibility of the ring-closure between C-3 and C-11, and only the alternative structure **11** would account for the ^{1}H- and ^{13}C-NMR spectral properties observed. Compound **12** showed the presence of NOE between H-2 and H-1 and between H-2 and one of the terminal methylene protons (δ 5.00) but not between H-2 and H-3. The H-18 proton at δ 5.00 showed NOE with H-13 (δ 2.41) simultaneously. This last NOE is possible only when H-3 is directed to the opposite side of the ring, with respect to C-18 and H-13, and indicated the *trans*-fusion of the bicyclic ring system in **11**. The molecular model of **12** showed that one of the C-18 methylene protons is equally close to H-2 and H-13. Examination of the HMBC spectrum of **12** indicated two- and three-bond correlations of the corresponding carbon and proton signals. C-4 (^{13}C-NMR, δ 150.0) was correlated to C-13 (δ 56.7) which, in turn, was correlated to H-11 (^{1}H-NMR, δ 4.92, m). NOE was observed between H-11 and H-13. These observations support the illustrated structure of **11**. The immediate precursor of **11** should be the allylic alcohol **4**, and the reaction should be triggered by removal of the hydroxyl group. The ring-closure took place with a conformation in which the 3,4- and 12,13-double bonds are spatially crossed over each other. This was confirmed by brief treatment of **4** with TsOH in benzene at 50 °C, giving **11** in 47% yield (Chart 5).

We have thus demonstrated that 11,12-epoxycembranolide is quite reactive, as in ten- and eleven-membered sesquiterpenes. It shows the potential of transannular cyclization of cembranoids in the synthesis of their bicyclic and, in some cases, tricyclic derivatives. It is also possible that similar biosynthetic cyclization processes occur in as yet unknown cembranoid-derived diterpenes, especially in soft corals which are a rich source of cembranoids.[20]

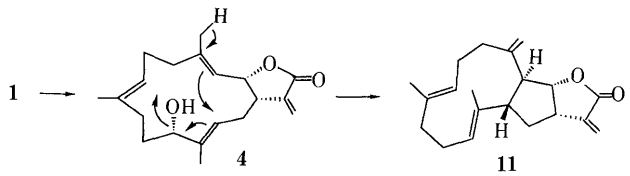


Chart 5

Experimental

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were determined on a JASCO A102 spectrometer. Ultraviolet (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, unless otherwise specified, in $CDCl_3$ on a JEOL JMS GX-270 spectrometer at 270 MHz (^{1}H) 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 insensitive nuclei enhanced by polarization transfer (INEPT). MS were determined on a JEOL JMS D300 spectrometer. Horeau determination was done using GC and HPLC as reported previously.[13] The work-up procedure includes first dilution of the reaction mixture with Et_2O, followed by washing the Et_2O layer with saturated $NaHCO_3$ solution, H_2O, and then saturated NaCl solution, and finally by evaporation *in vacuo*, unless otherwise specified. Chromatography was done by flash column chromatography,[21] using silica gel (Wako gel C-300, 200—300 mesh, Wako Pure Chemical Industries), and 7.5% $AgNO_3$-impregnated silica gel, with solvent systems: A, acetone–hexane; B, ethyl acetate–hexane; C, Et_2O–$CHCl_3$. The ratios of the solvents actually used are specified in parentheses.

Treatment of 1 with H_2SO_4 Compound **1** (298 mg) was dissolved in 5 ml of 0.5 N H_2SO_4 in dioxane–H_2O (4 : 1) and the mixture was stirred at room temperature for 1 h. After work-up, the mixture was subjected to chromatography with silica gel–solvent system A (0 : 10, 1 : 9, 1 : 4, and 2 : 3) to yield three mixtures containing **2** and **4**, **2** and **3**, and **5a**. Compounds **2** (42.3 mg) and **4** (18.7 mg) were purified by chromatography, first with $AgNO_3$-impregnated silica gel–solvent system A (1 : 4), and then with silica gel–solvent system C (1 : 19). Compound **3** (3.8 mg) was purified by chromatography on $AgNO_3$-silica gel with solvent system A (1 : 4), and then on silica gel with solvent system C (1 : 9). Compound **5a** (101.3 mg) was purified by silica gel chromatography with solvent system C (0 : 10, 1 : 9, 3 : 7).

Compound 2 mp 167.5—170 °C, $[\alpha]_D^{20}$ −19.8° (c=1.1). ^{1}H-NMR δ: 0.69 (3H, s, H-20), 1.69, 1.79 (each 3H, s), 3.02 (1H, m, H-1), 3.59 (1H, dd, J=9.9, 5.5 Hz, H-11), 5.21 (1H, m, H-9), 5.31 (1H, br d, J=9.5 Hz, H-3), 5.37 (1H, dd, J=9.5, 7.3 Hz, H-2), 5.64, 6.29 (each 1H, d (allylic coupling with H-1), J=2.2 Hz, H-16). ^{13}C-NMR δ: C-1 (41.1), C-2 (77.6), C-3,9 (118.6, 121.1), C-4,8 (137.2, 138.7), C-5 (41.1), C-6 (24.0), C-7 (43.8), C-10 (31.5), C-11 (70.2), C-12 (40.3), C-13 (32.7), C-14 (27.0), C-15 (140.3), C-16 (122.9), C-17 (170.4), C-18 (17.2), C-19 (21.2), C-20 (15.0). MS m/z: 316 (M^+), 301, 243, 138, 119, 81 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2029 (316.2038).

Compound 3 Oil, $[\alpha]_D^{20}$ −62° (c=0.25). ^{1}H-NMR δ: 0.60 (3H, s, H-20), 1.79 (3H, s), 2.98 (1H, m, H-1), 3.61 (1H, dd, J=12.5, 4.4 Hz, H-11), 4.86, 4.91 (each 1H, br s, H-19), 5.33—5.34 (2H, m, H-2,3), 5.66, 6.29 (each 1H, d, J=2.2 Hz, H-16). ^{13}C-NMR δ: C-1 (41.7), C-2 (77.6), C-3 (120.4), C-4 (139.4), C-5 (40.0), C-6 (23.3), C-7 (45.5), C-8 (147.8), C-9,13 (31.7, 33.7), C-10 (35.1), C-11 (72.6), C-12 (43.3), C-14 (28.2), C-15 (140.8), C-16 (123.0), C-17 (invisible), C-18 (17.6), C-19 (109.0), C-20 (14.7). MS m/z: 316 (M^+), 301, 119, 91, 53, 41 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2015 (316.2038).

Compound 4 Oil, $[\alpha]_D^{22}$ +27.1° (c=1.87). ^{1}H-NMR δ: 1.62, 1.68 (each 3H, s), 1.71 (3H, br s), 3.06 (1H, ddt, J=15.4, 7.3, 2.9 Hz, H-1), 4.51 (1H, dd, J=6.6, 6.2 Hz, H-11), 4.98 (1H, br dd, J=7.3, 6.2 Hz), 5.09 (1H, br d, J=9.2 Hz, H-3), 5.19 (1H, br dd, J=6.5, 6.0 Hz), 5.30 (1H, dd, J=9.5, 7.3 Hz, H-2), 5.66 (1H, d, J=2.2 Hz, H-16), 6.23 (1H, d, J=3.7 Hz, H-16). ^{13}C-NMR δ: C-1 (43.1), C-2 (77.8), C-3,7,13 (121.2, 122.9, 123.6), C-4,12 (139.2, 140.0), C-5 (39.5), C-6 (24.9), C-8 (135.0), C-9 (34.8), C-10 (31.8), C-11 (69.2), C-14 (27.2), C-15 (141.5), C-16 (121.5), C-17 (invisible), C-18,19,20 (15.9, 16.6, 17.5). MS m/z: 316 (M^+), 298, 105, 81 (base peak), 55. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2034 (316.2038).

Compound 5a Oil, $[\alpha]_D^{22}$ +3.7° (c=1.07). ^{1}H-NMR δ: 1.22 (3H, s, H-20), 1.63, 1.68 (each 3H, s, H-18,19), 2.78 (1H, m, H-1), 3.39 (1H, br t, J=5.5 Hz, H-11), 5.04 (1H, br t, J=6.2 Hz, H-7), 5.19 (1H, br d, J=9.2 Hz, H-3), 5.24 (1H, dd, J=9.2, 6.2 Hz, H-2), 5.58 (1H, d, J=1.1 Hz, H-16), 6.25 (1H, d, J=1.5 Hz, H-16). ^{13}C-NMR δ: C-1 (44.4), C-2 (78.0), C-3,7 (121.0, 122.7), C-4,8 (136.7, 139.5), C-5 (39.4), C-6,14 (23.7, 24.8), C-9 (36.7), C-10 (34.1), C-11 (74.8), C-12 (74.4), C-13 (28.7), C-15 (141.4), C-16 (122.0), C-17 (170.5), C-18,19 (15.7, 17.8), C-20 (25.1). MS m/z: 334 (M^+), 316, 235, 81, 43 (base peak). High-resolution MS [Found (Calcd)] m/z:

$C_{20}H_{30}O_4$ (M^+), 334.2137 (334.2143).

(−)- and (+)-MTPA Esters of 5a (a) A solution of **5** (40.0 mg) in pyridine (2 ml) was treated, at room temperature for 24 h, with the acid chloride (66.0 mg) prepared from (−)-MTPA. After usual work-up, the mixture was subjected to chromatography with silica gel–solvent system A (1 : 9) to give the (−)-MTPA ester **5b** (2.5 mg) as an oil. ^{1}H-NMR δ: 1.05 (3H, s), 1.57, 1.69 (each 3H, s), 2.84 (1H, m, H-1), 3.50 (3H, s), 5.09 (1H, d, J=8.9 Hz, H-3), 5.13 (1H, br t, J=5.9 Hz, H-7), 5.24—5.25 (2H, m, H-2,11), 5.55 (1H, d, J=1.5 Hz, H-16), 6.24 (1H, d, J=1.8 Hz, H-16). (b) Compound **5a** (41.4 mg) was treated in a same way as described in (a), giving the (+)-MTPA ester **5c** (22.5 mg) as an oil. ^{1}H-NMR δ: 0.98 (3H, s), 1.58, 1.69 (each 3H, s), 2.81 (1H, m, H-1), 3.58 (3H, s), 5.11 (1H, d, J= 9.2 Hz, H-3), 5.15 (1H, br t, J=6.2 Hz, H-7), 5.24—5.26 (2H, m, H-2,11), 5.55, 6.24 (each 1H, d, J=1.8 Hz, H-16).

Treatment of 1 with TsOH in MeOH Compound **1** (250 mg) was dissolved in 5 ml of MeOH. TsOH (32.5 mg) was added and the mixture was stirred at room temperature for 20 min. After work-up, the mixture was subjected to chromatography with silica gel–solvent system A (1 : 9) to give **8** (22.9 mg) and mixtures containing **7**, and **6** and **2**. Compound **7** (50.5 mg) was purified by chromatography with $AgNO_3$-impregnated silica gel–solvent system A (1 : 9). Compound **6** (14.9 mg) was purified by chromatography with silica gel–solvent system A (1 : 4). Compound **2** (3.9 mg) was purified by chromatography with silica gel–solvent system A (1 : 4), and then with silica gel–solvent system C (1 : 19).

Compound 6 mp 135.5—138.5 °C, $[\alpha]_D^{19}$ −43.5° (c=1.49). ^{1}H-NMR δ: 0.78 (3H, s, H-20), 1.19 (3H, s, H-19), 1.74 (3H, s, H-18), 3.15 (3H, s, OMe), 2.95 (1H, m, H-1), 3.48 (1H, br d, J=6.6 Hz, H-11), 5.33—5.34 (2H, overlapped, H-2,3), 5.63 (1H, d, J=1.8 Hz, H-16), 6.29 (1H, d, J= 2.7 Hz, H-16). ^{13}C-NMR δ: C-1 (41.4), C-2 (77.5), C-3 (120.5), C-4 (139.3), C-5 (41.9), C-6 (24.1), C-7 (46.5), C-8 (78.5), C-9,10 (34.4, 35.3), C-11 (72.7), C-12 (42.0), C-13,14 (28.2, 28.3), C-15 (140.6), C-16 (122.9), C-17 (170.4), C-18,20 (16.8, 17.2), C-19 (20.0), OMe (48.2). MS m/z: 348 (M^+), 316, 259, 86 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{32}O_4$ (M^+), 348.2295 (348.2300).

Compound 7 mp 148.5—150.0 °C, $[\alpha]_D^{19}$ +22.2° (c=1.11). ^{1}H-NMR δ: 1.19 (3H, s, H-20), 1.62, 1.68 (each 3H, s), 2.78 (1H, m, H-1), 3.22 (3H, s, OMe), 3.34 (1H, ddd, J=9.2, 6.2, 5.9 Hz, H-11), 5.04 (1H, br t, J=7.3 Hz, H-7), 5.19 (1H, br d, J=9.2 Hz, H-3), 5.24 (1H, dd, J=9.2, 5.9 Hz, H-2), 5.56, 6.25 (each 1H, d, J=1.5 Hz, H-16). ^{13}C-NMR δ: C-1 (44.5), C-2 (78.1), C-3,7 (120.9, 122.9), C-4,8 (136.9, 139.8), C-5 (39.6), C-6,14 (23.5, 24.9), C-9 (34.4), C-10 (32.3), C-11 (75.1), C-12 (enveloped by solvent peak), C-13 (29.1), C-15 (141.6), C-16 (121.6), C-17 (170.4), C-18,19 (15.5, 17.6), C-20 (19.3). MS m/z: 348 (M^+), 316, 217, 205, 85 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{32}O_4$ (M^+), 348.2288 (348.2300).

Compound 8 Oil, $[\alpha]_D^{19}$ +9.2° (c=2.29). ^{1}H-NMR δ: 1.08 (3H, d, J= 7.0 Hz, H-20), 1.63, 1.66 (each 3H, s), 2.95 (1H, m, H-1), 4.91 (1H, br t, J= 7.0 Hz), 5.09 (1H, br d, J=8.8 Hz, H-3), 5.23 (1H, dd, J=8.8, 7.3 Hz, H-2), 5.59 (1H, d, J=2.2 Hz, H-16), 6.25 (1H, d, J=2.6 Hz, H-16). ^{13}C-NMR δ: C-1 (45.2), C-2 (78.0), C-3,7 (120.2, 123.6), C-4,8 (134.5, 139.3), C-5,10 (38.9, 39.1), C-6,14 (24.7, 25.6), C-9 (31.9), C-11 (213.2), C-12 (43.2), C-13 (29.5), C-15 (141.4), C-16 (121.5), C-17 (170.5), C-18,19,20 (16.4, 16.4, 17.0). MS m/z: 316 (M^+), 298, 217, 151, 81 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2047 (316.2038).

Treatment of 1 with BF_3 Compound **1** (52 mg) was dissolved in 1 ml of benzene in an ice-bath. BF_3 etherate (5 μl) was added and the mixture was stirred for 1 h. After work-up, the mixture was purified by chromatography with silica gel–solvent system C (1 : 49) to give 45.7 mg of **2**. In another run, compound **1** (175 mg) in 2 ml of benzene was treated dropwise, at room temperature, with 0.07 ml of a solution made from 1 ml of BF_3 etherate and 9 ml of benzene, and stirred for 5 min. After work-up, the mixture was subjected to chromatography with silica gel–solvent system C (1 : 49 and 1 : 19) to give **2** (95.5 mg) and a mixture containing **9**. It was purified by chromatography with silica gel–solvent system A (1 : 19) and then $AgNO_3$-impregnated silica gel–solvent system B (1 : 9) to give **9** (5.6 mg).

Compound 9 mp 143—145.5 °C, $[\alpha]_D^{21}$ −39.2° (c=1.32). ^{1}H-NMR δ: 0.91 (3H, s, H-20), 1.38 (3H, s, H-19), 1.75 (3H, s), 3.19 (1H, m, H-1), 3.70 (1H, m, H-11), 5.09 (1H, br d, J=10.3 Hz, H-3), 5.36 (1H, dd, J=10.3, 9.2 Hz, H-2), 5.56, 6.33 (each 1H, d, J=3.3 Hz, H-16). ^{13}C-NMR δ: C-1 (42.2), C-2 (77.4), C-3 (122.0), C-4 (138.7), C-5 (40.6), C-6 (21.8), C-7 (49.2), C-8 (86.6), C-9 (42.0), C-10 (32.6), C-11 (86.3), C-12 (50.2), C-13,14 (25.9, 27.1), C-15 (140.2), C-16 (122.3), C-17 (170.4), C-18 (17.0), C-19 (26.5), C-20 (20.1). MS m/z: 316 (M^+), 298, 193, 107, 43 (base peak). IR no HO bands. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2052 (316.2038).

Treatment of 1 with TsOH in Benzene TsOH (26.9 mg) was added to a solution of **1** (302.5 mg) in 10 ml of benzene and the mixture was stirred at 55 °C for 30 min and worked up. Chromatography of the mixture with silica gel–solvent system A (1 : 9) gave mixtures containing **11** and **2**. Compounds **2** (79.8 mg) and **11** (103.0 mg) were purified by chromatography with $AgNO_3$-impregnated silica gel–solvent system A (1 : 9). In another run, the reaction was carried out at 50 °C for 30 min, using 32.0 mg of TsOH and 324 mg of **1**. Purification of the mixture, in the same way as above, gave **2** (83.5 mg) but the amount of **11** isolated was negligible. A small amount of **10** (26.2 mg) was isolated simultaneously.

Compound 10 mp 140—146 °C, $[\alpha]_D^{27}$ −105° (c=2.62). ^{1}H-NMR δ: 0.95 (3H, s, H-20), 1.69, 1.81 (each 3H, s), 2.94 (1H, m, H-1), 3.65 (1H, dd, J=7.3, 4.0 Hz, H-11), 5.11 (1H, br d, J=9.5 Hz, H-3), 5.30 (1H, dd, J= 9.5, 8.4 Hz, H-2), 5.60, 6.28 (each 1H, d, J=2.6 Hz, H-16). ^{13}C-NMR δ: C-1 (41.1), C-2 (77.6), C-3 (121.1), C-4 (138.9), C-5 (40.0), C-6,13,14 (26.4, 27.5, 29.5), C-7,8 (131.9, 132.7), C-9 (30.0), C-10 (35.2), C-11 (72.7), C-12 (43.2), C-15 (140.1), C-16 (122.8), C-17 (172.6), C-18 (16.9), C-19,20 (20.7, 24.0). MS m/z: 316 (M^+), 301, 175, 119 (base peak), 105. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_3$ (M^+), 316.2064 (316.2038).

Compund 11 mp 106—109 °C, $[\alpha]_D^{21}$ −115° (c=0.85). ^{1}H-NMR δ: 1.49 (6H, s), 3.39 (1H, ddt, J=17.9, 9.2, 2.6 Hz, H-1), 4.75 (1H, dd, J=8.8, 7.0 Hz, H-2), 4.92 (1H, br dd, J=7.7, 5.8 Hz, H-11), 5.03 (1H, d, J= 1.5 Hz, H-18), 5.08 (1H, br s, H-18), 5.10 (1H, br t, J=8.1 Hz, H-7), 5.62 (1H, d, J=2.2 Hz, H-16), 6.25 (1H, d, J=2.6 Hz, H-16). ^{13}C-NMR δ: C-1 (41.3), C-2 (87.9), C-3 (59.5), C-4 (149.2), C-5,14 (36.9, 37.4), C-6,10 (25.0, 26.2), C-7,11 (126.8, 127.9), C-8,12 (132.5, 132.5), C-9 (39.0), C-13 (56.2), C-15 (140.2), C-16 (122.4), C-17 (170.5), C-18 (109.8), C-19 (15.1), C-20 (13.2). MS m/z: 298 (M^+), 283, 133, 105, 81, 41 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{26}O_2$ (M^+), 298.1912 (298.1932).

MeOH Adduct of 11 A solution of **11** (27.0 mg) in 3% KOH–MeOH (3 ml) was left at room temperature for 10 min. The mixture was concentrated *in vacuo*, and was extracted with Et_2O. The Et_2O layer was washed with H_2O, 5% HCl solution, H_2O, and saturated NaCl solution, then the solvent was evaporated off. Chromatography of the residue with silica gel–solvent system A (1 : 9) gave 14.0 mg of **12** as an oil, $[\alpha]_D^{20}$ −129° (c=1.40). ^{1}H-NMR (400 MHz) δ: 1.49, 1.51 (each 3H, br s), 2.29 (1H, dd, J=12.0, 6.0 Hz, H-3), 2.41 (1H, overlapped, td, J=12.0, 5.5 Hz, H-13), 2.59 (1H, br dd, J=8.5, 3.7 Hz, H-15), 2.81 (1H, dtd, J=10.2, 8.2, 3.7 Hz, H-1), 3.35 (3H, s, OMe), 3.61 (1H, dd, J=9.1, 3.6 Hz, H-16), 3.67 (1H, dd, J=9.1, 4.9 Hz, H-16), 4.71 (1H, dd, J=8.4, 6.0 Hz, H-2), 4.92 (1H, br dd, J=8.2, 5.5 Hz, H-11), 5.00 (1H, d, J=1.6 Hz, H-18), 5.05 (1H, br s, H-18), 5.09 (1H, br t, J=7.5 Hz, H-7). ^{13}C-NMR δ: C-1 (41.3), C-2 (90.5), C-3 (59.2), C-4 (150.0), C-5 (37.2), C-6 (25.0), C-7 (126.9), C-8 (132.6), C-9 (39.0), C-10 (26.3), C-11 (127.7), C-12 (132.9), C-13 (56.7), C-14 (37.1), C-15 (49.0), C-16 (72.2), C-17 (178.0), C-18 (109.8), C-19 (15.2), C-20 (13.3), OMe (59.2). MS m/z: 330 (M^+), 315, 159, 134, 91, 45 (base peak). High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{30}O_3$ (M^+), 330.2201 (330.2196).

Conversion of 4 to 11 Compound **4** (10.8 mg) in benzene (1 ml) was treated with TsOH (1.1 mg) at 50 °C for 5 min. After work-up, the mixture was subjected to chromatography with $AgNO_3$-impregnated silica gel–solvent system A (1 : 9) to give 4.8 mg of **11**. This product was identical with **11** from **1**, by direct comparison of their ^{1}H-NMR and by chromatographic behavior in several thin layer chromatographic systems.

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