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# Unusual Transannular Cyclization Products of Sarcophytoxide, a 14-Membered Marine Cembranoid: Anomalous Stereochemistry of Epoxide–Ketone Rearrangement

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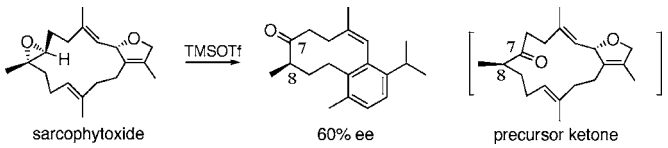
## ABSTRACT




**Treatment of sarcophytoxide with trimethylsilyl trifluoromethanesulfonate afforded an aromatic ketone as an unusual cyclization product. The modified Mosher's method and X-ray analysis performed on the aromatic ketone revealed that it is a 4:1 mixture of 8(*R*)- and 8(*S*)-enantiomers. It also suggested that the precursor ketone has 8(*R*)-configuration, which is contradictory to that expected from the ordinary epoxide–ketone rearrangement.**

Sarcophytoxide (**1**) is a cembranoid isolated from a soft coral, *Sarcophyton glaucum*.[1a] It is worth noting that this compound is contained in the organism in quite a large amount; 13 g of crystalline **1** is deposited by keeping the hexane extract of the *wet* soft coral (240 g) in a refrigerator overnight. Sarcophytoxide shows algacidal activity[2] and an inhibitory effect of the KCl-induced contraction of vascular smooth muscles.[1b] We intended to convert it chemically to compounds that have strong pharmaceutical activities. Similar studies starting from sarcophine (**2**) have also been reported.[3]

The structure of sarcophytoxide (**1**) is characterized by (i) an epoxide, (ii) a dihydrofuran, and (iii) three olefin bonds. Kobayashi treated **1** with perchloric acid and obtained ketone **7** (α-Me), an epoxide−ketone rearrangement product, and a diol.[4]

Expecting that a transannular reaction between a cation formed by cleavage of the epoxide ring and one of the olefins might occur by use of a Lewis acid, we treated **1** with 0.5 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[5] in benzene for 30 min,[6] during which time **1** was consumed completely and a major product appeared (TLC). The product (**3**), $[\alpha]^{27}_{D} = +94.2$ (*c* 0.97, $CHCl_3$), was separated in 15% yield, and its unique ketone structure with a benzene ring was elucidated by spectroscopic analysis.[7] Small amounts of two other related compounds, **4** and **5**, were also obtained in 1% and 0.3% yields, respectively (Scheme 1).

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(1) (a) Kashman, Y.; Zadock, E.; Neeman, I. *Tetrahedron* **1974**, *30*, 3615. (b) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Yamakado, T.; Matsuzaki, T.; Hirata, Y. *Experimentia* **1983**, *39*, 67.
(2) (a) Webb, L.; Coll, J. *Toxicon* **1983**, *3*, 485. (b) Bowden, B. F.; Michalek-Wagner, K. *J. Chem. Ecol.* **2000**, *26*, 1543.
(3) (a) Zjawiony, J. K.; Fahmy, H.; Khalifa, S. I.; Konoshima, T. *Marine Drugs* **2004**, *2*, 1. (b) Zjawiony, J. K.; Katsuyama, I.; Fahmy, H.; Khalifa, S. I.; Kilada, R. W.; Konoshima, T.; Takasaki, M.; Tokuda, H. *J. Nat. Prod.* **2002**, *65*, 1809.
(4) Kobayashi, M.; Hirase, T. *Chem. Pharm. Bull.* **1990**, *38*, 2442.
(5) Noyori, R.; Suzuki, M.; Takada, H. *J. Org. Chem.* **1982**, *47*, 902.

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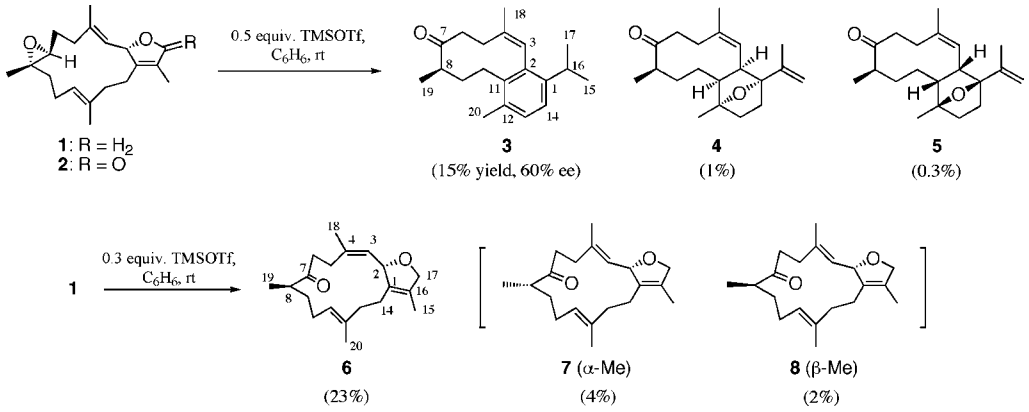
**Scheme 1**




Interestingly, the use of 0.3 equiv of TMSOTf (or less) resulted in the production of ketone **6** (23%),[8] $[\alpha]^{27}_D = +24$ (*c* 0.92, $CHCl_3$), and a mixture of other minor products, in which only a trace amount of **3** was detected by $^1$H NMR spectroscopy (Scheme 1). The relative stereochemistry of **6** was established by X-ray crystallography.

The aromatic product (**3**) was obtained as an optically active compound. To elucidate the absolute configuration, that is, the stereochemistry of 8-Me, the following chemical transformation was carried out (Scheme 2): Ketone **3** was reduced to alcohol **9**, which was afforded as an inseparable 2:3 diastereomeric mixture ($^1$H NMR). The mixture was treated with (*S*)-MTPA chloride. The $^1$H NMR spectrum of the (*R*)-MTPA ester unexpectedly showed four doublets assignable to 8-Me. This indicates that ketone **3** is partly racemized.

Fortunately, the MTPA diastereomers were separable by HPLC, and the relative stereochemistry of the respective (*R*)-MTPA esters, **10**−**13**, was deduced by *J* values of the protons and the NOEs observed in their NOESY spectra. Then, the proton chemical shifts of **10** were subtracted from those of **11**. {*Note: The NMR spectrum of* ***11****(****R****-α,α) is identical to that of its enantiomer [(S)-MTPA ester of* ***10****] (****S****-β,β).*} ($\Delta\delta = \delta_{S-\mathrm{MTPA}} - \delta_{R-\mathrm{MTPA}}$ in the modified Mosher's method).[9] The resultant $\Delta\delta$ values are shown in **10-MTPA**, indicating a 7(*S*)-configuration of **10**. In the same manner, the 7(*R*)-configuration of **12** was derived by $\delta_{13} - \delta_{12}$ (**12-MTPA**). When kept in a refrigerator, oily **10** deposited a crystal that was subjected to X-ray analysis (**10-X-ray**). Because **10** has a chiral auxiliary [(*R*)-MTPA], the X-ray result leads to the absolute configuration that is the same as the one predicted by the modified Mosher's method.

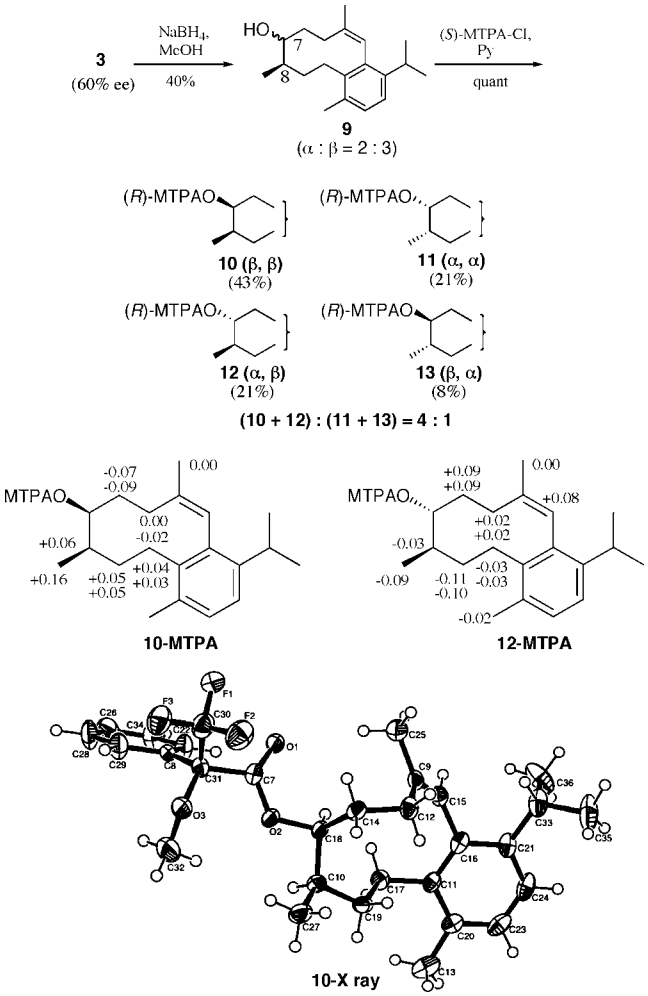
(6) To a solution of sarcophytoxide (**1**, 500 mg), $[\alpha]^{26}_D = 184$ (*c* 1.03, $CHCl_3$), in benzene (25 mL) cooled in an icebath was added TMSOTf (0.15 mL, 0.5 equiv), and the mixture was stirred for 10 min and then stirred at room temperature for 20 min. The solution was washed with a sodium bicarbonate solution and water and then dried over sodium sulfate. Evaporation of the solvent afforded a residue (496 mg), which was subjected to silica gel chromatography, affording crude **3** (ca. 90% purity, 166 mg). Purification by normal-phase HPLC gave pure **3** (75 mg). Minor products **4** and **5** were obtained by HPLC separation of the silica gel chromatography fractions.

(7) Compound **3**. IR($cm^{-1}$) 1710, 818. $[\alpha]^{27}_D = +210$ (*c* 0.17, $CHCl_3$). $^1$H NMR (400 MHz, $C_6D_6$) $\delta$: 7.13 ($d_{ab}$, 1H, $J$ = 8.1 Hz, H-14), 7.09 ($d_{ab}$, 1H, $J$ = 8.1 Hz, H-13), 6.01 (s, 1H, H-3), 3.14 (sept, 1H, $J$ = 6.9 Hz, H-16), 2.95 (td, 1H, $J$ = 13.4, 3.7 Hz, H-10), 2.57 (td, 1H, $J$ = 13.4, 5.1 Hz, H-5), 2.53 (m, 1H, H-10′), 2.26 (m, 1H, H-9), 2.25 (m, 1H, H-8), 2.21 (s, 3H, H-20), 2.11 (m, 1H, H-6), 2.10 (m, 1H, H-6′), 1.86 (s, 3H, H-18), 1.66 (dt, 1H, $J$ = 13.1, 3.2 Hz, H-5′), 1.56 (td, 1H, $J$ = 12.5, 4.6 Hz, H-9′), 1.28 (d, 3H, $J$ = 6.8 Hz, H-17), 1.13 (d, 3H, $J$ = 6.8 Hz, H-15), 0.67 (d, 3H, $J$ = 6.6 Hz, H-19). $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$: 212.8 (s, C-7), 144.4 (s, C-1), 138.1 (s, C-12), 137.3 (s, C-2), 136.8 (s, C-4), 133.8 (s, C-11), 130.1 (d, C-13), 126.1 (d, C-3), 123.1 (d, C-14), 39.3 (d, C-8), 38.9 (t, C-6), 30.6 (d, C-16), 30.6 (t, C-9), 29.4 (t, C-5), 28.8 (t, C-10), 24.5 (q, C-15), 23.6 (q, C-17), 21.1 (q, C-18), 19.9 (q, C-20), 19.6 (q, C-19). GCMS *m*/*z* 284. HREIMS *m*/*z* 284.2136 (−0.5 mmu). Compound **4**. IR ($cm^{-1}$) 1710, 1120, 895. $[\alpha]^{27}_D = +60$ (*c* 0.51, $CHCl_3$). $^1$H NMR (400 MHz, $C_6D_6$) $\delta$: 5.29 (s, 1H, H-15), 5.02 (d, 1H, $J$ = 10.7 Hz, H-3), 4.94 (s, 1H, H-15), 3.09 (t, 1H, $J$ = 11.2 Hz, H-2), 2.54 (td, 1H, $J$ = 12.9, 5.9 Hz, H-5), 2.36 (m, 1H, H-8), 2.25 (td, 1H, $J$ = 12.4, 5.8 Hz, H-6), 2.20 (m, 1H, H-6), 2.18 (m, 1H, H-9), 2.07 (ddd, 1H, $J$ = 12.0, 9.0, 3.2 Hz, H-14), 1.92 (s, 3H, H-17), 1.75 (s, 3H, H-18), 1.65 (m, 1H, H-14), 1.58 (m, 1H, H-11), 1.58 (m, 1H, H-5), 1.50 (m, 1H, H-13), 1.36 (s, 3H, H-20), 1.27 (m, 1H, H-13), 0.88 (m, 1H, H-10), 0.81 (m, 1H, H-9), 0.78 (d, 3H, $J$ = 7.1 Hz, H-19), 0.35 (m, 1H, H-10). $^{13}$C NMR (100 MHz, $C_6D_6$): 212.0 (s, C-7), 147.8 (s, C-16), 136.3 (s, C-4), 126.4 (d, C-3), 109.9 (t, C-15), 91.0 (s, C-1), 86.8 (s, C-12), 53.9 (d, C-11), 47.5 (d, C-2), 39.3 (d, C-8), 38.5 (t, C-6), 34.3 (t, C-9), 32.0 (t, C-14), 30.6 (t, C-13), 27.8 (t, C-5), 22.6 (q, C-18), 21.7 (t, C-10), 20.8 (q, C-20), 19.7 (q, C-17), 19.7 (q, C-19). GCMS *m*/*z* 302. HREIMS *m*/*z* 302.2239 (−0.7 mmu). Compound **5**. IR($cm^{-1}$) 1710, 1135, 896. $[\alpha]^{24}_D = +40$ (*c* 0.38, $CHCl_3$). $^1$H NMR (400 MHz, $C_6D_6$) $\delta$: 5.18 (d, 1H, $J$ = 11.7 Hz, H-3), 5.13 (s, 1H, H-15), 4.87 (s, 1H, H-15), 3.09 (t, 1H, $J$ = 11.7 Hz, H-2), 2.87 (td, 1H, $J$ = 13.3, 3.5 Hz, H-5), 2.32 (ddd, 1H, $J$ = 13.7, 10.7, 3.9 Hz, H-6), 2.22 (m, 1H, H-11), 2.17 (m, 1H, H-8), 2.06 (m, 1H, H-14), 2.00 (m, 1H, H-9), 1.97 (m, 1H, H-6), 1.92 (s, 3H, H-17), 1.70 (m, 1H, H-14), 1.63 (s, 3H, H-18), 1.62 (m, 1H, H-13), 1.57 (m, 1H, H-5), 1.37 (s, 3H, H-20), 1.31 (m, 1H, H-13), 1.21 (m, 1H, H-9), 1.11 (m, 2H, H-10), 0.79 (d, 3H, $J$ = 7.1 Hz, H-19). $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$: 213.5 (s, C-7), 147.7 (s, C-16), 134.8 (s, C-4), 127.2 (d, C-3), 110.3 (t, C-15), 90.9 (s, C-1), 87.0 (s, C-12), 55.1 (d, C-11), 49.6 (d, C-8), 47.0 (d, C-2), 38.1 (t, C-6), 32.5 (t, C-9), 31.3 (t, C-14), 30.9 (t, C-13), 29.8 (t, C-5), 25.8 (t, C-10), 23.8 (q, C-18), 20.6 (q, C-20), 19.2 (q, C-17), 18.4 (q, C-19). GCMS *m*/*z* 302. HREIMS *m*/*z* 302.2239 (−0.7 mmu).

(8) Compound **6**. $[\alpha]^{24}_D = +49$ (*c* 0.40, $CHCl_3$). $^1$H NMR (400 MHz, $C_6D_6$) $\delta$: 5.77 (br. s, 1H, H-2), 5.38 (d, 1H, $J$ = 8.5 Hz, H-3), 4.98 (dd, 1H, $J$ = 8.0, 1.9 Hz, H-11), 4.64 (dd, 1H, $J$ = 11.7, 5.1 Hz, H-17), 4.51 (d, 1H, $J$ = 11.7 Hz, H-17), 2.90 (td, 1H, $J$ = 13.2, 2.4 Hz, H-5), 2.48 (ddd, 1H, $J$ = 18.5, 12.2, 5.6 Hz, H-6), 2.36 (m, 1H, H-14), 2.24 (td, 1H, $J$ = 18.5, 12.7, 2.9 Hz, H-6), 2.15 (overlap, 1H, H-9), 2.06 (overlap, 1H, H-8), 2.02 (overlap, 1H, H-5), 2.01 (overlap, 1H, H-13), 1.97 (m, 2H, H-10), 1.86 (m, 1H, H-13), 1.59 (m, 1H, H-14), 1.56 (s, 3H, H-18), 1.49 (s, 3H, H-20), 1.39 (s, 3H, H-15), 1.33 (m, 1H, H-9), 0.93 (d, 3H, $J$ = 6.8 Hz, H-19). $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$: 212.6 (s, C-7), 136.3 (s, C-12), 136.0 (s, C-4), 133.4 (s, C-1), 128.5 (s, C-16), 128.3 (d, C-3), 124.5 (d, C-11), 84.9 (d, C-2), 78.4 (t, C-17), 45.9 (d, C-8), 42.1 (t, C-6), 38.2 (t, C-13), 33.6 (t, C-9), 26.8 (t, C-10), 26.2 (t, C-5), 23.0 (q, C-18), 23.0 (t, C-14), 18.8 (q, C-19), 15.2 (q, C-20), 9.2 (q, C-15). EIMS *m*/*z* 302. HREIMS *m*/*z* 302.2247 (+0.2 mmu).

(9) Kusumi, T.; Ohtani, I.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

**Scheme 2**

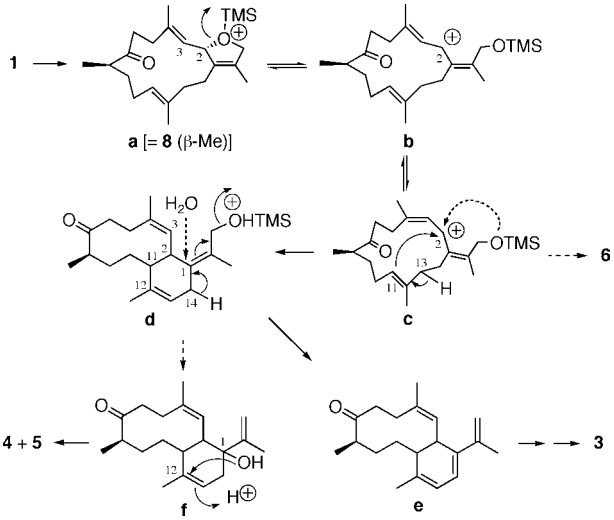



From the integration of the doublets due to 8-Me appearing separately in the $^1$H NMR spectrum of the mixture of **10**−**13**, it turned out that the ratio of 8$\beta$-Me isomers (**10** + **12**) and 8$\alpha$-Me isomers (**11** + **13**) was 4:1, indicating that ketone **3** is composed of 8(*R*)- and 8(*S*)-enantiomers in a 4:1 ratio (60% ee).

A presumable mechanism to give cyclized compounds **3**−**5** and ketone **6** is shown in Scheme 3. Rearrangement of the epoxide of **1** through a hydride shift (vide infra) affords mainly 8$\beta$-methyl ketone **a** (**8**). Then, the doubly allylic cation (**b**) is produced by acid (TMS)-assisted ether cleavage (**a** to **b**).[1a,10] Isomerization of the 3-olefin followed by recyclization of the TMS-oxy group (**c**) affords **6**. The *Z*-configuration of the 3-olefin (**c**) is crucial for the transannular cyclization to afford **d**. Formation of the carbonyl group (**a**) at C-7 seems to also be necessary so that the conformation of the 14-membered ring may become flexible and the distance between C-2 and C-11 may be close enough to achieve the cyclization. Dehydration accompanied by the multistep hydride shifts produces the stable aromatic ketone

(10) Coll, J. C.; Bowden, B. F.; Heaton, A.; Konig, G. *J. Nat. Prod.* **1987**, *50*, 650.

**Scheme 3**

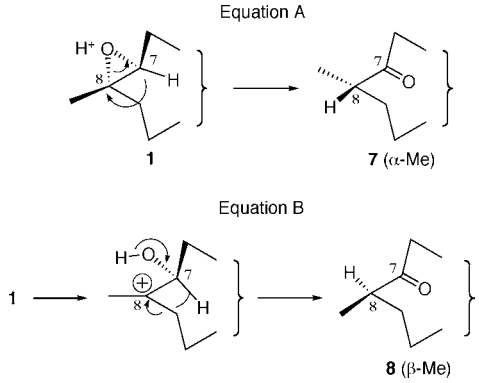



**3**. Addition of water (from the solvent?) to **d** and concomitant intramolecular ether formation give rise to ethers **4** and **5**.

It should be noted that **8** ($\beta$-Me) ought to be formed first as the major enantiomer by the Lewis acid-catalyzed (pinacol-type) rearrangement of the epoxide (**1**). From the textbook aspect of the rearrangement, the product is supposed to be **7** ($\alpha$-Me) because the hydride attacks from the backside of the leaving C−O bond in eq A.[4,11] Therefore, it seems natural that the structure of the acid-catalyzed rearrangement product ($HClO_4$) has been proposed to be **7** on the basis of the reaction mechanism.[4]

We have carried out the reaction under the reference conditions ($HClO_4$)[4] to obtain a ketone, whose spectral data are identical to those of the "supposed **7**". However, its structure including the absolute configuration was proved to be **8** (X-ray of its diastereomer and the modified Mosher's method; the details will be reported as an article elsewhere). Epimerization at C-8 of **7** and **8** did not occur at all under an acidic condition ($HClO_4$), although treatment of either **7** or **8** with a base ($NaOH/CD_3OD$) resulted in a 1:1 mixture of both compounds deuterated at C-6 and 8. When **8** (ee > 99%) was treated with 0.5 equiv of TMSOTf in bezene, **3**,

**Scheme 4**



$[\alpha]^{27}_D = +210$ ($c$ 0.17, $CHCl_3$) (ee 98%), was obtained in 28% yield. This experiment also eliminates the possibility of acid-catalyzed epimerization of 8-Me in the reaction course from **8** to **3** (Scheme 3).

The above experiments indicate that the epoxide−ketone rearrangement does not take place through eq A (Scheme 4). We tentatively assume that the reaction would occur in two steps via a cation eq B. The cation would take a particular conformation that allows the hydride to shift from the α-side, giving 8$\beta$-Me ketone **8**. Such anomalous epoxide−ketone rearrangements have also been documented.[12]

The aromatic compound (**3**) exhibits cytotoxic activity ($ID_{50} = 67$ nmol/mL) against the A549 cell.

**Supporting Information Available:** NOE data of compounds **10**−**12** and X-ray data of compounds **6** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Kashman, Y.; Czarkie, D.; Carmely, S.; Groweiss, A. *Tetrahedron* **1985**, *41*, 1049.

(12) (a) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron* **2001**, *57*, 815. (b) Neef, G.; Baesler, S.; Depke, G.; Vierhufe, H. *Tetrahedron Lett.* **1999**, *40*, 7969.