

BCSJ Award Article

Acid-Catalyzed Reactions of Sarcophytoxide, a Marine Cembranoid: An Apparently Enantio-Directive Reaction, Unusual Products and Stereochemical Reconsideration of Epoxide–Ketone Rearrangement

Keiji Nii,[1] Keiko Tagami,[1] Masaru Kijima,[1] Tatsuo Munakata,[2] Takashi Ooi,[1] and Takenori Kusumi*[1]

[1]Faculty of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770-8505

[2]Department of Pharmaceutical Sciences, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara 324-8501

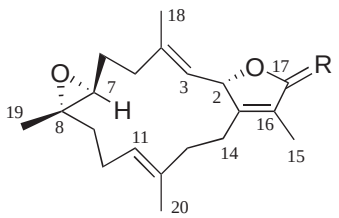
Received December 25, 2007; E-mail: tkusumi@ph.tokushima-u.ac.jp

Perchloric acid treatment of sarcophytoxide, a marine cembranoid possessing an epoxide, brought about epoxide–ketone rearrangement affording ketones. When the reaction time was long (22 h), a minor ketone that was antipodal to the ketone obtained in a short-time (10 min) reaction was formed. These puzzling findings, considering that the starting epoxide had three asymmetric carbons, were interpreted by surveying the structures of other ketonic products. The stereochemistry of a major ketone, which had been wrongly assigned, was corrected by extensive analyses of NMR spectra. The correct stereochemistry indicated that the epoxide–ketone rearrangement took a course via a cationic intermediate.

In the course of our study on pharmaceutically active marine natural products, we found that a hexane extract of the soft coral *Sarcophyton glaucum*, collected off Ishigaki Island, deposited a large amount of crystalline material (ca. 13 g from 240 g of dry body). By analyzing the physical properties, the material was identified as sarcophytoxide [(+)-**1**] (Figure 1),[1] a marine cembranoid. The structure of (+)-**1** has been established by X-ray crystallography and its absolute configuration has been determined by chemical conversion of (+)-**1** to sarcophine (**2**)[2] and sarcophytonine.[3] The chiroptical property of our sample, $[\alpha]_D = +153^\circ$ (*c* 1.0, methanol), is the same as that reported in the literature,[1b] $[\alpha]_D = +157^\circ$ (*c* 1.0, methanol).

Not much has been reported on pharmaceutical activity of sarcophytoxide; it has algacidal activity,[4] antifeedant activity against a mollusk,[5] and inhibitory effect of the KCl-induced contraction of vascular smooth muscles.[1b] In the present study, no activity was observed for (+)-**1** against lung cancer cells and pathogenic fungi, although it shows moderate activity (2 ppm) in a brine shrimp assay. This finding reinforces the supposition that sarcophytoxide may serve as a self-defense substance to protect the nude body of the soft coral from predators such as fish and mollusks.[5]

Considering the large content of (+)-**1** that can be a useful resource for a drug we intended to convert (+)-**1** chemically to compounds having stronger pharmaceutical activities. Similar studies[6] have been carried out starting from sarcophine (**2**), a cembranolide abundant in soft corals.



R = H_2: sarcophytoxide [(+)-**1**]
R = O : sarcophine[(+)-**2**]

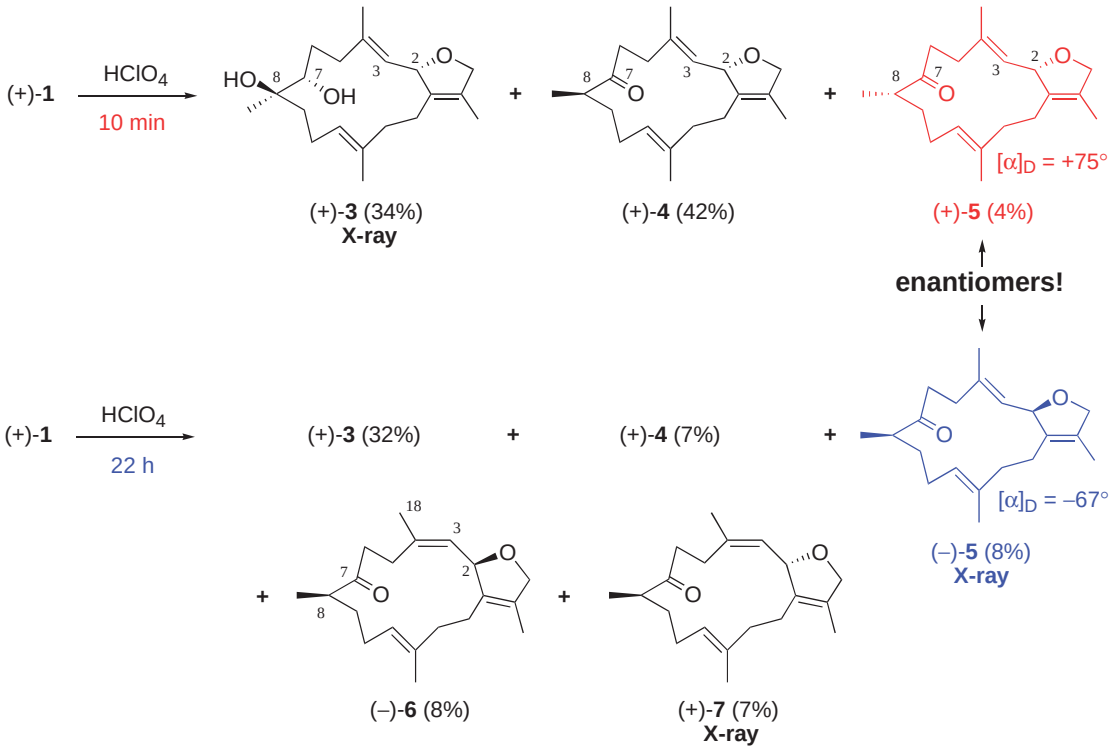
Figure 1. The structure of sarcophytoxide [(+)-**1**] and sarcophine [(+)-**2**].

Three kinds of chemically active functional groups are included in (+)-**1**: (i) an epoxide, (ii) a dihydrofuran whose ether oxygen is footed on a doubly allylic carbon (C-2), and (iii) three olefin bonds, two of which are included in the 14-membered ring, and one in the dihydrofuran ring. They are all acid-susceptible groups, and, therefore, (+)-**1** was treated with several Brønsted acids, and this paper deals with the structural investigation of the unique products as well as formation of enantiomeric ketones depending on the reaction conditions, and critical reconsideration of the stereochemistry of the commonly known epoxide–ketone rearrangement.

Results and Discussion

Formation of Enantiomeric Ketones (+)-5 and (−)-5. It would be better to start with the puzzling experimental results

Published on the web May 14, 2008; doi:10.1246/bcsj.81.562



Scheme 1. The compounds produced (%; isolation yield) by treatment of sarcophytoxide [(+)-**1**] with 25% perchloric acid in THF for 10 min (above) and 22 h (below). The 22 h reaction afforded other minor products (+)-**23**–(+)-**25** in Scheme 10 in 1–5% yields.

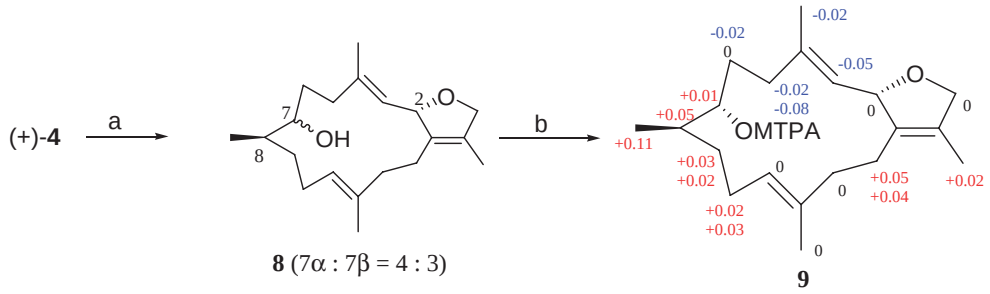
obtained in the earliest stage of this study. An acid-catalyzed reaction of sarcophytoxide [(+)-**1**] had been reported.[7] According to the reference conditions, sarcophytoxide was treated with aqueous 25% perchloric acid ($HClO_4$) in tetrahydrofuran (THF). After 10 min, the spot of the starting material disappeared in thin-layer chromatography (TLC), and new spots appeared. The reaction was stopped, and the products were separated (Scheme 1 [above]). Besides a reported diol and a ketone[7] [structure: vide infra (v.i.)], a new minor ketone, (+)-**5** ($[\alpha]_D = +75°$), was isolated in 4% yield. The NMR properties [a secondary methyl (Me) group, two trisubstituted *E*-olefins, a dihydrofuran] indicated that this product must be a diastereomer of the major ketone. When the reaction time was extended to 22 h (Scheme 1 [below]), the "identical" product was separated in 8% yield from a rather complex reaction mixture. The NMR (^1H and ^{13}C) properties and chromatographic behaviors [TLC and high-performance liquid chromatography (HPLC)] were identical with those of the former minor ketone (10 min). Surprisingly, this minor ketone (22 h), (−)-**5**, showed the inverse sign of the specific rotation, $[\alpha]_D = -67°$. The circular dichroism (CD) spectra of the enantiomers were antipodal to each other. It was curious enough that the respective enantiomers were produced from (+)-**1**, possessing three asymmetric carbons, depending on the reaction time.

Structure Correction of the Major Ketone. Fortunately, the minor ketone (−)-**5** was crystallized and the crystal was subjected to X-ray analysis, determining the structure to be **5** (relative).[8] The X-ray crystallography also revealed that the crystal applied to the analysis was racemic, that is, a racemate crystallized out from (−)-**5**. The smaller $[\alpha]_D$ absolute value (67) of (−)-**5** than that of (+)-**5** (75) suggests that this material is enantiomerically impure [enantiomeric excess (ee) of (−)-**5**: 79% based on the $[\alpha]_D$ value of (+)-**5**]. Probably the racemate tends to form a good crystal. The ^1H NMR spectra of the crystalline part and the oily residue were identical. At this stage, however, the reason why (+)-**1** having three asymmetric carbons affords enantiomeric ketones remained unclear.

Another annoying fact is that, in the literature,[7] the structure of the ketone produced by the perchloric acid reaction had been assigned as **5**. The physical data of the present minor ketone (+)-**5**, however, were different from those reported for the major ketone **5**. The authors of reference 7 deduced the stereochemistry of the major ketone from the mechanism of epoxide–ketone rearrangement. The present result of X-ray analysis necessitates correction of the structure **5** of the major ketone to (+)-**4** (or its enantiomer), which is a diastereomer of **5**.

Structural Determination of the Products. Among the products depicted in Scheme 1, diol (+)-**3** and major ketone (+)-**4** (corrected structure) are known. The stereochemistry of (+)-**3** had been deduced from the reaction mechanism.[7] In the present study, the absolute stereochemistry of (+)-**3** was confirmed by X-ray data obtained for cyclic sulfinate **12b** (v.i.).

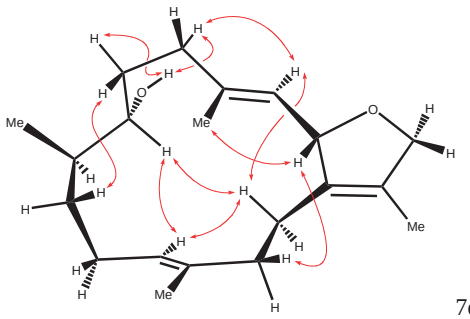
As mentioned above, the relative stereochemistry of (+)-**4** deduced based on the X-ray structure of (−)-**5** was still circumstantial. The major ketone, (+)-**4**, was reduced with sodium tetrahydroborate ($NaBH_4$) in methanol (MeOH) to give a separable mixture of 7α- and 7β-alcohols (4:3 by ^1H NMR) **8** in a quantitative yield (Scheme 2). Of the epimeric alcohols, 7α-alcohol **8** gives the ^1H NMR spectrum (C_6D_6) with excellent signal separation, and the relative stereochemistry was firmly established by the NOESY spectrum and analysis of



8 (7α : 7β = 4 : 3)

9

a: $NaBH_4$ in MeOH, rt (100%), b: 7α-alcohol, (*R*)- and (*S*)-MTPACl in pyridine, rt (50 − 60%)



7α-**8**

Scheme 2. Absolute configuration determination of (+)-**4** by the modified Mosher's method[9] performed on (7α-OH)-**8**. The Δδ values [$\delta_{(S)\text{-MTPA}} - \delta_{(R)\text{-MTPA}}$] depicted in **9** were obtained for a $CDCl_3$ solution. The stereochemistry of 7α-**8** was established by the NOESY spectrum and analysis of the coupling constants.

the coupling constants, which eventually verified structure **4**. The secondary alcohol was treated with (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) to give the (*S*)- and (*R*)-MTPA esters **9**, respectively. The Δδ values [$\Delta\delta = \delta_{(S)\text{-MTPA ester}} - \delta_{(R)\text{-MTPA ester}}$] of all the protons were obtained for **9**, and, based on the distribution pattern of the positive and negative values,[9] the 2*S*,7*S*,8*R*-configuration of **8** (7α-OH), and thus, 2*S*,8*R*-configuration of (+)-**4** was unambiguously determined (Scheme 2).

Treatment of (+)-**4** with sodium hydroxide in MeOH for 5 d at room temperature (rt) gave rise to a 1:2 mixture of two ketones. These were separated and identified with starting (+)-**4** and (+)-**5**, respectively. Therefore, the absolute stereochemistry of (+)-**5**, and therefore of (−)-**5**, was determined as shown in Scheme 1.

When the reaction time was extended to 22 h, two new ketones, (−)-**6** and (+)-**7**, were produced besides (+)-**3**, (+)-**4**, and (−)-**5** (Scheme 1 [below]). The structure of (+)-**7** was determined by X-ray crystallography. The NMR properties of the isomer (−)-**6** revealed that one of the two trisubstituted *E*-olefins of (+)-**1** changed to a *Z*-olefin [^{13}C: δ 22.8 (C-18), ^{1}H: NOE between H-3 and H-18], and because other features are similar to those of (+)-**7**, structure **6** was assigned to this isomer. The absolute configurations of (−)-**6** and (+)-**7** were confirmed by converting (+)-**4** to the respective compounds by treatment with $DClO_4$ for 22 h. Note that 8-protons of both ketones were not replaced with deuterium, which confirmed that the 8*R*-configuration of (+)-**4** was retained in them.

It should be noteworthy that the compounds with the *S*-configuration at C-2 such as (+)-**1**, (+)-**3**, (+)-**4**, (+)-**5**, and (+)-**7** show positive $[\alpha]_D$ values, and those with the *R*-configuration at C-2 [(−)-**5** and (−)-**6**] have negative $[\alpha]_D$ values. This chiroptical property greatly helped us to presume the absolute configuration of the products.

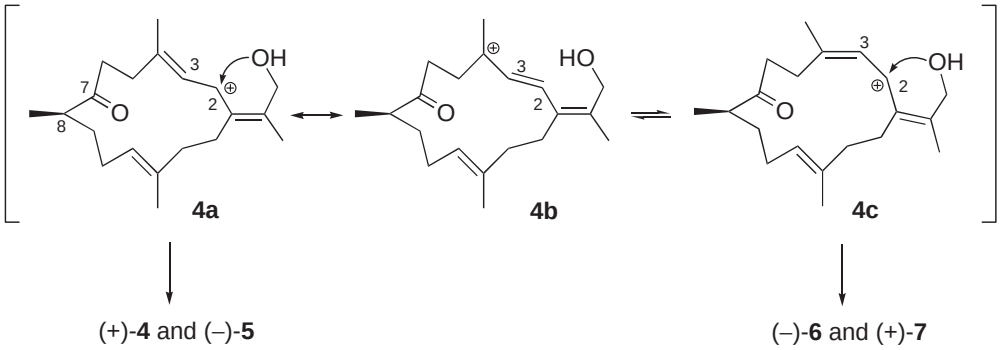
Reaction Mechanism. Formation of diol (+)-**3** is interpretable as the S_N2-type attack of the water molecule on C-8 of (+)-**1**, which gives 7*S*,8*R*-diol (+)-**3**. In both of the 10-min and 22-h reactions, the yield of the diol is practically the same.

In the 10-min reaction, ketones (+)-**4** (42%) and (+)-**5** (4%) must be directly formed from (+)-**1** by the epoxide–ketone rearrangement. Treatment of (+)-**1** with $DClO_4/D_2O$ in THF-d_8 gave (+)-**4** and (+)-**5**, in which no deuterium was incorporated (^{1}H NMR; doublets due to C-8 Me's) thus confirming that no epimerization at the C-8 position occurred in the ketones.

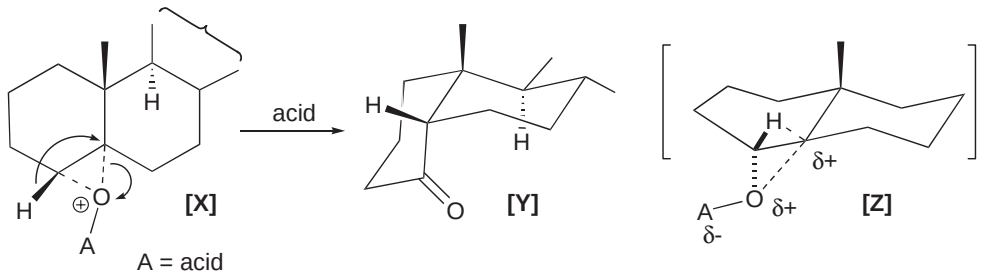
In the 22-h reaction, the yield of the ketone (+)-**4** greatly decreases (7%), and, at the same time, the enantiomer (−)-**5** (8%) and 3*Z* isomers (−)-**6** (8%) and (+)-**7** (7%) are formed. This suggests that the latter three are produced from the major ketone (+)-**4**. As mentioned above, treatment of (+)-**4** with $DClO_4$ for 22 h afforded non-deuterated (−)-**6** and (+)-**7** together with (−)-**5**.

Production of these compounds from (+)-**4** is understandable by assuming the cationic intermediates **4a** and **4c** (Scheme 3), which result from acid-assisted cleavage of the doubly allylic ether linkage at C-2 of (+)-**4**. The cation **4a** is stabilized by resonance with several cations such as **4b**, which can be isomerized to 3*Z*-isomer **4c**. Recombination of the ether linkage at C-2 of **4a** and **4c** will give (+)-**4**, (−)-**5** and (−)-**6**, (+)-**7**, respectively.

The minor ketone (+)-**5** initially formed from (+)-**1** will follow the same fate as (+)-**4**. The yield of (+)-**5** is, however, so low (4% after 10 min) that the supposed products [(−)-**4**, (+)-**6**, and (−)-**7**] may serve as the components that result



Scheme 3. A mechanism to produce isomeric ketones (+)-**4**, (−)-**5**, (−)-**6**, and (+)-**7** from double allylic cations **4a** and **4c** formed by acid-cleavage of the ether linkage at C-2 of (+)-**4**.



Scheme 4. A commonly granted mechanism of the rearrangement of epoxide [**X**] to ketone [**Y**]. The configuration of the migrated hydrogen is retained because the reaction is supposed to proceed concertedly via an intermediate [**Z**].

in lowering the enantiomeric excess of the respective enantiomers.

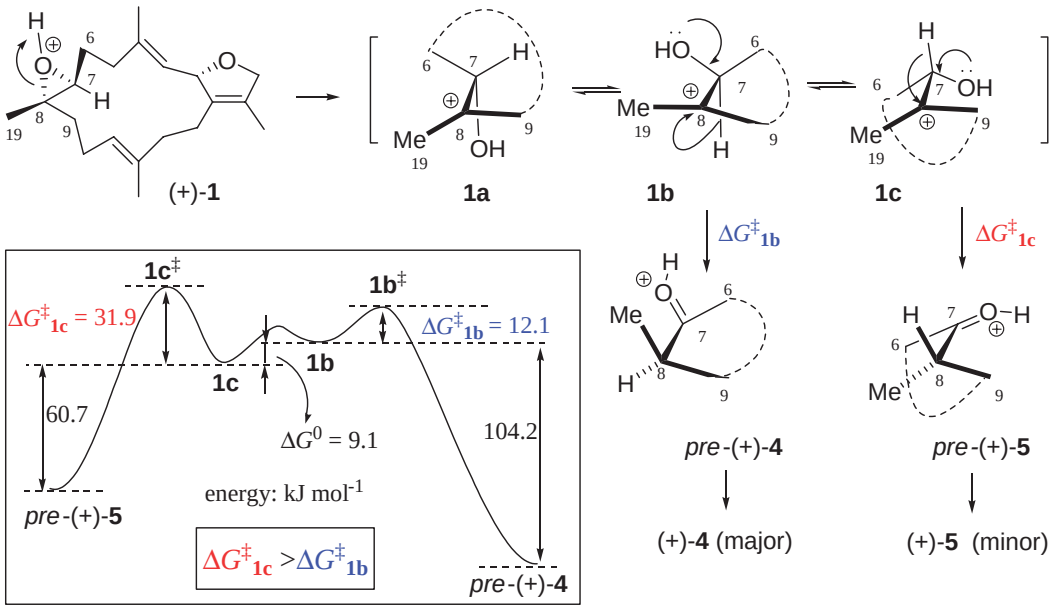
Reconsideration of the Epoxide–Ketone Rearrangement. It is well known that an epoxide can give a ketone when it is treated with acid. With respect to the stereochemistry of the epoxide–ketone rearrangement, the process has been considered, in many cases, a concerted reaction, in which a substituent such as hydrogen migrates from the backside of the cleaving C–O bond ([**X**]) via the transition state ([**Z**]), giving the product [**Y**] (Scheme 4).[10] On the basis of this reaction mechanism, the stereochemistry of the major ketone had been erroneously proposed as **5**, in which the hydrogen at C-7 of (+)-**1** shifts from the β-side of C-8.

So, why is (+)-**4** obtained as a major ketone in the epoxide–ketone rearrangement? The rearrangement cannot proceed in a concerted manner, because, to give (+)-**4**, H-7 of (+)-**1** must migrate from the same side of the cleaving C–O bond at C-8. We here propose the presence of a cation as a "distinct" intermediate; that is, this rearrangement proceeds in an S_N1 manner (Scheme 5). Cleavage of the epoxide C–O bond at C-8 of (+)-**1** gives a tertiary cation **1a**. The lifetime of the cation may be long enough to change its conformation into **1b** and **1c**, in each of which the sp^3 orbital of (C-7)–H is parallel with the vacant 2p-orbital at C-8. It is the difference between the activation energies, $\Delta G^{\ddagger}_{\mathbf{1b}}$ [from **1b** to pre-(+)-**4**] and $\Delta G^{\ddagger}_{\mathbf{1c}}$ [from **1c** to pre-(+)-**5**] (not the energy difference between **1b** and **1c**, which is 9.1 kJ mol^{-1}), that determines the ratio of the products (Curtin–Hammett principle),[11] and, thus, $\Delta G^{\ddagger}_{\mathbf{1c}}$ would be larger than $\Delta G^{\ddagger}_{\mathbf{1b}}$ in the present case. The activation energies were calculated: All geometries were initially constructed on the basis of the most stable conformation of (+)-**1** and then subjected to optimization for the intermediates **1b** and **1c** or to search for the transition state **1b**‡ and **1c**‡ at the AM1. All energies were calculated using the AM1 geometries at the B3LYP/6-31G* level, which indicated $\Delta G^{\ddagger}_{\mathbf{1b}}$ and $\Delta G^{\ddagger}_{\mathbf{1c}}$ to be 12.1 and 31.9 kJ mol^{-1} respectively [Scheme 5, left bottom: The conformations of pre-(+)-**4** and pre-(+)-**5** were presumed to be the same as those of **1b** and **1c** in the calculation of the activation energies.]. These results agree with the experimental results.

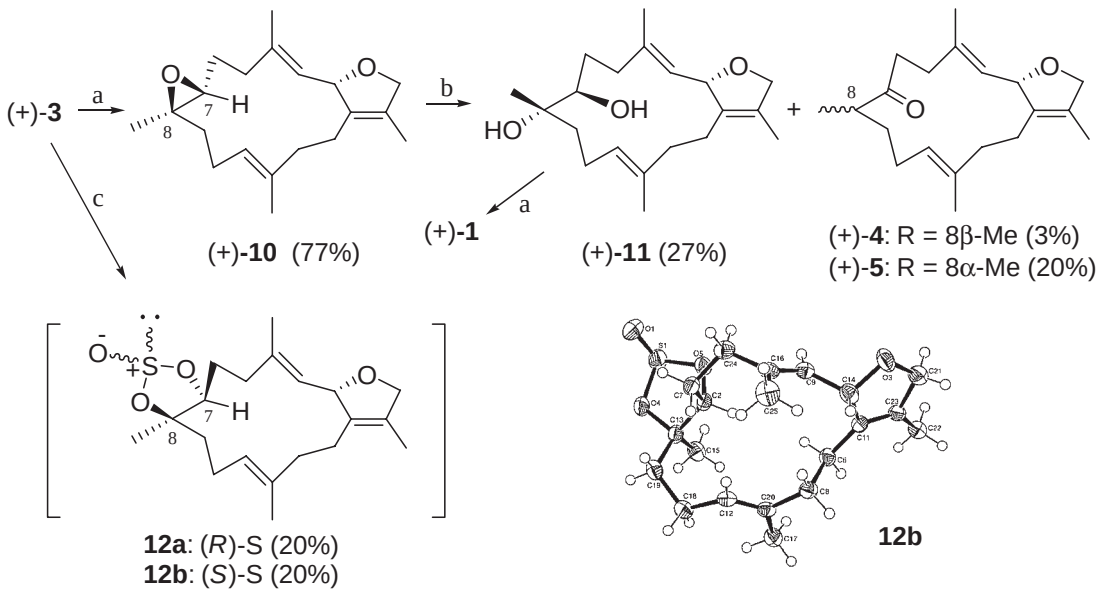
A similar discussion about the cation intermediate of an epoxide–ketone rearrangement has been made,[12] and the critical role of activation energy in the products ratio in the chemical reactions of sarcophine (**2**) has been recently discussed.[6b]

Inverted-Sarcophytoxide. In order to further investigate the stereochemical course of the epoxide–ketone rearrangement, (+)-**10** (inv-sarcophytoxide),[3] the 7*R*,8*R* diastereomer of (+)-**1**, was synthesized from diol (+)-**3**, and it was subjected to the $HClO_4$ reaction (Scheme 6). The acid-reaction was a little slower than the case of sarcophytoxide; it took 2 h until the starting inv-epoxide disappeared (TLC) when diol (+)-**11**, ketone (+)-**5**, and ketone (+)-**4** were obtained in 27, 20, and 3% yields, respectively. The stereochemistry of (+)-**11** was determined by converting it to (+)-**1**. Noteworthy is the fact that ketones, (+)-**4** and (+)-**5**, were afforded in 1:7 ratio; that is, H-7 appears to have migrated to C-8 from the same side of the leaving oxygen in the major ketone, (+)-**5**. This "invalid" hydrogen shift is also interpretable by assuming the intermediacy of the C-8 cation that is a diastereomer (7*R*) of **1a** in Scheme 5.

During the synthesis of (+)-**10**, we encountered a strange product: Reaction of (+)-**3** with methanesulfonyl chloride (MsCl) followed by potassium carbonate treatment gave (+)-**10** (77%) together with a minute amount (2%) of 1:1 mixture



Scheme 5. An S_N1-type mechanism of the epoxide–ketone rearrangement via a distinct cation. Acid-catalyzed cleavage of the epoxide ring of (+)-**1** produces the C-8 cation. Three conformations of the cation, **1a**–**1c**, are shown. Hydrogen (H-7) shift via **1b** and **1c** gives (+)-**4** (major) and (+)-**5** (minor), respectively. $\Delta G^{\ddagger}_{\mathbf{1b}}$ and $\Delta G^{\ddagger}_{\mathbf{1c}}$ are the activation energy of the hydrogen shift. The left bottom illustrates a calculated (B3LYP/6-31G*) energy diagram of the hydrogen shifts in cations **1b** and **1c** (Figure 5) to give ketones, pre-(+)-**4** and pre-(+)-**5**, respectively (see text).

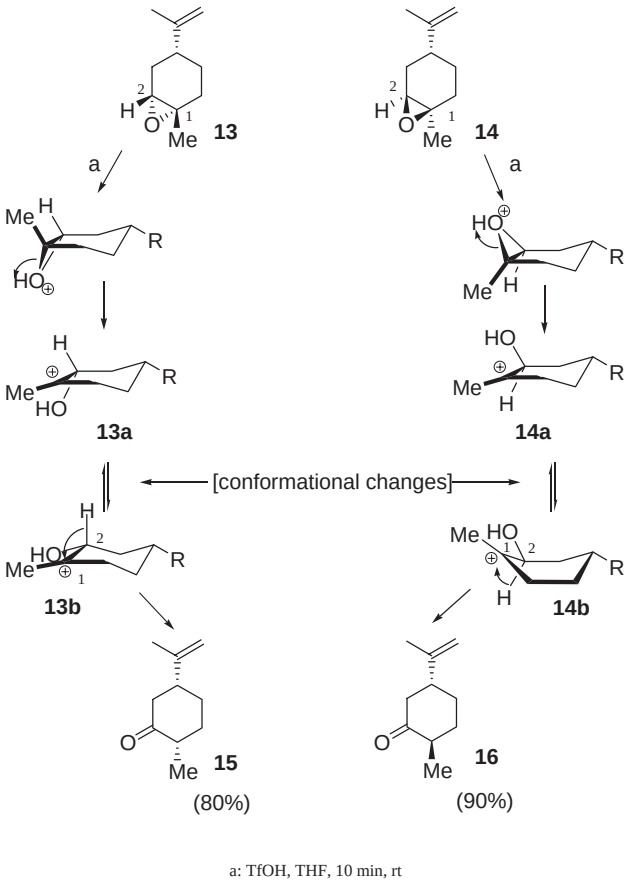


a: MsCl, triethylamine in CH_2Cl_2, then K_2CO_3 in MeOH. b: $HClO_4$ in THF, 2 h, c: $SOCl_2$, triethylamine in CH_2Cl_2, rt.

Scheme 6. Synthesis of inv-sarcophytoxide [(+)-**10**] and the products, (+)-**11**, (+)-**4**, and (+)-**5**, obtained by perchloric acid treatment. Other products were too polar (TLC) to be isolated. Stereochemistry of (+)-**11** was confirmed by conversion to (+)-**1**. Cyclic sulfinates **12a** and **12b** were produced in reaction a. An ORTEP drawing of structure **12b** is shown.

of diastereomers **12a** and **12b** (Scheme 6) that were separable by HPLC. One of them crystallized and the crystal was subjected to X-ray analysis, revealing that it was a cyclic sulfinate **12b**. This compound cannot be produced by the action of MsCl, but possibly formed by reaction with thionyl chloride that might have been present as a minor contaminant of the commercial MsCl. Actually, treatment of (+)-**3** with thionyl chloride afforded a diastereomeric mixture of **12a** and **12b** (1:1). The important thing is that, thanks to sulfur as a heavy atom, the absolute configuration of **12b**, thus (+)-**3**, has been established by the X-ray analysis.

Rearrangement of Limonene Oxides. As the reference experiments, the acid-catalyzed reactions were worked for (+)-*trans*-(**13**) and (+)-*cis*-limonene 1,2-epoxides (**14**) (Scheme 7). The reaction using $HClO_4$ was sluggish. Treatment of both epoxides with trifluoromethanesulfonic acid



Scheme 7. Acid-catalyzed reactions worked for (+)-*trans*-limonene 1,2-epoxide (**13**) and (+)-*cis*-limonene 1,2-epoxide (**14**) affording rearranged ketones **15** and **16**, respectively. Possible conformations of the cations, **13a**, **13b**, **14a**, and **14b**, are shown.

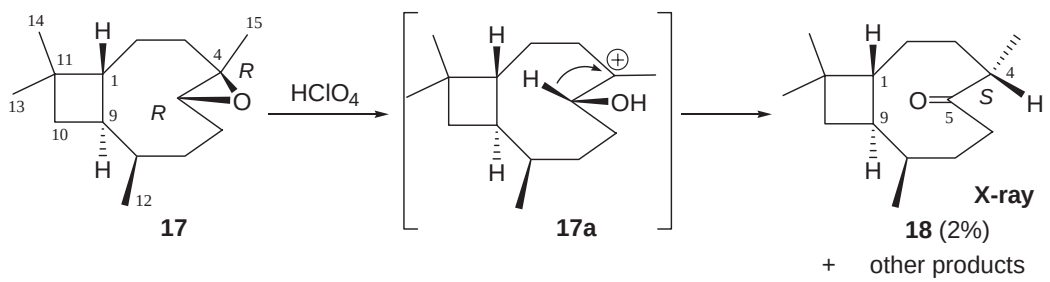
(TfOH) (0.1 molar amount) in THF for 10 min at room temperature gave good yields of ketones, **15** and **16**.[13] It appears that the rearrangements took place in a concerted way; that is, the hydrogen (H-2) shifts from the opposite side of the leaving oxygen at C-1. However, we rather propose that, even in these well-known cases, the reaction proceeds in an S_N1 manner via cationic intermediate such as **13a** and **13b** or **14a** and **14b**. In the case of **13**, initially formed cation **13a** is conformationally changed into **13b**, in which the (C-2)–(H-2) orbital is parallel with the vacant p-orbital of C-1. There are no alternatives of **13b**, owing to rigidity of the 6-membered ring. This situation is different from the case of (+)-**1**: Because of the flexibility of the 14-memberd ring, the cation formed from (+)-**1** can take two conformations, **1b** and **1c** (Scheme 5), which can bring about hydrogen shift.

Another evidence of the cation-intermediate mechanism was obtained in the $HClO_4$ reaction of (−)-dihydrocaryophyllene oxide (**17**),[14] giving a ketone **18** as a minor (2%) but a sole ketonic product (Scheme 8). The stereochemistry of **18** was confirmed by X-ray crystallography. The *S*-configuration of the newly formed secondary methyl group indicates that this reaction proceeded via a cation intermediate **17a** rather than a concerted hydride shift. The detail of this reaction will be published elsewhere.

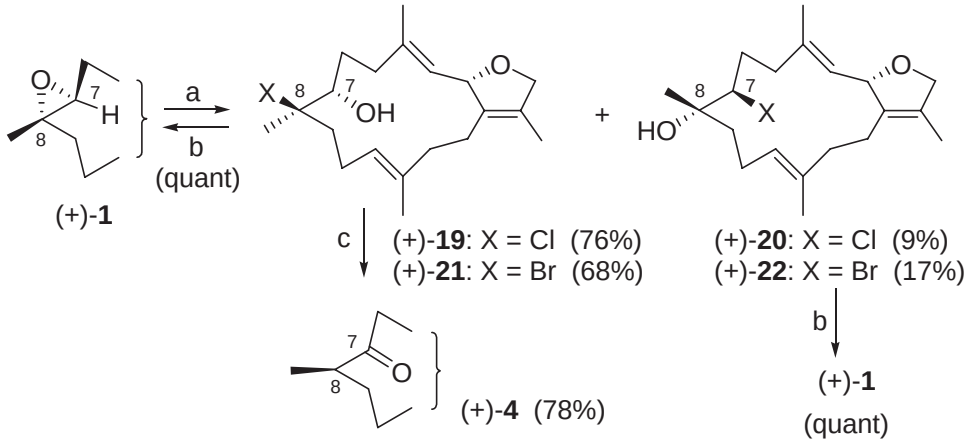
Treatment of (+)-1 with TfOH, Hydrochloric Acid, and Hydrobromic Acid. Treatment of (+)-**1** with TfOH (0.01 molar amount) in dry THF for 1 h afforded (+)-**4** and (+)-**5** in 80% and 8% yields, respectively. The ratio of the two ketones is the same as that obtained in the reaction with $HClO_4$. Naturally, diol, (+)-**3**, was not obtained under this anhydrous reaction condition.

When (+)-**1** was allowed to react with hydrochloric acid and hydrobromic acid in THF, no ketonic products were obtained, and, instead, isomeric chlorohydrines, (+)-**19** and (+)-**20**, and bromohydrines, (+)-**21** and (+)-**22**, were afforded, respectively (Scheme 9). Surprisingly, chlorohydrine (+)-**19** was changed into (+)-**4** by just letting its solutions to stand in $MeOH/H_2O$ (2:1) at room temperature for 22 h. Bromohydrine (+)-**21** more smoothly gave (+)-**4** after 1 h under the same conditions. In these reactions, the hydrides apparently shift from the opposite side of the leaving halogen. In such a polar solvent, however, the C–X bond may have a tendency to be cleaved spontaneously, giving a stable tertiary cation at C-8, onto which H-7 migrates. When polarity of the solvent was decreased (MeOH), the halohydrines remained unchanged and production of (+)-**4** was not detected even after 48 h.

It should be noted that the spectral data (^1H and ^{13}C) of chlorohydrine (+)-**19** are completely identical with those of a natural product, the structure of which was reported as a 7-diastereomer of diol (+)-**3**.[7] The authors of reference 7 obtained "isodiol" [actually (+)-**19**], which they thought to be a diastereomer of diol (+)-**3**, from the same soft coral. They found that isodiol was not cleaved with sodium periodate but it produced a ketone by treatment with $HClO_4$ in $MeOH–H_2O$. The latter result seemed to them as a pinacol rearrangement, which made them erroneously conclude that the compound had a 1,2-diol moiety.

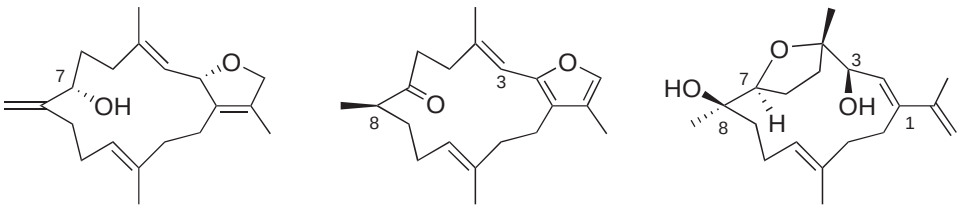


Scheme 8. Reaction of (−)-dihydrocaryophyllene oxide (**17**) with $HClO_4$ producing a ketone **18** as a sole ketonic compound (2%) besides other products. The major product (65%) of this reaction was an allyl alcohol. The detailed features of the reaction will be published elsewhere. Presence of a cationic intermediate **17a** is assumed in this epoxide–ketone rearrangement.



a: 35% HClaq in THF or 48% HBraq in THF at rt, 10 min, b: K_2CO_3 in MeOH, c: MeOH/H_2O (2 : 1), rt, 22 h

Scheme 9. Halohydrines, (+)-**19**/(+)-**20**, and (+)-**21**/(+)-**22**, obtained by the reaction of (+)-**1** and hydrochloric acid and hydrobromic acid, respectively, and chemical transformations to elucidate their stereochemistry. Halohydrines, (+)-**19** and (+)-**21**, afford the ketone (+)-**4**.



Scheme 10. Compounds obtained as the minor products of the acid treatments of (+)-**1**.

Minor Products Obtained by Acid Treatments of (+)-1. In the aforementioned reactions, minor compounds depicted in Scheme 10 were isolated from the reaction mixtures in 1%–5% yields; (+)-**23**[7] [$HClO_4$ (22 h), TfOH], (+)-**24** [$HClO_4$ (22 h)], (+)-**25** [$HClO_4$ (22 h)]. The absolute stereochemistry of (+)-**25** was determined by chemical conversion and exciton chirality method (see Experimental Section).

Pharmaceutical Activities of the Synthetic Compounds. Activities of all the compounds against MRSA and lung cancer cells were tested. Sarcophytoxide [(+)-**1**], the major ketone [(+)-**4**], and the chlorohydrine [(+)-**20**] are weakly active against MRSA (Inhibitory zones of ϕ 12–14 mm sizes were observed on agar dishes after 24 h, when the 33 mM solutions of (+)-**20** in dimethyl sulfoxide were applied to ϕ 6 mm filter papers.). Cytotoxicity against lung cancer cells (A549) (IC_{50} $\mu g\,mL^{-1}$) is as follows: (+)-**4** (16), (+)-**5** (14), (−)-**5** (14), (−)-**6** (15), and (+)-**7** (16). Other compounds were inactive.

Conclusion

Perchloric acid treatment of sarcophytoxide (+)-**1**, a marine cembranoid abundant in a soft coral *Sarcophyton glaucum*, gave ketone (+)-**4**, whose stereochemistry had been wrongly reported. The correct stereochemistry indicates that the acid-catalyzed epoxide–ketone rearrangement of (+)-**1** proceeds in a different way from that deduced by a "concerted mechanism" that would give 8(*S*)-Me [as in (+)-**5**] instead of the actual 8(*R*)-Me [(+)-**4**]. Similarly, acid treatment of inv-sarcophytoxide [(+)-**10**] and (−)-dihydrocaryophyllene oxide (**17**) gave ketone (+)-**5** and **18**, respectively, whose stereochemistry was different from that deduced by a concerted mechanism. Based on these findings, we have proved that the acid-catalyzed epoxide–ketone rearrangement takes an S_N1-like pathway through cationic intermediates such as **1c** in Scheme 5.

Depending on the reaction times of the acid treatment, enantiomers (+)-**5** and (−)-**5** were formed as minor products. This curious phenomenon was interpreted by assuming the epimerization of the doubly allylic C–O linkage at C-2 of (+)-**1**.

Experimental

General. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were determined in $CHCl_3$ on a JASCO P-1010 digital polarimeter. Circular dichroism (CD) spectra were measured on a JASCO J600 CD spectrometer. Infrared (IR) absorption spectra were recorded on a JASCO FT-IR420 spectrometer. MS spectra were measured on Waters LCT Premier XE and JEOL JMS-SX102A mass spectrometers. NMR spectra were recorded in $CDCl_3$ or C_6D_6 solution on a JEOL JNM AL400 spectrometer at 400 MHz (^1H), on a JEOL JNM AL300 spectrometer at 75 MHz (^{13}C), and on a Bruker ARX400 spectrometer (2D NMR) at 400 MHz (^1H)/100 MHz (^{13}C). X-ray crystallography was performed on a Rigaku R-AXIS RAPID X-ray diffractometer. Chromatography was done by flash column chromatography using silica gel (Merck silica gel 60, 0.040–0.063 mm, 230–400 mesh ASTM). Preparative TLC purification was done using silica gel plate (15 PLC

plates 20 × 20 cm silica gel 60 F_{254}, 1 mm). Recycle-HPLC was carried out using a JAI LC-908 apparatus and normal phase HPLC column (Merck Hibar RT250-25 LiChrosorb si 60, 7 μm). TLC was done using silica gel plate (25 TLC plates 20 × 20 cm silica gel 60 F_{254}). (−)-Caryophyllene oxide was purchased from Aldrich Chemical Company Inc.

Crystallographic Data. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition numbers CCDC-675018 for **3**, CCDC-675019 for **5**, CCDC-675020 for **12b**, and CCDC-675021 for **18**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Sarcophytoxide (1). *Sarcophyton glaucum* was collected at the Ishigaki Island, Okinawa Prefecture, Japan in 1997 and the whole body was freeze-dried. The freeze-dried soft coral (240 g) was extracted successively with hexane, CH_2Cl_2, and EtOAc. After the hexane extract was concentrated, it was stored in a refrigerator overnight, when massive crystals deposited in the oily hexane extract. About a half of the crystals was collected by filtration with the aid of hexane. The weight of this crystalline material was 6.5 g. By analyzing the physical data, this substance was identified as (2*S*,7*S*,8*S*)-sarcophytoxide [(+)-**1**].[1]

Perchloric Acid Treatment of Sarcophytoxide [(+)-1] (10 min). A solution of (+)-**1** (500 mg, 1.7 mmol) in THF (50 mL) was treated with 25% perchloric acid (6.0 mL) for 10 min at room temperature. The reaction mixture was added to a saturated $NaHCO_3$ solution (25 mL), and the mixture was extracted with ether (3 × 30 mL). The ether layer was washed with water (50 mL), brine (50 mL), and dried over Na_2SO_4. After the ether was evaporated, the residue (490 mg) was applied to a silica gel column. The column was eluted with hexane–EtOAc (30–100%). Compounds (+)-**4** and (+)-**5** were eluted with hexane–EtOAc (7:3) as a mixture (252 mg) (TLC: $R_f = 0.6$, hexane–EtOAc = 1:1). Compound (+)-**23**[2] was eluted with the same eluting solvent (10 mg, $R_f = 0.5$, 0.03 mmol). Compound (+)-**3**[7] was eluted with hexane–EtOAc = 3:7 (172 mg, $R_f = 0.18$, 0.54 mmol). The mixture of (+)-**4** and (+)-**5** was separated by recycle-HPLC (flow rate 10 mL min^{-1}) with hexane–isopropyl alcohol = 95:5. (+)-**4** (217 mg, 0.72 mmol) was eluted at $Rt = 62$ min and (+)-**5** (20 mg, 0.07 mmol), $Rt = 65$ min. (+)-**4**: a colorless oil; $[\alpha]_D^{25} = +135.8^\circ$ (*c* 0.92, $CHCl_3$); HR-EI-MS *m*/*z* 302.2278 (calcd for $C_{20}H_{30}O_2$, 302.2246); ^{1}H NMR (400 MHz, C_6D_6) δ 5.65 (m, 1H, H-2), 5.42 (d, 1H, $J = 9.8$ Hz, H-3), 4.93 (t, 1H, $J = 6.0$ Hz, H-11), 4.59 (ABX, 2H, $J_{AB} = 11.5$, $J_{AX-BX} = 4.6$ Hz, H-17), 2.35 (m, 1H, H-6), 2.29–2.27 (overlap, 2H, H-5, 14), 2.20–2.18 (overlap, 3H, H-5, 6, 8), 2.09 (m, 1H, H-10), 2.00 (m, 1H, H-13), 1.96–1.94 (overlap, 4H, H-9, 10, 13, 14), 1.87 (s, 3H, H-18), 1.53 (s, 3H, H-20), 1.44 (s, 3H, H-15), 1.33 (m, 1H, H-9), 0.86 (d, 3H, $J = 6.7$ Hz, H-19); ^{13}C NMR (75 MHz, C_6D_6) δ 212.0 (s, C-7), 139.7 (s, C-4), 136.4 (s, C-12), 134.6 (s, C-1), 128.3 (s, C-16), 127.3 (d, C-3), 123.5 (d, C-11), 84.8 (d, C-2), 78.5 (t, C-17), 46.6 (d, C-8), 39.7 (t, C-6), 37.1 (t, C-13), 32.8 (t, C-5), 32.4 (t, C-9), 26.6 (t, C-10), 24.4 (t, C-14), 19.0 (q, C-19), 17.9 (q, C-18), 15.9 (q, C-20), 10.1 (q, C-15). (+)-**5**: white powder; $[\alpha]_D^{27} = +74.6^\circ$ (*c* 0.99, $CHCl_3$); HR-EI-MS *m*/*z* 302.2239 (calcd for $C_{20}H_{30}O_2$, 302.2246); ^{1}H NMR (400 MHz, C_6D_6) δ 5.74 (d, 1H, $J = 10.3$ Hz, H-3), 5.70 (m, 1H, H-2), 4.89 (t, 1H, $J = 7.6$ Hz, H-11), 4.60 (m, 2H, H-17), 2.81 (dd, 1H, $J = 11.2$, 2.2 Hz, H-5), 2.34–2.33 (overlap, 2H, H-14, 6), 2.22 (m, 1H, H-10), 2.13 (m, 1H, H-14), 2.03–2.01 (overlap, 3H, H-6, 9, 8), 1.93 (m, 1H, H-13), 1.86 (m, 1H, H-13), 1.77–1.74 (overlap, 2H, H-5, 10), 1.61 (s, 3H, H-18), 1.54 (s, 3H, H-20), 1.43 (s, 3H, H-15), 1.29 (ddd, 1H, $J = 11.6$, 6.7, 3.42 Hz, H-9), 0.87 (d, 3H, $J = 6.6$ Hz, H-19); ^{13}C NMR (75 MHz, C_6D_6) δ 210.1 (s, C-7), 136.5 (s, C-4), 135.9 (s, C-12), 134.8 (s, C-1), 128.9 (d, C-3), 127.7 (s, C-16), 123.6 (d, C-11), 84.5 (d, C-2), 78.8 (t, C-17), 46.7 (d, C-8), 38.2 (t, C-6), 36.7 (t, C-13), 33.3 (t, C-5), 32.6 (t, C-9), 27.0 (t, C-10), 24.5 (t, C-14), 18.9 (q, C-19), 15.8 (q, C-20), 15.6 (q, C-18), 10.0 (q, C-15).

Perchloric Acid Treatment of Sarcophytoxide [(+)-1] (22 h). A solution of (+)-**1** (1.00 g, 3.3 mmol) in THF (100 mL) was treated with 25% perchloric acid (12 mL) for 22 h at room temperature. The reaction mixture was added to a saturated $NaHCO_3$ solution (50 mL), and the mixture was extracted with ether (3 × 60 mL). The ether layer was washed with water (100 mL), brine (100 mL), and dried over Na_2SO_4. After concentration, the residue (1.17 g) was applied to a silica gel column. The column was eluted with hexane–EtOAc (30–100%). Compound (+)-**24** (14 mg, 0.05 mmol) was obtained in the first fraction. A mixture of (+)-**4**, (−)-**5**, (−)-**6**, and (+)-**7** (520 mg) was eluted with hexane–EtOAc = 7:3. Compound (+)-**23**[2] (48 mg, 0.16 mmol) was eluted with the same solvent. Compound (+)-**25** (4.0 mg, 0.01 mmol) was eluted with hexane–EtOAc = 1:1 and purified by HPLC. Compounds (+)-**3** was eluted with hexane–EtOAc = 3:7 (397 mg, 1.2 mmol). The mixture of the ketones (350 mg) was separated by recycle-HPLC using four columns connected in series (flow rate 10 mL min^{-1}) with hexane–isopropyl alcohol = 95:5. (+)-**4** (56 mg, 0.19 mmol), (−)-**5** (72 mg, 0.24 mmol), (−)-**6** (61 mg, 0.20 mmol), and (+)-**7** (57 mg, 0.19 mmol) were eluted at $Rt = 60$, 63, 54, and 58 min, respectively. (−)-**5**: a yellow oil that gives colorless crystals (mp 85–87 °C); $[\alpha]_D^{25} = -67.0^\circ$ (*c* 0.58, $CHCl_3$). Other physical properties were the same with those of (+)-**5**. (−)-**6**: a colorless oil; $[\alpha]_D^{27} = -68.5^\circ$ (*c* 0.98, $CHCl_3$); HR-EI-MS *m*/*z* 302.2220 (calcd for $C_{20}H_{30}O_2$, 302.2246); ^{1}H NMR (400 MHz, C_6D_6) δ 5.80 (m, 1H, H-2), 5.35 (d, 1H, $J = 8.4$ Hz, H-3), 5.05 (t, 1H, $J = 7.2$ Hz, H-11), 4.62 (dd, 1H, $J = 12.0$, 5.6 Hz, H-17), 4.50 (dd, 1H, $J = 12.0$, 0.8 Hz, H-17), 2.70 (ddd, 1H, $J = 13.6$, 11.4, 4.0 Hz, H-5), 2.42–2.40 (overlap, 2H, H-8, 6), 2.32–2.28 (overlap, 2H, H-6, 14), 2.15–2.13 (overlap, 2H, H-5, 10), 2.05 (m, 1H, H-13), 1.92–1.88 (overlap, 2H, H-13, 9), 1.70 (m, 1H, H-14), 1.60 (s, 3H, H-18), 1.56 (overlap, 2H, H-9, 9), 1.48 (s, 3H, H-20), 1.41 (s, 3H, H-15), 0.88 (d, 3H, $J = 7.3$ Hz, H-19); ^{13}C NMR (75 MHz, C_6D_6) δ 212.4 (s, C-7), 136.8 (s, C-4), 136.7 (s, C-12), 134.1 (s, C-1), 128.0 (d, C-3), 127.8 (s, C-16), 124.6 (d, C-11), 84.9 (d, C-2), 78.3 (t, C-17), 46.8 (d, C-8), 38.7 (t, C-13), 38.4 (t, C-6), 34.1 (t, C-9), 26.5 (t, C-5), 26.0 (t, C-10), 23.1 (q, C-18), 22.7 (t, C-14), 17.6 (q, C-19), 15.6 (q, C-20), 9.7 (q, C-15). (+)-**7**: colorless needles, mp 89–91 °C; $[\alpha]_D^{26} = +49.2^\circ$ (*c* 0.40, $CHCl_3$); HR-EI-MS *m*/*z* 302.2247 (calcd for $C_{20}H_{30}O_2$, 302.2246); ^{1}H NMR (400 MHz, C_6D_6) δ 5.77 (m, 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 (ddd, 1H, $J = 18.5$, 12.7, 2.9 Hz, H-6), 2.15–2.06 (overlap, 2H, H-9, 8), 2.02–1.97 (overlap, 3H, H-5, 13, 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 (75 MHz, C_6D_6) δ 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). (+)-**24**: a yellow oil; $[\alpha]_D^{25} = +70.2^\circ$ (*c* 1.36, $CHCl_3$); HR-EI-MS *m/z* 300.2064 (calcd for $C_{20}H_{28}O_2$, 300.2090); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H, H-17), 5.65 (s, 1H, H-3), 4.90 (t, 1H, $J = 6.4$ Hz, H-11), 2.72 (ddd, 1H, $J = 15.1$, 9.0, 2.2 Hz, H-6), 2.60 (dd, 1H, $J = 13.4$, 7.1 Hz, H-8), 2.47–2.45 (overlap, 2H, H-5, 14), 2.38–2.35 (overlap, 2H, H-6, 14), 2.29 (m, 1H, H-5), 2.13 (m, 1H, H-13), 2.03 (m, 1H, H-10), 1.95 (overlap, 1H, H-13), 1.93 (s, 3H, H-18), 1.86 (s, 3H, H-15), 1.85 (overlap, 1H, H-10), 1.71 (m, 1H, H-9), 1.19 (s, 3H, H-20), 1.16 (m, 1H, H-9), 1.03 (d, 3H, $J = 7.3$ Hz, H-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0 (s, C-7), 149.6 (s, C-2), 137.4 (d, C-17), 136.6 (s, C-12), 133.7 (s, C-4), 125.6 (d, C-11), 122.0 (s, C-1), 120.5 (s, C-16), 112.1 (d, C-3), 43.3 (d, C-8), 38.3 (t, C-13), 38.2 (t, C-6), 35.2 (t, C-5), 30.9 (t, C-9), 24.5 (t, C-10), 24.3 (t, C-14), 18.4 (q, C-18), 17.8 (q, C-19), 17.7 (q, C-20), 8.1 (q, C-15). (+)-**25**: a colorless oil; $[\alpha]_D^{25} = +206.1^\circ$ (*c* 0.28, $CHCl_3$); HR-EI-MS *m/z* 320.2336 (calcd for $C_{20}H_{32}O_3$, 320.2352); ^{1}H NMR (400 MHz, C_6D_6 containing 2 µL of CD_3OD/0.4 mL) δ 5.87 (d, 1H, $J = 9.5$ Hz, H-2), 5.20 (dd, 1H, $J = 10.5$, 4.0 Hz, H-11), 5.15 (s, 1H, H-15), 5.02 (s, 1H, H-15), 4.10 (d, 1H, $J = 9.7$ Hz, H-3), 3.88 (dd, 1H, $J = 8.6$, 6.0 Hz, H-7), 2.51–2.48 (overlap, 2H, H-10, 14), 2.32–2.23 (overlap, 3H, H-14, 13, 5), 2.05 (dd, 1H, $J = 13.6$, 8.6 Hz, H-13), 1.92 (m, 1H, H-10), 1.87 (s, 3H, H-17), 1.85–1.82 (overlap, 2H, H-9, 6), 1.71–1.70 (overlap, 2H, H-5, 6), 1.67 (s, 3H, H-20), 1.41 (dd, 1H, $J = 14.1$, 9.1 Hz, H-9), 1.33 (s, 3H, H-18), 1.06 (s, 3H, H-19); ^{13}C NMR (100 MHz, C_6D_6 containing 2 µL of CD_3OD/0.4 mL) δ 144.5 (s, C-16), 143.8 (s, C-1), 130.7 (s, C-12), 129.5 (d, C-11), 127.2 (d, C-2), 113.6 (t, C-15), 84.3 (s, C-4), 79.8 (d, C-7), 73.2 (s, C-8), 71.1 (d, C-3), 39.4 (t, C-9), 37.6 (t, C-5), 37.5 (t, C-13), 26.3 (t, C-6), 25.3 (t, C-14), 23.2 (q, C-19), 22.0 (t, C-10), 21.7 (q, C-17), 20.1 (q, C-18), 17.0 (q, C-20).

Benzoylation of (+)-25. A solution of (+)-**25** (0.5 mg, 0.0016 mmol) in pyridine (50 µL) was treated with benzoyl chloride (4.4 µL, 0.04 mmol) for 20 h at room temperature. The reaction was quenched by *N*,*N*-dimethyl-1,3-propanediamine (5 µL, 0.04 mmol). The solvent was evaporated and the residue was subjected to a silica gel short column eluted with CH_2Cl_2. The benzoyl ester of (+)-**25** (0.5 mg, 0.0016 mmol) was obtained by preparative TLC ($R_f = 0.75$, hexane–EtOAc = 1:1). CD (0.12 mM, EtOH) $\Delta\varepsilon_{\lambda_{max}}$ +20.0 (241 nm), −12.5 (223 nm).

Sodium Tetrahydroborate Reduction of (+)-4. A solution of (+)-**4** (27.4 mg, 0.09 mmol) in MeOH (3.0 mL) was treated with $NaBH_4$ (26 mg, 0.7 mmol) for 30 min at room temperature. The reaction mixture was concentrated, water was added, and the mixture was extracted with ether. The ether layer was dried over Na_2SO_4. The mixture of two diastereomeric alcohols **8** (28.0 mg, 0.09 mmol) was obtained (TLC; $R_f = 0.5$, hexane–EtOAc = 1:1). The mixture was separated by recycle-HPLC (flow rate 10 mL min^{-1}) with hexane–isopropyl alcohol = 95:5. 7α-Alcohol **8** (8.9 mg, 0.03 mmol, *Rt* = 44 min, two cycles) and 7β-alcohol **8** (12.4 mg, 0.04 mmol, *Rt* = 48 min, two cycles) were obtained. 7α-**8**: a colorless oil; HR-EI-MS *m/z* 304.2393 (calcd for $C_{20}H_{32}O_2$, 304.2402); ^{1}H NMR (750 MHz, C_6D_6) δ 5.73 (m, 1H, H-2), 5.38 (dt, 1H, $J = 10.0$, 1.3 Hz, H-3), 5.13 (ddd, 1H, $J = 7.8$, 6.7, 1.3 Hz, H-11), 4.63 (br s, 2H, H-17), 3.65 (ddd, 1H, $J = 10.5$, 6.0, 1.5 Hz, H-7), 2.38 (ddd, 1H, $J = 19.6$, 9.7, 3.2 Hz, H-14), 2.36 (dd, 1H, $J = 13.2$, 9.2 Hz, H-5), 2.12 (m, 2H, H-10), 2.01 (dd, 1H, $J = 14.7$, 8.5 Hz, H-5), 1.99 (overlap, 2H, H-13), 1.92 (m, 1H, H-14), 1.71 (dddd, 1H, $J = 14.2$, 8.2, 3.4, 2.2 Hz, H-9), 1.58 (overlap, 1H, H-8), 1.58 (s, 3H, H-18), 1.57 (s, 3H, H-20), 1.51 (tdd, 1H, $J = 14.0$, 4.1, 2.2 Hz, H-6), 1.45 (s, 3H, H-15), 1.23 (dtd, 1H, $J = 14.1$, 8.3, 3.4 Hz, H-9), 1.07 (ddt, 1H, $J = 13.9$, 10.8, 4.0 Hz, H-6), 0.83 (d, 3H, $J = 7.1$ Hz, H-19); ^{13}C NMR (100 MHz, C_6D_6) δ 137.7 (s, C-4), 134.4 (s, C-1), 134.2 (s, C-12), 128.3 (d, C-3), 128.1 (s, C-16), 125.9 (d, C-11), 84.3 (d, C-2), 78.7 (t, C-17), 70.2 (d, C-7), 40.7 (d, C-8), 37.0 (t, C-13), 36.1 (t, C-5), 31.3 (t, C-9), 28.2 (t, C-6), 26.5 (t, C-10), 24.4 (t, C-14), 15.7 (q, C-20), 15.3 (q, C-18), 15.2 (q, C-19), 10.1 (q, C-15). 7β-**8**: a colorless oil. Because the ^{1}H NMR signals were heavily overlapped in δ 1.35–2.30 region, further characterization was not carried out.

(*R*)-MTPA Ester 9. A solution of 7α-**8** (3.0 mg, 0.01 mmol) in pyridine (50 µL) was treated with (*S*)-MTPACl (10 µL, 0.045 mmol) for 5 h at room temperature. The reaction was quenched by *N*,*N*-dimethyl-1,3-propanediamine (12 µL, 0.10 mmol). The mixture was concentrated and the residue was subjected to a silica gel short column eluted with CH_2Cl_2. Separation by TLC ($R_f = 0.48$, hexane–isopropyl alcohol = 95:5) gave (*R*)-MTPA ester **9** (1.8 mg, 0.003 mmol): a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H, $J = 6.8$ Hz, H-MTPA), 7.36 (overlap, 3H, H-MTPA), 5.53 (m, 1H, H-2), 5.27 (d, 1H, $J = 8.4$ Hz, H-7), 4.96 (d, 1H, $J = 5.6$ Hz, H-11), 4.91 (d, 1H, $J = 10.4$ Hz, H-3), 4.49 (s, 2H, H-17), 3.50 (s, 3H, H-MTPA), 2.53 (dt, 1H, $J = 10.4$, 8.6 Hz, H-14), 2.16 (overlap, 2H, H-10), 2.11 (m, 1H, H-5), 2.00 (overlap, 1H, H-13), 1.97 (overlap, 1H, H-5), 1.94 (overlap, 1H, H-8), 1.87 (overlap, 1H, H-13), 1.86 (overlap, 1H, H-14), 1.81 (s, 3H, H-18), 1.72 (overlap, 1H, H-6), 1.69 (s, 3H, H-20), 1.64 (overlap, 1H, H-6), 1.64 (s, 3H, H-15), 1.45 (m, 1H, H-9), 1.28 (m, 1H, H-9), 0.73 (d, 3H, $J = 6.4$ Hz, H-19).

(*S*)-MTPA Ester (9). A solution of 7α-**8** (0.5 mg, 0.0016 mmol) was treated with (*R*)-MTPACl in the same manner as described above. (*S*)-MTPA ester **9** (0.3 mg, 0.0006 mmol) was obtained: a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H, $J = 7.2$ Hz, H-MTPA), 7.35 (overlap, 3H, H-MTPA), 5.53 (m, 1H, H-2), 5.28 (d, 1H, $J = 10.4$ Hz, H-7), 4.96 (m, 1H, H-11), 4.86 (d, 1H, $J = 10.0$ Hz, H-3), 4.49 (s, 2H, H-17), 3.52 (s, 3H, H-MTPA), 2.58 (dt, 1H, $J = 10.4$, 8.6 Hz, H-14), 2.18 (overlap, 2H, H-10), 2.03 (m, 1H, H-5), 2.00 (overlap, 1H, H-13), 1.99 (overlap, 1H, H-8), 1.90 (overlap, 1H, H-14), 1.88 (overlap, 1H, H-5), 1.86 (overlap, 1H, H-13), 1.78 (s, 3H, H-18), 1.70 (overlap, 1H, H-6), 1.69 (s, 3H, H-20), 1.66 (s, 3H, H-15), 1.64 (overlap, 1H, H-6), 1.47 (m, 1H, H-9), 1.29 (m, 1H, H-9), 0.84 (d, 3H, $J = 6.4$ Hz, H-19).

Sodium Hydroxide Treatment of (+)-4 (MeOH). A solution of (+)-**4** (3.6 mg, 0.012 mmol) in MeOH (0.5 mL) was treated with 2 drops of a NaOH solution, made of MeOH (1.0 mL) and NaOH (100 mg), for 5 days at room temperature. The mixture was added to water and extracted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. The crude material was separated by recycle-HPLC with hexane–isopropyl alcohol = 95:5, giving (+)-**4** [2.9 mg, 0.01 mmol, $[\alpha]_D^{25} = +135.0^\circ$ (*c* 0.29, $CHCl_3$), *Rt* = 72 min, six cycles] and (+)-**5** [5.7 mg, 0.02 mmol, $[\alpha]_D^{25} = +75.0^\circ$ (*c* 0.57, $CHCl_3$), *Rt* = 78 min, six cycles].

Deuterated Perchloric Acid Treatment of (+)-1 in THF-d_8. A solution of (+)-**1** (5.1 mg, 0.017 mmol) in THF-d_8 (0.5 mL) was treated with 25% $DClO_4$ (22 µL) (in D_2O) at room temperature. The reaction was followed by ^{1}H NMR spectra. After 20 min, the signals of (+)-**1** disappeared and the signals due to diol [(+)-**3**] and ketones (+)-**4** and (+)-**5** appeared. The methyl signals

at C-8 of the two ketones were observed as doublets indicating no incorporation of deuterium at C-8.

Sulfuric Acid Treatment of (+)-1. A solution (+)-**1** (1.52 g, 5.0 mmol) in THF (150 mL) was treated with 50% H_2SO_4 (5.4 mL) for 15 min at room temperature. After workup, the crude product was applied to silica gel flash chromatography. The column was eluted with hexane–EtOAc = 4:6. Compound (+)-**3** [1.36 g, 4.2 mmol, $[\alpha]_D^{18} = +112.5^\circ$ (*c* 0.91, $CHCl_3$)] was obtained as a powdery solid. Recrystallization from ether afforded very fine needles, mp 112–115 °C (lit. 93–95 °C).[7]

Inv-Sarcophytoxide (+)-10. To a solution of (+)-**3** (150 mg, 0.47 mmol) and triethylamine (170 μL, 1.2 mmol) in CH_2Cl_2 (2.5 mL) cooled at 0 °C was added methanesulfonyl chloride (55 μL, 0.70 mmol), and the mixture was stirred for 30 min. The mixture was warmed to room temperature and triethylamine (100 μL, 0.7 mmol) was added. After stirring for 30 min, a solution of K_2CO_3 (295 mg, 2.1 mmol) in MeOH (8.8 mL) was added, and the mixture was allowed to stand at room temperature for 20 h. After filtration, the filtrate was extracted with EtOAc, and the organic phase was washed with brine and dried over Na_2SO_4. Inv-sarcophytoxide (+)-**10** (108 mg, 0.36 mmol) was obtained by flash column chromatography (hexane–EtOAc = 1:1) of the crude product: (+)-**10**: a colorless oil; $[\alpha]_D^{20} = +82.5^\circ$ (*c* 0.86, $CHCl_3$); HR-ESI-MS *m/z* 325.2100 (calcd for $C_{20}H_{30}O_2Na$, 325.2144); ^{1}H NMR (400 MHz, C_6D_6) δ 5.54 (m, 1H, H-2), 5.42 (d, 1H, $J = 9.5$ Hz, H-3), 5.13 (t, 1H, $J = 7.3$ Hz, H-11), 4.62 (dd, 1H, $J = 11.3$, 5.0 Hz, H-17), 4.53 (dd, 1H, $J = 11.9$, 3.4 Hz, H-17), 2.75 (t, 1H, $J = 5.5$ Hz, H-7), 2.24–2.22 (overlap, 2H, H-13, 14), 2.14–2.12 (overlap, 2H, H-5, 10), 2.06 (m, 1H, H-5), 1.99–1.95 (overlap, 2H, H-9, 13), 1.85 (m, 1H, H-10), 1.71 (m, 1H, H-6), 1.69 (s, 3H, H-18), 1.65 (overlap, 1H, H-14), 1.56 (m, 1H, H-6), 1.47 (s, 3H, H-20), 1.44 (s, 3H, H-15), 1.23 (td, 1H, $J = 12.8$, 3.5 Hz, H-9), 1.15 (s, 3H, H-19); ^{13}C NMR (75 MHz, C_6D_6) δ 139.2 (s, C-4), 135.5 (s, C-12), 134.6 (s, C-1), 128.5 (s, C-16), 126.6 (d, C-3), 124.1 (d, C-11), 85.8 (d, C-2), 78.5 (t, C-17), 61.8 (d, C-7), 59.2 (s, C-8), 39.3 (t, C-9), 38.8 (t, C-13), 35.3 (t, C-5), 28.0 (t, C-6), 23.9 (t, C-14), 23.5 (t, C-10), 17.6 (q, C-18), 16.6 (q, C-19), 15.4 (q, C-20), 10.3 (q, C-15). From the less polar fraction eluted with the same solvent, **12b** (1 mg, 0.003 mmol) was obtained as a crystal, which was subjected to X-ray analysis. In the ^{1}H NMR spectrum of the crude reaction mixture, the signals due to **12a** and **12b** were found as very small ones. Characterization of **12a** and **12b** was performed on the synthetic products (v.i.).

Perchloric Acid Treatment of (+)-10. A solution of (+)-**10** (29.6 mg, 0.1 mmol) in THF (3.0 mL) was treated with 25% perchloric acid (0.36 mL) for 120 min at room temperature. The reaction mixture was treated with a saturated $NaHCO_3$ solution and the mixture was extracted with ether. The ether layer was washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude product (35.5 mg). Compound (+)-**11** (7.9 mg, 0.025 mmol) was obtained by preparative TLC of the crude product. Compounds (+)-**4** (0.8 mg, 0.003 mmol) and (+)-**5** (6.0 mg, 0.02 mmol) were separated by recycle HPLC (flow rate 10 mL min^{-1}, hexane–isopropyl alcohol = 95:5) of the less polar TLC fraction. (+)-**11**: a colorless oil; $[\alpha]_D^{24} = +98.1^\circ$ (*c* 0.78, $CHCl_3$); HR-ESI-MS *m/z* 343.2268 (calcd for $C_{20}H_{32}O_3Na$, 343.2249); ^{1}H NMR (400 MHz, C_6D_6) δ 5.58 (m, 1H, H-2), 5.46 (d, 1H, $J = 9.8$ Hz, H-3), 5.20 (t, 1H, $J = 7.3$ Hz, H-11), 4.63 (dd, 1H, $J = 11.9$, 4.5 Hz, H-17), 4.52 (d, 1H, $J = 12.0$ Hz, H-17), 3.39 (t, 1H, $J = 7.5$ Hz, H-7), 2.20–2.12 (overlap, 4H, H-5, 10, 13, 14), 2.04–2.00 (overlap, 2H, H-10, 13), 1.85 (m, 1H, H-14), 1.83 (s, 3H, H-18), 1.70–1.67 (overlap, 2H, H-6, 9), 1.56–1.54 (overlap, 2H, H-6, 9), 1.54 (s, 3H, H-20), 1.44 (s, 3H, H-15), 1.16 (s, 3H, H-19); ^{13}C NMR (100 MHz, C_6D_6) δ 140.6 (s, C-4), 135.9 (s, C-12), 134.7 (s, C-1), 128.3 (s, C-16), 126.4 (d, C-3), 125.8 (d, C-11), 85.7 (d, C-2), 78.6 (t, C-17), 75.1 (s, C-8), 74.0 (d, C-7), 38.7 (t, C-9), 37.9 (t, C-13), 36.8 (t, C-5), 30.4 (t, C-6), 24.8 (q, C-19), 24.0 (t, C-14), 23.1 (t, C-10), 17.6 (q, C-18), 16.0 (q, C-20), 10.4 (q, C-15).

Treatment of (+)-3 with Thionyl Chloride. A solution of diol (+)-**3** (31.0 mg, 0.1 mmol) in CH_2Cl_2 (1.4 mL) was treated with thionyl chloride (28 μL, 0.4 mmol) and triethylamine (70 μL, 0.5 mmol) at room temperature for 25 min. The reaction mixture was added to water (2 mL), and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The CH_2Cl_2 layer was washed with brine (2 mL) and dried over Na_2SO_4. After concentration, the residue (33.2 mg) was separated by recycle-HPLC (flow rate 30 mL min^{-1}) with hexane–isopropyl alcohol = 95:5 to produce **12b** (6.4 mg, 0.02 mmol, *Rt* = 16 min, three cycles) and **12a** (6.0 mg, 0.02 mmol, *Rt* = 17 min, three cycles). **12a**: a colorless oil; $[\alpha]_D^{30} = +60.7^\circ$ (*c* 0.60, $CHCl_3$); HR-ESI-MS *m/z* 389.1761 (calcd for $C_{20}H_{30}O_4NaS$, 389.1763); ^{1}H NMR (400 MHz, C_6D_6) δ 5.56 (m, 1H, H-2), 5.31 (d, 1H, $J = 10.3$ Hz, H-3), 4.60 (m, 1H, H-11), 4.57 (brs, 2H, H-17), 4.44 (dd, 1H, $J = 9.8$, 3.2 Hz, H-7), 2.24 (overlap, 2H, H-5, 14), 1.92 (td, 1H, $J = 11.5$, 2.9 Hz, H-13), 1.85 (overlap, 1H, H-10), 1.82 (overlap, 1H, H-5), 1.79–1.78 (overlap, 2H, H-10, 13), 1.64 (t, 2H, $J = 5.3$ Hz, H-9), 1.60 (overlap, 1H, H-14), 1.58 (s, 3H, H-18), 1.56 (s, 3H, H-19), 1.45 (s, 3H, H-15), 1.32 (s, 3H, H-20), 1.30 (m, 2H, H-6); ^{13}C NMR (100 MHz, C_6D_6) δ 137.7 (s, C-4), 137.6 (s, C-12), 133.7 (s, C-1), 128.9 (s, C-16), 127.8 (d, C-3), 122.6 (d, C-11), 91.9 (s, C-8), 88.2 (d, C-7), 84.6 (d, C-2), 78.7 (t, C-17), 37.4 (t, C-13), 35.1 (t, C-5), 33.1 (t, C-9), 29.1 (t, C-6), 25.4 (t, C-14), 25.1 (q, C-19), 22.6 (t, C-10), 16.6 (q, C-18), 15.0 (q, C-20), 10.2 (q, C-15). **12b**: colorless needles; $[\alpha]_D^{30} = -37.1^\circ$ (*c* 0.64, $CHCl_3$); HR-ESI-MS *m/z* 389.1782 (calcd for $C_{20}H_{30}O_4NaS$, 389.1763); ^{1}H NMR (400 MHz, C_6D_6) δ 5.57 (brs, 1H, H-2), 5.31 (d, 1H, $J = 10.3$ Hz, H-3), 4.63 (dd, 1H, $J = 8.6$, 5.8 Hz, H-11), 4.54 (s, 2H, H-17), 4.10 (d, 1H, $J = 11.4$ Hz, H-7), 2.46 (overlap, 1H, H-5), 2.44 (overlap, 1H, H-6), 2.28 (overlap, 1H, H-14), 2.11 (overlap, 1H, H-5), 1.96 (overlap, 1H, H-9), 1.88 (overlap, 1H, H-13), 1.83 (overlap, 1H, H-9), 1.80 (overlap, 2H, H-10), 1.72 (overlap, 1H, H-13), 1.58 (s, 3H, H-18), 1.57 (overlap, 1H, H-6), 1.51 (overlap, 1H, H-14), 1.42 (s, 3H, H-15), 1.32 (s, 3H, H-20), 1.02 (s, 3H, H-19); ^{13}C NMR (100 MHz, C_6D_6) δ 138.4 (s, C-4), 137.9 (s, C-12), 133.4 (s, C-1), 128.8 (s, C-16), 127.4 (d, C-3), 122.2 (d, C-11), 93.5 (s, C-8), 86.1 (d, C-7), 84.5 (d, C-2), 78.6 (t, C-17), 37.1 (t, C-13), 35.5 (t, C-5), 32.8 (t, C-9), 29.9 (t, C-6), 26.0 (t, C-14), 23.8 (q, C-19), 23.0 (t, C-10), 16.4 (q, C-18), 14.8 (q, C-20), 10.2 (q, C-15).

Trifluoromethanesulfonic Acid Treatment of 13. A solution of **13** (4.0 mg, 0.03 mmol) in THF (0.5 mL) was treated with TfOH (0.3 μL, 0.003 mmol) for 10 min at room temperature. The reaction mixture was treated with a saturated $NaHCO_3$ solution and the mixture was extracted with ether. The ether layer was washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude product, from which **15**[13] (3.2 mg, 0.02 mmol) was obtained by preparative TLC.

Trifluoromethanesulfonic Acid Treatment of 14. Compound **14** (4.0 mg, 0.03 mmol) was treated with TfOH (0.3 μL, 0.003 mmol) in the same manner as described above, giving **16**[13] (3.6 mg, 0.02 mmol).

(−)-Dihydrocaryophyllene Oxide (17). A mixture of (−)-caryophyllene oxide (1000 mg, 4.5 mmol) and palladium–charcoal (10%) (1000 mg) in MeOH (200 mL) was stirred under an atmospheric pressure of hydrogen at room temperature for 3 h. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue (1120 mg). The residue was applied to a silica gel column. The column was eluted with hexane–EtOAc = 9:1. The eluted crude product (924 mg) was separated by recycle-HPLC using four columns connected in series (flow rate 30 mL min^{-1}) with hexane–EtOAc = 95:5 to give compound **17** (716 mg, 3.2 mmol, *Rt* = 77 min, 3 cycles). **17**: colorless needles; mp 68.2 °C (lit.[14] mp 66–67 °C); $[\alpha]_D^{26} = -51.7°$ (*c* 0.59, $CHCl_3$); HR-ESI-MS *m/z* 245.1903 (calcd for $C_{15}H_{26}O_2Na$, 245.1881); ^{1}H NMR (400 MHz, C_6D_6) δ 2.76 (dd, 1H, *J* = 10.8, 4.0 Hz, H-5), 2.04 (m, 1H, H-6), 1.97 (dddd, 1H, *J* = 12.6, 4.4, 2.8, 1.2 Hz, H-3), 1.89 (tdd, 1H, *J* = 10.0, 8.0, 4.8 Hz, H-9), 1.59 (t, 1H, *J* = 9.8 Hz, H-1), 1.52 (overlap, 1H, H-8), 1.47–1.46 (overlap, 3H, H-2, 7, 10), 1.22 (t, 1H, *J* = 10.4 Hz, H-10), 1.17 (overlap, 1H, H-6), 1.17 (s, 3H, H-15), 1.14 (overlap, 1H, H-2), 1.13 (overlap, 1H, H-7), 0.98 (td, 1H, *J* = 14.0, 5.2 Hz, H-3), 0.94 (s, 3H, H-14), 0.93 (s, 3H, H-13), 0.78 (d, 3H, *J* = 6.8 Hz, H-12); ^{13}C NMR (100 MHz, C_6D_6) δ 64.2 (d, C-5), 59.1 (s, C-4), 47.0 (d, C-9), 45.9 (d, C-1), 39.3 (t, C-3), 35.0 (t, C-10), 34.1 (d, C-8), 33.5 (s, C-11), 30.0 (q, C-14), 28.8 (t, C-6), 27.8 (t, C-2), 27.6 (t, C-7), 21.6 (q, C-13), 19.7 (q, C-12), 17.5 (q, C-15).

Perchloric Acid Treatment of 17. A solution of **17** (300 mg, 1.4 mmol) in CH_2Cl_2 (30 mL) was treated with 25% perchloric acid (3.6 mL) for 30 min at room temperature. The reaction mixture was added to a saturated $NaHCO_3$ solution (30 mL), and the mixture was extracted with ether (3 × 30 mL). The ether layer was washed with water (50 mL) and brine (50 mL) and dried over Na_2SO_4. After the ether was evaporated, the residue (345 mg) was applied to a silica gel column. The column was eluted with hexane–EtOAc = 8:2. The eluted crude product (65.9 mg) was purified by recycle-HPLC (flow rate 30 mL min^{-1}) with hexane–isopropyl alcohol = 95:5 to give compound **18** (5.3 mg, 0.02 mmol, *Rt* = 11 min, 3 cycles). **18**: colorless needles; mp 56–57 °C; $[\alpha]_D^{24} = +13.9°$ (*c* 0.27, $CHCl_3$); HR-ESI-MS *m/z* 277.2141 [calcd for $C_{16}H_{30}O_2Na$ (M^+ + Na + MeOH), 277.2144]; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.64 (dd, 1H, *J* = 11.2, 15.4 Hz, H-6), 2.60 (sext, 1H, *J* = 6.3 Hz, H-4), 2.12 (ddd, 1H, *J* = 15.4, 9.8, 1.4 Hz, H-6), 1.96 (br t, 1H, *J* = 13.3 Hz, H-7), 1.91 (qd, 1H, *J* = 9.8, 2.5 Hz, H-9), 1.78 (overlap, 2H, H-3), 1.64 (overlap, 1H, H-8), 1.57 (overlap, 2H, H-1, 7), 1.42 (dd, 1H, *J* = 9.8, 8.4 Hz, H-10), 1.33 (m, 1H, H-2), 1.22 (t, 1H, *J* = 10.5 Hz, H-10), 1.18 (m, 1H, H-2), 0.96 (d, 3H, *J* = 6.3 Hz, H-15), 0.90 (d, 3H, *J* = 7.0 Hz, H-12), 0.89 (s, 3H, H-14), 0.88 (s, 3H, H-13); ^{13}C NMR (100 MHz, acetone-d_6) δ 213.8 (s, C-5), 47.9 (d, C-4), 46.4 (d, C-1), 40.7 (d, C-9), 37.2 (t, C-10), 37.2 (t, C-6), 35.7 (d, C-8), 34.1 (s, C-11), 31.7 (t, C-3), 30.2 (t, C-7), 29.5 (q, C-14), 25.0 (t, C-2), 22.4 (q, C-13), 16.1 (q, C-15), 16.0 (q, C-12).

Hydrochloric Acid Treatment of (+)-1. A solution of (+)-**1** (100 mg, 0.3 mmol) in THF (10 mL) was treated with 35% hydrochloric acid (0.28 mL) for 10 min at room temperature. The reaction mixture was added to a saturated $NaHCO_3$ solution (5 mL), and the mixture was extracted with ether (3 × 6 mL). The ether layer was washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. The crude product (150 mg) was separated by recycle-HPLC (flow rate 10 mL min^{-1}) with hexane–isopropyl alcohol = 95:5. Chlorohydrine (+)-**19** (84.5 mg, 0.25 mmol) was eluted at *Rt* = 35 min (two cycles) and (+)-**20** (10.1 mg, 0.03 mmol) at *Rt* = 31 min (two cycles). (+)-**19**: a colorless oil; $[\alpha]_D^{29} = +115.9°$ (*c* 0.97, $CHCl_3$); HR-ESI-MS *m/z* 361.1904, 363.1903 (calcd for $C_{20}H_{31}O_2{}^{35}ClNa$, 361.1910, $C_{20}H_{31}O_2{}^{37}ClNa$, 363.1881); ^{1}H NMR (400 MHz, C_6D_6) δ 5.68 (m, 1H, H-2), 5.39 (d, 1H, *J* = 10.0 Hz, H-3), 5.07 (t, 1H, *J* = 7.2 Hz, H-11), 4.58 (m, 2H, H-17), 3.76 (dd, 1H, *J* = 11.4, 8.5 Hz, H-7), 2.33–2.27 (overlap, 3H, H-5, 10, 14), 2.21 (m, 1H, H-9), 2.08 (m, 1H, H-10), 1.99–1.84 (overlap, 5H, H-5, 6, 13, 13, 14), 1.79 (ddd, 1H, *J* = 14.1, 7.9, 3.4 Hz, H-9), 1.63 (s, 3H, H-18), 1.52 (s, 3H, H-20), 1.51 (s, 3H, H-19), 1.43 (s, 3H, H-15), 1.32 (m, 1H, H-6), 1.05 (m, 1H, OH); ^{13}C NMR (75 MHz, C_6D_6) δ 137.4 (s, C-4), 135.7 (s, C-12), 134.2 (s, C-1), 128.5 (d, C-3), 128.0 (s, C-16), 123.3 (d, C-11), 84.4 (d, C-2), 78.7 (t, C-17), 78.4 (s, C-8), 72.3 (d, C-7), 39.4 (t, C-9), 36.5 (t, C-13), 35.8 (t, C-5), 28.0 (t, C-6), 26.6 (q, C-19), 25.2 (t, C-10), 24.3 (t, C-14), 16.0 (q, C-20), 15.3 (q, C-18), 10.1 (q, C-15). (+)-**20**: a colorless oil; $[\alpha]_D^{30} = +106.5°$ (*c* 1.05, $CHCl_3$); HR-ESI-MS *m/z* 361.1937, 363.1893 (calcd for $C_{20}H_{31}O_2{}^{35}ClNa$, 361.1910, $C_{20}H_{31}O_2{}^{37}ClNa$, 363.1881); ^{1}H NMR (400 MHz, C_6D_6) δ 5.51–5.48 (overlap, 2H, H-2, 3), 5.25 (m, 1H, H-11), 4.64 (dd, 1H, *J* = 11.4, 3.9 Hz, H-17), 4.45 (d, 1H, *J* = 11.7 Hz, H-17), 3.94 (dd, 1H, *J* = 9.5, 1.7 Hz, H-7), 2.33–2.26 (overlap, 3H, H-5, 6, 10), 2.16–2.12 (overlap, 2H, H-5, 13), 2.07–2.02 (overlap, 5H, H-9, 10, 13, 14, 14), 1.76 (m, 1H, H-6), 1.74 (overlap, 4H, H-18, OH), 1.61 (t, 1H, *J* = 10.7 Hz, H-9), 1.54 (s, 3H, H-20), 1.43 (s, 3H, H-15), 1.26 (s, 3H, H-19); ^{13}C NMR (75 MHz, C_6D_6) δ 137.9 (s, C-4), 136.9 (s, C-12), 134.2 (s, C-1), 129.1 (s, C-16), 125.7 (d, C-3), 124.9 (d, C-11), 85.5 (d, C-2), 78.4 (t, C-17), 75.8 (s, C-8), 66.9 (d, C-7), 38.5 (t, C-9), 38.0 (t, C-13), 35.6 (t, C-5), 30.4 (t, C-6), 23.9 (q, C-19), 23.6 (t, C-10), 23.4 (t, C-14), 18.1 (q, C-18), 16.0 (q, C-20), 10.4 (q, C-15).

Conversion of (+)-19 to (+)-1. To a solution of (+)-**19** (2.6 mg, 0.01 mmol) in MeOH (300 µL) was added K_2CO_3 (41.5 mg, 0.3 mmol) and the mixture was allowed to stand at room temperature overnight. The crude product was applied to silica gel column chromatography eluted with CH_2Cl_2 to give (+)-**1** (2.8 mg, 0.01 mmol).

Conversion of (+)-20 to (+)-1. To a solution of (+)-**20** (1.0 mg, 0.003 mmol) in MeOH (60 µL) was added K_2CO_3 (22.3 mg, 0.16 mmol) and the mixture was allowed to stand overnight. The crude product was applied to silica gel column chromatography eluted with CH_2Cl_2 to give (+)-**1** (1.0 mg, 0.003 mmol).

Conversion of (+)-19 to (+)-4. A solution of (+)-**19** (3.0 mg, 0.01 mmol) in CD_3OD/D_2O (2:1, 0.6 mL) was allowed to stand for 22 h at room temperature. The ^{1}H NMR spectrum of the product mainly consisted of the signals due to (+)-**4**. The yield of (+)-**4** was deduced to be >70% by integration of the signals in the ^{1}H NMR spectrum.

Hydrobromic Acid Treatment of (+)-1. A solution of (+)-**1** (30 mg, 0.1 mmol) in THF (3 mL) was treated with 48% hydrobromic acid (108 µL) for 10 min at room temperature. The reaction mixture was added to a saturated $NaHCO_3$ solution (1.5 mL), and the mixture was extracted with ether (3 × 2 mL). The combined ether layer was washed with water (3 mL), brine (3 mL), and dried over Na_2SO_4. After concentration, the residue (45 mg) was separated by recycle-HPLC (flow rate 10 mL min^{-1}) with hexane–isopropyl alcohol = 93:7. (+)-**21** (25.3 mg, 0.07 mmol) was eluted at *Rt* = 47 min (three cycles) and (+)-**22** (4.9 mg, 0.01 mmol) at *Rt* = 126 min (9 cycles). (+)-**21**: a colorless oil; $[\alpha]_D^{31} = +105.2°$ (*c* 0.42, $CHCl_3$); HR-ESI-MS *m/z*

405.1388, 407.1385 (calcd for $C_{20}H_{31}O_2{}^{79}BrNa$, 405.1405, $C_{20}H_{31}O_2{}^{81}BrNa$, 407.1385); ^{1}H NMR (400 MHz, C_6D_6) δ 5.69 (m, 1H, H-2), 5.40 (d, 1H, $J = 10.1$ Hz, H-3), 5.00 (t, 1H, $J = 6.8$ Hz, H-11), 4.58 (m, 2H, H-17), 3.57 (t, 1H, $J = 9.8$ Hz, H-7), 2.33 (m, 1H, H-5), 2.26–2.23 (overlap, 3H, H-9, 10, 14), 2.11 (m, 1H, H-10), 2.02 (m, 1H, H-6), 1.96–1.85 (overlap, 4H, H-5, 9, 13, 13), 1.82 (m, 1H, H-14), 1.71 (s, 3H, H-19), 1.64 (s, 3H, H-18), 1.50 (s, 3H, H-20) 1.41 (s, 3H, H-15), 1.35 (m, 1H, H-6), 0.95 (m, 1H, OH); ^{13}C NMR (75 MHz, C_6D_6) δ 137.4 (s, C-4), 135.9 (s, C-12), 134.1 (s, C-1), 128.5 (d, C-3), 128.1 (s, C-16), 123.1 (d, C-11), 84.4 (d, C-2), 79.1 (s, C-8), 78.7 (t, C-17), 72.8 (d, C-7), 40.6 (t, C-9), 36.6 (t, C-13), 35.9 (t, C-5), 29.5 (t, C-6), 28.1 (q, C-19), 26.4 (t, C-10), 24.3 (t, C-14), 15.9 (q, C-20), 15.4 (q, C-18), 10.1 (q, C-15). The chemical shifts of C-3 and C-16 (overlapped with C_6D_6 signals) were determined by HMBC. (+)-**22**: a colorless oil; $[\alpha]_D^{29} = +78.6^\circ$ (c 0.10, $CHCl_3$); HR-ESI-MS m/z 405.1407, 407.1396 (calcd for $C_{20}H_{31}O_2{}^{79}BrNa$, 405.1405, $C_{20}H_{31}O_2{}^{81}BrNa$, 407.1385); ^{1}H NMR (400 MHz, C_6D_6) δ 5.50 (overlap, 2H, H-2, 3), 5.26 (m, 1H, H-11), 4.64 (d, 1H, $J =$ 10.8 Hz, H-17), 4.43 (d, 1H, $J = 11.6$ Hz, H-17), 4.01 (dd, 1H, $J = 10.6$, 2.4 Hz, H-7), 2.43–2.41 (overlap, 2H, H-6, 10), 2.25 (m, 1H, H-5), 2.17–2.11 (overlap, 3H, H-5, 9, 13), 2.03–2.01 (overlap, 4H, H-10, 13, 14, 14), 1.87 (dddd, 1H, $J = 19.1$, 9.8, 6.4, 2.9 Hz, H-6), 1.80 (s, 1H, OH), 1.71 (s, 3H, H-18), 1.66 (ddd, 1H, $J = 14.9$, 10.9, 3.9 Hz, H-9), 1.54 (s, 3H, H-20), 1.41 (s, 3H, H-15), 1.32 (s, 3H, H-19); ^{13}C NMR (100 MHz, C_6D_6) δ 137.5 (s, C-12), 137.3 (s, C-4), 134.1 (s, C-1), 129.4 (s, C-16), 127.8 (d, C-3), 124.9 (d, C-11), 85.5 (d, C-2), 78.4 (t, C-17), 75.8 (s, C-8), 62.3 (d, C-7), 39.2 (t, C-9), 38.1 (t, C-13), 36.0 (t, C-5), 30.9 (t, C-6), 24.5 (q, C-19), 23.7 (t, C-10), 23.3 (t, C-14), 18.2 (q, C-18), 16.0 (q, C-20), 10.4 (q, C-15).

Conversion of (+)-21 to (+)-4. A solution of (+)-**21** (1.8 mg, 0.005 mmol) in CD_3OD/D_2O (2:1, 0.36 mL) was allowed to stand for 1 h at room temperature. The ^{1}H NMR spectrum of the product showed exclusively the signals of (+)-**4**. The yield of (+)-**4** was deduced to be >80% from the integration of the ^{1}H NMR signals.

Professor Keisuke Suzuki (Graduate School of Science and Engineering, Tokyo Institute of Technology) is gratefully acknowledged for giving us a suggestion about Curtin–Hammett principle.

Supporting Information

^{1}H NMR and ^{13}C NMR data for all new compounds, CD spectra of (+)-**5**, (−)-**5**, and the benzoyl ester of (+)-**25**, and crystal structures of (+)-**3**, (−)-**5**, **12b**, and **18**. This material is available free of charge on the web at: http://www.csj.jp/journals/bcsj/.

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