Chemical Simulation of Polycyclic Diterpenoid Biosynthesis Using Mercury(II) Triflate/*N*,*N*-Dimethylaniline Complex: Mechanistic Aspects of a Biomimetic Olefin Cyclization

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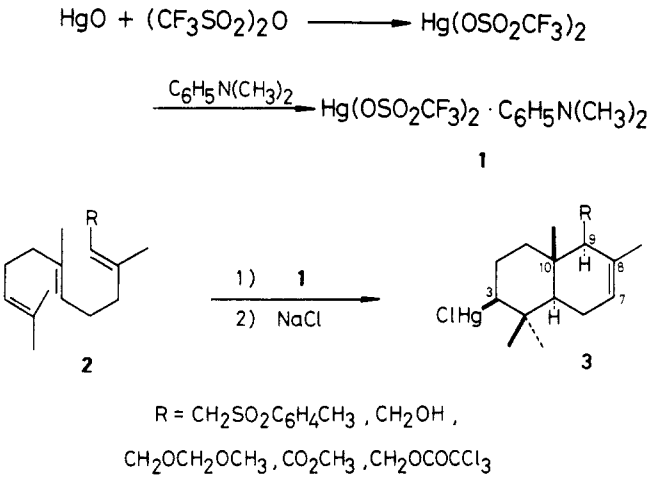
A new effective olefin cyclization reagent, mercury(II) triflate/*N*,*N*-dimethylaniline complex (**1**), has been developed. By use of **1**, (*E*,*E*,*E*)-geranylgeranyl *p*-nitrobenzoate (**4a**) has been efficiently cyclized to give spongian (**5**) and labdane (**6** and **7**) type products. When acetate **4b** is employed as the substrate, a unique hydroxylative cyclization takes place, affording C-13 hydroxylated products **14** and its stereoisomers. One of the stereoisomers is derived to **17**, which is identified with a marine natural diterpenoid, isoaplysin-20, and the reported formula is corrected. On the cyclization of **4b** with **1** in the presence of water (or methanol), intermediates in each stage can be trapped to give mono-, bi-, and tricyclic tertiary alcohols **19ab**, **20ab**, and **14**. The structures of bicyclic alcohols **20a** and **20b** have been definitely established by completion of the total synthesis of (±)-(13*E*)-13-labdene-8,15-diol (**21**) and (±)-aplysin-20 (**22b**), respectively. These results provide clear experimental evidence on the mechanism of a biomimetic olefin cyclization which takes place in a *stepwise* manner via conformationally *flexible* cationic intermediates such as **27**, **28** and **29**.

Introduction

A variety of terpenoids are enzymatically synthesized by cyclization of polyprenoids such as farnesol, geranylgeraniol, and squalene in biological systems.[1] The chemical simulation of this elegant biosynthetic process has been developed as an important methodology in organic synthesis.[2] van Tamelen's approach induced by the oxirane ring opening[3a] and Johnson's approach via the acid catalyzed cyclization of polyenic acetals[3b] must be the most important contribution to this field. Alternative approaches to the biomimetic olefin cyclization are the treatment of polyprenoids with a variety of electrophiles such as proton,[4] bromonium ion,[5] acyl cation,[6] Lewis acid,[7] or mercuric salt.[8] Among these electrophiles, mercuric salt is the most versatile reagent[9] because a mercury group introduced at the initiated position of the cyclization is easily transformed into various functionalities (hydrogen,[10] hydroxy,[11] halogen,[12] etc.). Mercury(II) trifluoroacetate has usually been employed for this purpose.[9] However, there are some limitations, namely poor selectivity and lack of general applicability.

Scheme I



We have planned to develop an efficient olefin cyclization reagent and discovered that a nitromethane solution of a tertiary amine complex of mercury(II) trifluoromethanesulfonate (hereafter triflate) shows a remarkable improvement for an olefin cyclization.[9] Described herein are the preparation of this new reagent and its application to the chemical simulation of polycyclic diterpenoid biosynthesis. In the presence of nucleophiles, such as water or methanol, the cyclization could be interrupted at each cyclization stage and mono-, bi-, and tricyclic tertiary alcohols have been competitively produced. According to these results, we propose an adequate mechanism for this

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(2) (a) Lynen, F.; Henning, U. *Angew. Chem.* **1960**, *72*, 820. (b) Ruzicka, L. *Proc. Chem. Soc. London* **1959**, 341. (c) Tchen, T. T.; Bloch, K. *J. Am. Chem. Soc.* **1955**, *77*, 6085. (d) Goldsmith, D. *Prog. Chem. Org. Nat. Prod.* **1971**, *29*, 363.

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(9) When (*E*,*E*)-farnesyl *p*-tolyl sulfone was treated with mercury(II) trifluoroacetate in nitromethane at −20 °C for 2 h, **3** was isolated in 30% yield along with a variety of products, whereas the same compound was obtained in 74% yield by using **1**. See ref 13.

(10) Hoye, T. R.; Caruso, A. J.; Kurth, M. J. *J. Org. Chem.* **1981**, *46*, 3550.

(11) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

(12) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.

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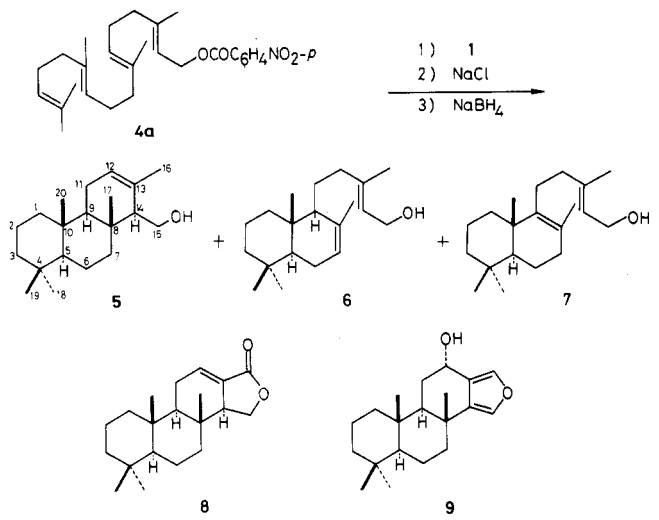
Scheme II



biomimetic olefin cyclization which proceeds in a *stepwise* manner via conformationally *flexible* cationic intermediates.

Development of Mercury(II) Triflate/*N*,*N*-Dimethylaniline Complex

Mercury(II) triflate was prepared from yellow mercuric oxide and an equimolar amount of triflic anhydride in nitromethane (Scheme I). A resulting white suspension was not effective for the olefin cyclization, probably due to some side reaction by the liberated trifluoromethanesulfonic acid. Addition of 1 equiv of amine was expected to quench the liberated super acid. When a variety of tertiary amines was added, the white suspension of mercuric triflate turned into a pale yellow clear solution instantaneously, in which the mercury(II) triflate/amine complex was formed. This new reagent, prepared in situ, showed remarkable efficiency for the olefin cyclization as described below. (*E*,*E*)-Farnesol derivatives **2** were first attempted for cyclization. Bicyclic products **3** with A/B trans, $\Delta^{7,8}$, 9/10 cis decaline systems were obtained in 50 to 75% yield with satisfactory high selectivity (Scheme I). Although a variety of tertiary amines such as diisopropylethylamine and 2,6-di-*tert*-butylpyridine are similarly applicable for preparation of the reagent, we have mainly employed *N*,*N*-dimethylaniline complex **1** because of its better selectivity.[13] Secondary and primary amines afforded less satisfactory results. Synthetic application of farnesol derivatives[14] will be detailed elsewhere.

Cyclization of (*E*,*E*,*E*)-Geranylgeranyl *p*-Nitrobenzoate

Our first expectation for the cyclization of geranylgeraniol derivatives was the simultaneous one-step formation of three-ring systems analogous to decalin formation from farnesol derivatives. In contrast to a great many reports with farnesol derivatives, only a few works have been recorded about the geranylgeraniol cyclization.[15] This may be due to increased difficulty in control of the reaction course.

We examined the cyclization of (*E*,*E*,*E*)-geranylgeranyl *p*-nitrobenzoate (**4a**) with the reagent **1** at −20 °C in nitromethane. After successive treatment of the reaction mixture with aqueous sodium chloride and sodium borohydride, three kinds of cyclization products were isolated and characterized (Scheme II).[16] A tricyclic product **5** (22% yield) was identified with the authentic material which had been reported to be an intermediate toward the total synthesis of spongian diterpenoids such as isoagatholactone (**8**) and 12α-hydroxyspongia-13(16),14-diene (**9**) by Nakano.[17] Thus, the stereoselective one-step formation of the three-ring system was realized in a moderate yield. Two kinds of byproducts **6** and **7** were also isolated in 9% and 19% yield, respectively. Both of these products were identified with labdane diterpenoids isolated from *Nicotiana setchelli*.[18] Thus, the simulation of the biosynthesis of spongian and labdane diterpenoids was easily accomplished under our conditions.

Cyclization of (*E*,*E*,*E*)-Geranylgeranyl Acetate: Synthesis and Structure Determination of (±)-Isoaplysin-20

When (*E*,*E*)-farnesyl acetate (**2**, R = CH_2OAc) was used as the starting material, we have found that the cyclization proceeds in a somewhat different manner. A tertiary alcohol **11** was obtained as the major product in 45% yield along with 20% of **3** (R = CH_2OAc) (Scheme III).[19] The formation of **11** is recognized by the intramolecular participation of the carbonyl group which stabilizes the resulting tertiary cation as shown in **10**. As expected from the electronic reason, trichloroacetate **2** (R = $CH_2OCOCCl_3$) did not give any carbinol products. Thus, we developed an efficient procedure for the stereospecific introduction of a hydroxyl group to the C-8 position of the decalin skeleton.[13]

If an analogous cyclization takes place with (*E*,*E*,*E*)-geranylgeranyl acetate (**4b**), the total synthesis of a bromine-containing tricyclic diterpenoid, (±)-isoaplysin-20 (reported as structure **16**),[20,21] would be accomplished in only two steps. Therefore, we tried the reaction of **4b** with **1** under the same conditions as described above. By the treatment of the reaction mixture with aqueous KBr solution, two kinds of products **13** and **14** were easily isolated by column chromatography, followed by recrystallizations, in 16% and 17% yield, respectively (Scheme IV). The structures of these products were confirmed by the chemical transformation to known demercuration products **5**[16] and **15**, respectively. The latter was identified with so-called debromoisoaplysin-20 reported by Rüveda.[21] Therefore, the compound **14** appeared to have the corresponding stereochemistry for (±)-isoaplysin-20. The bromination of **14** was simply achieved by applying the Hoye's procedure ($LiBr/Br_2$/Pyridine/O_2).[12] The stereochemistry at the C-3 bromine of the product **16a** was clearly shown to be β-equatorial on the basis of the ^1H NMR data of the C-3 proton (δ 3.94, dd, J = 12 and 6 Hz). However, the whole spectrum of **16a** was not identical with that of the natural isoaplysin-20 acetate. Thus, we concluded that the structure of isoaplysin-20 is not **16**, which

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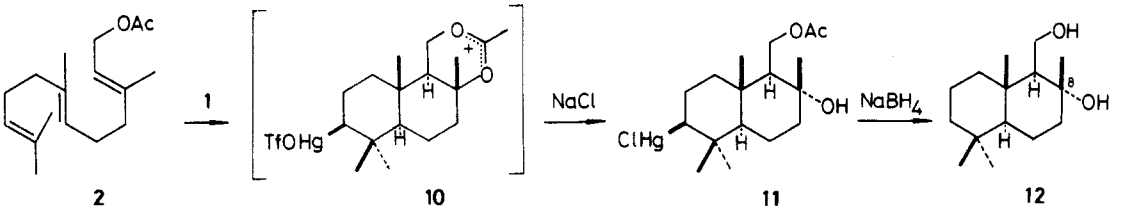
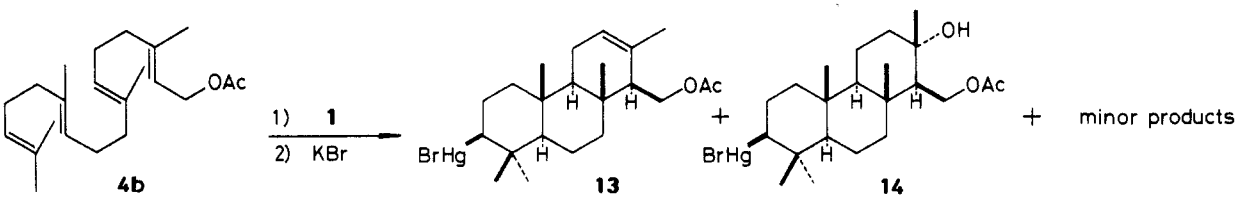
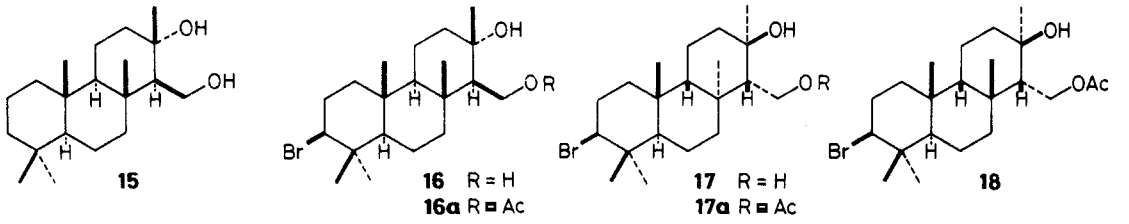
(21) Imamura, P. M.; Rüveda, E. A. *J. Org. Chem.* **1980**, *45*, 510.

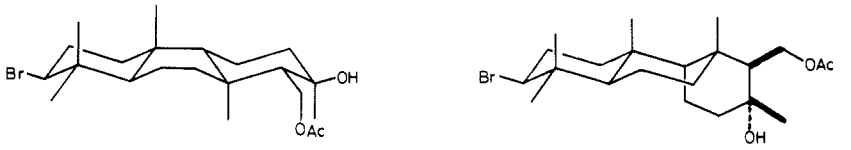
Scheme III

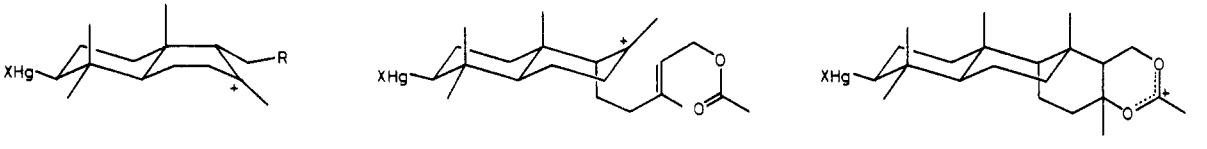


Scheme IV









has been proposed by Yamamura[20] and Rūveda.[21]

The cyclization of **4b** was not entirely stereospecific, and the contamination with some minor stereoisomeric products was detected in the recrystallization mother liquor of **14**. This mixture was subjected to the bromination as mentioned above and exhaustive purification by HPLC. Two kinds of tricyclic compounds **17a** (mp 178 °C, 1.8% yield from **4b**) and **18** (mp 147 °C, 1.6% yield from **4b**) were isolated as crystals. The structures of these minor tricyclic products were established by the single-crystal X-ray diffraction studies to be **17c** and **18c**.[22,24] The ^{1}H NMR spectrum of **17a** was entirely superimposable with that of the natural isoaplysin-20 acetate. Hydrolysis of **17a** afforded a diol **17**, which was also identified with natural isoaplysin-20. Thus, the correct structure of (±)-isoaplysin-20 was definitely established to be **17**.[22]

The perhydrophenanthrene skeleton of **17a**, confirmed by the X-ray analysis, involves an anti/syn/anti ring juncture which forces the ring system to take the chair/boat/chair conformation depicted in formula **17c**. Thus, the preparation of a perhydrophenanthrene derivative with a boat form B-ring was realized by means of a biomimetic olefin cyclization. It is particularly interesting to note that the enzymatic transformation of squalene oxide to lanosterol has been shown to take place via an analogous intermediate with the boat form B-ring.[23]

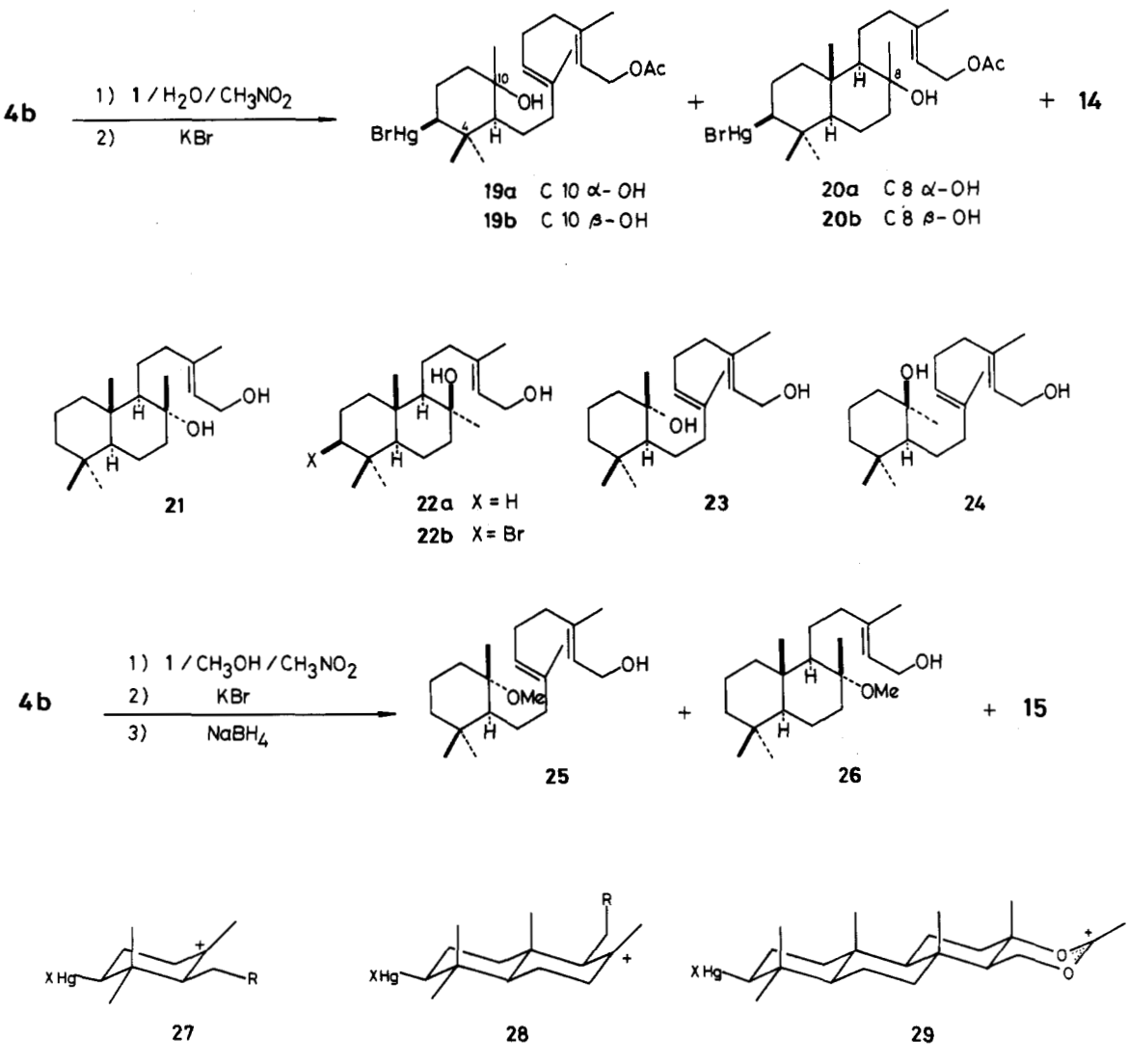
The structure of the other minor product **18** involves an unusual anti/syn/syn ring juncture which was also confirmed by the X-ray analysis.[24] The formation of this novel perhydrophenanthrene derivative is also very interesting from the mechanistic standpoint, which will be discussed in the next section.

(22) Nishizawa, M.; Takenaka, H.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4290.

(23) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225.

(24) The X-ray diffraction analysis was conducted by Dr. K. Hirotsu and Dr. T. Higuchi of the Department of Chemistry, Faculty of Science, Osaka City University. The experimental details will be reported elsewhere.

Scheme V



Cyclization of (*E*,*E*,*E*)-Geranylgeranyl Acetate in the Presence of Water and Mechanistic Discussion of This Biomimetic Olefin Cyclization

Little direct evidence has been obtained for deciding whether the cationic polyene cyclization proceeds by a *stepwise* or *synchronous* mechanism. The pioneering workers in this field have explained their stereospecific results by a synchronous reaction.[4] According to Johnson, the balance of the evidence is somewhat in favor of a synchronous process.[3b,25] van Tamelen and Sharpless have indicated a stepwise mechanism which involves a series of conformationally rigid cationic intermediates.[26] On the theoretical point of view, Dewar recently reported the existence of an intermediate, olefin–carbenium ion π-complex, based on the MINDO/3 calculation.[27a] In 1974, Gleiter also discussed the mechanism of olefin cyclization on the theoretical basis (CNDO/2 and INDO) to be a nonconcerted reaction.[27b]

We have found that our cyclization reagent **1** is stable but still reactive enough in the presence of water. When the cyclization of (*E*,*E*,*E*)-geranylgeranyl acetate (**4b**) with **1** was conducted in nitromethane at −20 °C in the presence of water (12 equiv), five kinds of tertiary alcohols **19a**, **19b**, **20a**, **20b**, and **14** were isolated in 4.9%, 0.8%, 9.0%, 2.9%, and 8.8% yields, respectively, along with 40% recovery of the starting material (Scheme V) after the treatment with aqueous KBr solution.[28] The tricyclic product **14** was the same compound with that obtained by the cyclization under anhydrous conditions. The structure of the bicyclic product **20a** was established by the conversion to (±)-(13*E*)-13-labdene-8,15-diol (**21**), a diterpenoid isolated from *Nicotiana tabaccum*,[29] by means of the demercuration with sodium borohydride.[10] The structure of **20b** was confirmed by the completion of the total synthesis of (±)-aplysin-20 (**22b**), a marine diterpenoid from *Aplysia kurodai*,[30,31] using Hoye's bromination.[12] The structures of monocyclic products **19a** and **19b** were determined by the spectral analyses especially the ^{13}C NMR spectra of both compounds and their demercuration products **23** and **24** (Figure 1).[32]

(25) Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501. Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *Ibid.* **1977**, *99*, 8341.

(26) (a) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950. van Tamelen, E. E.; *Ibid.* **1982**, *104*, 6480. (b) Sharpless, K. B. Ph.D. Thesis, Stanford University, July 1968.

(27) (a) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744. (b) Gleiter, R.; Müllen, K. *Helv. Chim. Acta* **1974**, *57*, 823.

(28) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522.

(29) Wahlberg, I.; Wallin, I.; Nordfors, K.; Nishida, T.; Enzell, C. R.; Reid, W. W. *Acta Chem. Scand.* **1979**, *B33*, 541.

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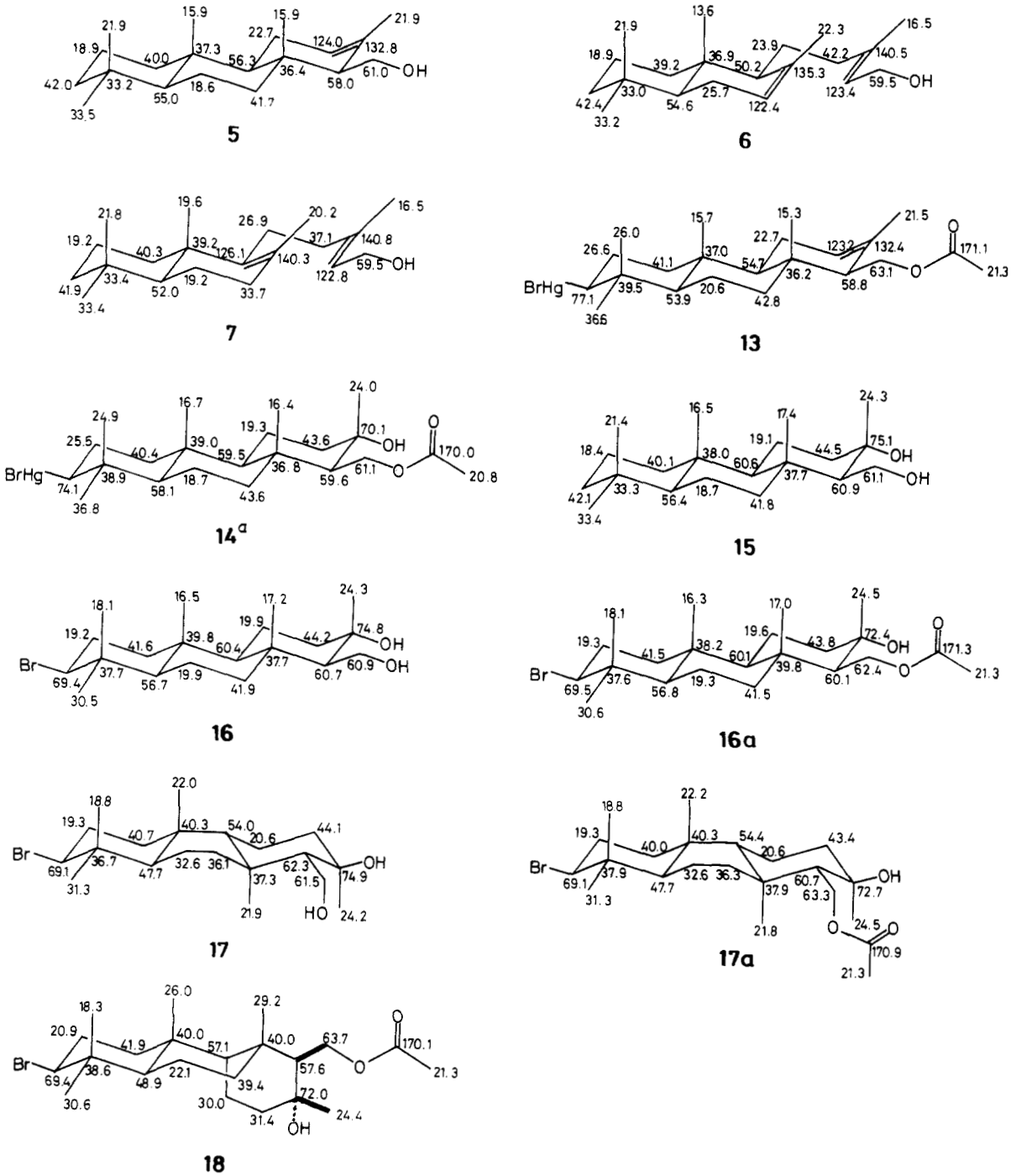


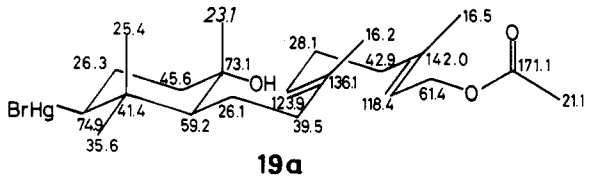
Figure 1. ^{13}C NMR Chemical Shifts (δ in $CDCl_3$, [a] in Me_2SO-d_6).

The cyclization of **4b** in the presence of 1.2 equiv of water also afforded mono-, bi-, and tricyclic alcohols **19ab**, **20ab**, and **14**, but the ratio was changed to 1.3:5.4:11.2 (5.7:11.9:8.8 for 12 equiv of water; the numbers represent the isolated yields of each ring system products). Addition of methanol (12 equiv), instead of water, was also effective for trapping the cationic intermediates to give the corresponding α-methoxylated products **25** and **26**[32] in 7.8% and 12.7% yield, respectively, along with 4.6% of **15**. Interestingly, β-methoxylated products were not detected in the latter case. However, in every experiment throughout this study, there was not detected the formation of any oxymercuration products without forming rings.[33]

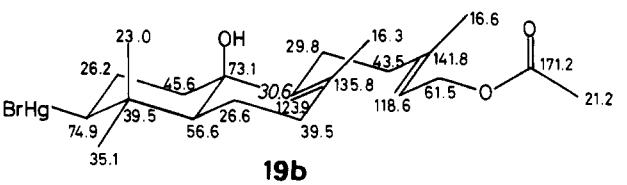
The result obtained by the cyclization of (*E*,*E*,*E*)-geranylgeranyl acetate in the presence of a nucleophile (water or methanol) clearly showed the existence of cationic intermediates such as **27**, **28**, and **29** (Scheme V). These intermediates should maintain sufficient stability via solvation to be slowly converted to each hydroxylated or methoxylated product in competition with the subsequent ring closure. Important are the predominant formation of α-equatorial alcohols (**19a**:**19b** = 6:1, **20a**:**20b** = 3:1) and the exclusive formation of α-methoxylated products **25** and **26**. If the conformation of the alkyl side chain of the

(32) The β-axial methyl groups at C-10 (for **19a**, **23**, **25**) and C-8 (for **20a**, **21**, **26**) gave signals at δ 23.1, 23.2, 20.0, 23.9, 24.1, and 19.8, respectively, whereas the corresponding α-equatorial methyl signals of **19b**, **24**, **20b**, **22a**, and **22b** appeared were at δ 30.6, 30.7, 30.8, 30.7, and 30.7, respectively. See Figure 1.

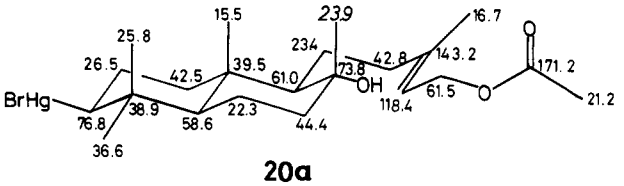
(33) van Tamelen has described that the first step of his biomimetic olefin cyclization, the oxirane ring opening, should be concerted by the olefinic π-bond participation (ref 26). See also: Bartlett, P. A. In "Asymmetric Synthesis"; Morrison, J. E., Ed.; Academic Press: New York, 1984; Vol 3, 341.



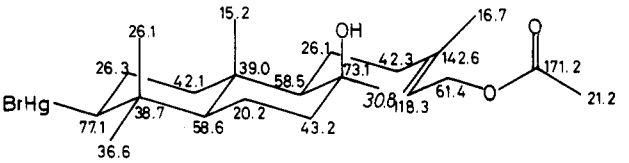
19a



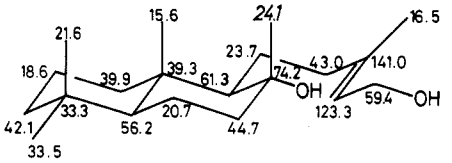
19b



20a



20b



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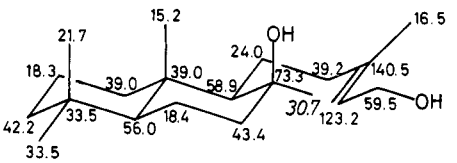

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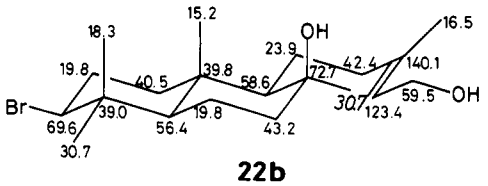

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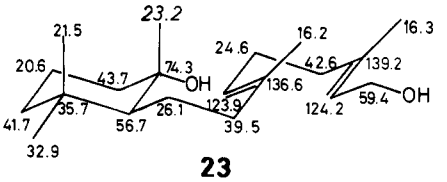

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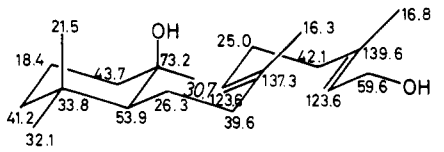
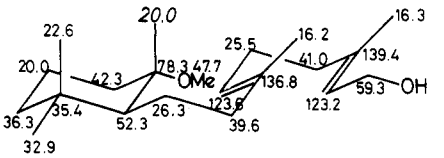


24



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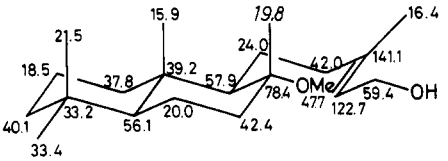
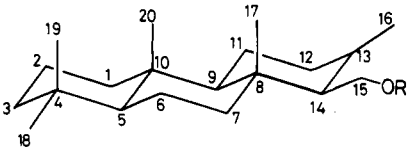


26



numbering of spongian skeleton

cationic intermediates is fixed via π-complexation with the next olefinic bond as stated by van Tamelen[26] or Dewar,[27] the α-side of the cation should be entirely shielded and the nucleophile should attack from the β side predominantly. Thus, the conformation of the polyenyl side chain should be flexible.

On the cyclization of **4b** without any nucleophiles (Scheme IV), a tricyclic byproduct **18** with an unusual anti/syn/syn perhydrophenanthrene skeleton (**18c**) was obtained as mentioned above. Formation of **18** from (*E,E,E*)-geranylgeranyl acetate is rationally explained as follows. After the formation of a chair/boat bicyclic cation **A**, the B-ring will flip to a stable chair conformer to form a chair/chair cation **B**, which undergoes an intramolecular α-face attack by the next olefinic π-orbital to give a cation **C** via the participation of the acetoxyl moiety. This result indicates that the conformation of the cationic intermediates is flexible not only in the side chain but also in the ring systems.

Thus, we propose that the biomimetic olefin cyclization under our conditions takes place by a *stepwise* mechanism through the conformationally *flexible* cationic intermediates.

Experimental Section

General Procedures. Infrared spectra (IR) were recorded on a JASCO A-100 infrared photometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 100 MHz on a JEOL FX-100 or a JEOL PS-100 spectrometer. ^{13}C NMR spectra were determined at 25 MHz on a JEOL FX-100 spectrometer. The chemical shifts were presented in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were taken at an ionization voltage of 30 eV on a JEOL JMS D-300 spectrometer. High-performance liquid chromatography (HPLC) was performed

on a JASCO TRI ROTOR-II instrument equipped with an ALTEX RI detector using a Develosil-ODS column or Develosil C-30-3 column. Analytical thin layer chromatography (TLC) was done on Merck silica gel 60 F_{254} precoated plates. Fuji-Devison BW-820 MH silica gel was employed for column chromatography.

(*E,E,E*)-Geranylgeraniol was supplied from Kuraray Co. Ltd., and triflic anhydride was obtained from Aldrich Chemical Co.. Yellow mercuric oxide was dried in vacuo over phosphorus pentoxide. Nitromethane, *N,N*-dimethylaniline, and pyridine were distilled over calcium hydride, and other solvents and liquid reagents were distilled before use.

Cyclization of (*E,E,E*)-Geranylgeranyl *p*-Nitrobenzoate (4a). Triflic anhydride (130 mg, 0.462 mmol) was added to a suspension of yellow mercuric oxide (100 mg, 0.462 mmol) in nitromethane (10 mL), and the mixture was stirred at room temperature for 2 h. To the resulting white suspension of mercury(II) triflate was added *N,N*-dimethylaniline (56 mg, 0.462 mmol) to give complex 1 as a pale yellow solution in nitromethane, which was cooled to −20 °C. To this was added a solution of **4a** (169 mg, 0.385 mmol) in nitromethane (2 mL) and the mixture was stirred at the same temperature for 2 h. After the addition of saturated sodium chloride solution, the heterogeneous solution was warmed to room temperature and stirred for an additional 3 h. The precipitated material was removed by filtration through a cotton–Celite pad, and the filtrate was extracted wth dichloromethane. Column chromatography of the concentrated extracts on silica gel (30 g) with hexane and ethyl acetate (10:1) afforded a mixture of oragnomercuric products (170 mg) as a syrup. A solution of sodium borohydride (96 mg, 2.52 mmol) and sodium hydroxide (100 mg, 5.05 mmol) in water (0.4 mL) was added to the solution of above organomercuric products (170 mg) in dichloromethane (5 mL) and ethanol (5 mL), and the mixture was stirred at room temperature for 30 min. After removal of the precipitated inorganic materials through a cotton–Celite pad, the filtrate was diluted with brine and extracted with dichloromethane. Column chromatography of the concentrated extracts on silica gel (20 g) using a 10:1 mixture of hexane and ethyl acetate afforded the tricyclic product **5** as a colorless syrup (24 mg, 22% yield) [IR ($CHCl_3$) 3630, 3450 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.82 (3 H, s), 0.83 (3 H, s), 0.86 (3 H, s) 0.89 (3 H, s), 1.78 (3 H, s), 3.76 (2 H, m), 5.48 (1 H, br); high-resolution mass spectrum, 290.2624 (M^+), calcd for $C_{20}H_{34}O$ 290.2609] and a mixture of bicyclic products (31 mg). The former was fully identified with authentic material supplied by Nakano.[17] The latter mixture was purified by using HPLC with Develosil ODS column and a 6:1 mixture of acetonitrile and water to give **6** (8 mg, 9% yield) [IR ($CHCl_3$) 3630, 3450, 1660 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.76 (3 H, s), 0.84 (3 H, s), 0.87 (3 H, s), 1.72 (6 H, s), 4.13 (2 H, d, J = 7 Hz), 5.45 (2 H, br); high-resolution mass spectrum, 272.2489 ($M^+ - H_2O$), calcd for $C_{20}H_{32}$ 272.2502] and **7** (18 mg, 19% yield) [IR ($CHCl_3$) 3630, 3450, 1680 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.83 (3 H, s), 0.88 (3 H, s), 0.93 (3 H, s), 1.56 (3 H, s), 1.69 (3 H, s), 4.12 (2 H, d, J = 7 Hz), 5.39 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 290.2621 (M^+), calcd for $C_{20}H_{34}O$ 290.2609] as colorless syrups. Both of these bicyclic products showed identical spectral properties with those of natural products, obtained from *Nicotiana setchelli*,[18] respectively.

Cyclization of (*E,E,E*)-Geranylgeranyl Acetate (4b). To a cooled (−20 °C) solution of mercury(II) triflate/*N,N*-dimethylaniline complex (**1**) prepared by mixing yellow mercuric oxide (3.91 g, 18.1 mmol), triflic anhydride (5.10 g, 18.1 mmol), and *N,N*-dimethylaniline (2.19 g, 18.1 mmol) in nitromethane (300 mL) was added a solution of **4b** (5.00 g, 15.1 mmol) in nitromethane (20 mL). The mixture was stirred at −20 °C for 2 h and then saturated potassium bromide solution (300 mL) was added. After stirring for an additional 3 h at room temperature, inorganic precipitates were removed by filtration. The filtrate was extracted with dichloromethane, and the concentrated crude product was chromatographed with silica gel (200 g) by using a mixture of hexane and ethyl acetate (20:1 to 1:1) to give **13** (1.54 g, 17% yield) and **14** (1.55 g, 16% yield). Recrystallizations from hexane and ethyl acetate afforded analytical samples. **13**: mp 188.5–190 °C; IR (KBr) 1750, 1240, 1040 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.95 (3 H, s), 1.05 (3 H, s), 1.08 (3 H, s), 1.27 (3 H, s), 1.67 (3 H, s), 2.04 (3 H, s), 2.80 (1 H, dd, J = 10, 4 Hz), 4.00 (1 H, dd, J = 10, 6 Hz), 4.22 (1 H, dd, J = 10, 4 Hz), 5.40 (1 H, br). Anal. Calcd for $C_{22}H_{35}O_2HgBr$: C, 43.18, H, 5.76. Found: C, 43.55, H, 5.83. **14**: mp 222–223 °C; IR (KBr) 3550, 3450, 1720, 1260, 1040 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.86 (6 H, s), 1.03 (3 H, s), 1.06 (3 H, s), 1.16 (3 H, s), 2.04 (3 H, s), 2.81 (1 H, dd, J = 12, 4 Hz), 4.27 (2 H, dd, J = 6, 3 Hz). Anal. Calcd for $C_{22}H_{37}O_3HgBr$: C, 41.94; H, 5.92. Found: C, 42.29; H, 5.94.

(±)-Spongia-13α,15-diol (15). A solution of sodium borohydride (25 mg, 0.65 mmol) and sodium hydroxide (52 mg, 1.32 mmol) in water (0.2 mL) was added to a solution of **14** (41 mg, 0.064 mmol) in dichloromethane (1.5 mL) and ethanol (1.5 mL). The mixture was stirred at room temperature for 30 min, and the resulting precipitate was removed by filtration. The filtrate was diluted with brine and extracted with dichloromethane. Column chromatography of the extracts on silica gel (14 g) with a 3:1 mixture of hexane and ethyl acetate gave diol **15** (16 mg, 80% yield). Recrystallization from hexane and ether gave colorless needles: mp 194.5–195 °C; IR ($CHCl_3$) 3600, 3360, 1140, 1020 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.82 (9 H, s), 0.87 (3 H, s), 1.35 (3 H, s), 3.87 (2 H, d, J = 6 Hz); high-resolution mass spectrum, 290.2623 ($M^+ - H_2O$), calcd for $C_{20}H_{34}O$ 290.2609. These spectral properties were identical with those reported.[21]

(±)-3β-Bromo-15-acetoxyspongia-13α-ol (16a). The organomercuric compound **14** (1.15 g, 1.83 mmol) was dissolved in pyridine (10 mL) and the solution was saturated with oxygen. A solution of bromine (786 mg, 4.91 mmol) and lithium bromide (855 mg, 9.83 mmol) in dry pyridine (10 mL) also saturated with oxygen was added, and the mixture was stirred in the dark for 20 h under oxygen atmosphere. The solution was diluted with 1 N hydrochloric acid and extracted with dichloromethane. The organic phase was washed with sodium hydrogen carbonate solution. The concentrated extract was subjected to column chromatography on silica gel (50 g) with a 5:1 mixture of hexane and ethyl acetate to give **16a** (505 mg, 64% yield) as a colorless syrup. Recrystallization from hexane and ether afforded an analytical sample: mp 166.5–167 °C; IR ($CHCl_3$) 3600, 3450, 1730, 1250, 1160, 1035, 880 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.86 (6 H, s), 0.94 (3 H, s), 1.05 (3 H, s), 1.16 (3 H, s), 2.03 (3 H, s), 3.94 (1 H, dd, J = 12, 4 Hz), 4.18 (1 H, dd, J = 12, 4 Hz), 4.32 (1 H, dd, J = 12, 4 Hz). Anal. Calcd for $C_{22}H_{37}O_3Br$: C, 61.53; H, 8.68. Found: C, 61.48; H, 8.69.

(±)-Isoaplysin-20 Acetate (17a). The concentrated mother liquid of the crystallization of **14** (280 mg) was brominated as described above, and the crude product was subjected to HPLC purification (Develosil ODS column with a 7:3 mixture of acetonitrile and water) to give **16a** (116 mg) and the mixture of minor products (75 mg). The latter was further purified by using a Develosil C-30-3 column with a 3:1 mixture of hexane and ethyl acetate to give (±)-isoaplysin-20 acetate (**17a**) (18 mg, 1.8% yield from **4b**) [mp 178 °C; IR ($CHCl_3$) 3600, 3400, 1730, 1275, 1160, 880 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.92 (3 H, s), 0.97 (3 H, s), 1.03 (6 H, s), 1.20 (3 H, s), 2.01 (3 H, s), 3.90 (1 H, dd, J = 10, 6 Hz), 4.16 (1 H, dd, J = 12, 6 Hz), 4.31 (1 H, dd, J = 12, 4 Hz); mass spectrum, m/z 370, 368, 355, 353, 312, 310, 289. Anal. Calcd for $C_{22}H_{37}O_3Br$: C, 61.53; H, 8.68. Found: C, 61.46; H, 8.73.] and **18** (13 mg, 1.6% yield from **4b**) [mp 147 °C; IR ($CHCl_3$) 3600, 3440, 1730, 1235, 1028 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.94 (3 H, s), 1.05 (3 H, s), 1.24 (3 H, s), 1.27 (6 H, s), 2.06 (3 H, s), 3.91 (1 H, dd, J = 11, 5 Hz), 4.20 (1 H, dd, J = 12, 6 Hz), 4.39 (1 H, dd, J = 12, 5 Hz); mass spectrum, m/z 370, 368, 355, 353, 352, 350. Anal. Calcd for $C_{22}H_{37}O_3Br$: C, 61.53; H, 8.68. Found: C, 61.37; H, 8.61.].

(±)-Isoaplysin-20 (17). A solution of **17a** (6 mg, 0.014 mmol) and sodium hydroxide (5.5 mg, 0.138 mmol) in ethanol (1.0 mL) was stirred at 0 °C for 10 min and then diluted with brine. The mixture was extracted with dichloromethane, and the organic extract was washed with 1 N hydrochloric acid. Column chromatography of the concentrated extract on silica gel (2 g) using a 1:1 mixture of hexane and ethyl acetate afforded diol **17** (5.3 mg, 100% yield): mp 162–163 °C; IR ($CHCl_3$) 3600, 1060, 1000, 915, 870 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.93 (3 H, s), 0.95 (3 H, s), 0.98 (3 H, s), 1.04 (3 H, s), 1.32 (3 H, s), 3.74–4.00 (3 H); mass spectrum, m/z 370, 368, 355, 353, 312, 310. Anal. Calcd for $C_{20}H_{35}O_2Br$: C, 62.01; H, 9.11. Found: C, 61.86; H, 9.18. These spectral data were identical with those of natural isoaplysin-20.[20]

Cyclization of (*E,E,E*)-Geranylgeranyl Acetate (4b) in the Presence of Water. To a solution of 1 prepared by mixing

yellow mercuric oxide (155 mg, 0.714 mmol), triflic anhydride (201 mg, 0.714 mmol), and *N,N*-dimethylaniline (86.5 mg, 0.714 mmol) in nitromethane (12 mL) was added water (129 mg, 7.14 mmol) and then was cooled to −20 °C. To this was added a solution of **4b** (200 mg, 0.595 mmol) in nitromethane (3 mL), and the mixture was stirred at the same temperature for 2 h. After the addition of saturated potassium bromide solution (15 mL), the mixture was warmed to room temperature and stirred for an additional 3 h. Insoluble inorganic precipitate was removed by filtration, and the filtrate was extracted with dichloromethane. The crude product was subjected to column chromatography on silica gel (30 g) using a mixture of hexane and ethyl acetate (20:1 to 1:1) to give recovery of **4b** (80 mg, 40%), **14** (33 mg, 8.8% yield), **19a** [18.4 mg, 4.9% yield; IR ($CHCl_3$) 3650, 3600, 3520, 1720, 1130, 1020, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 1.04 (3 H, s), 1.13 (3 H, s), 1.19 (3 H, s), 1.62 (3 H, s), 1.71 (3 H, s), 2.05 (3 H, s), 2.76 (1 H, m), 4.58 (2 H, d, J = 7 Hz), 5.11 (1 H, br), 5.35 (1 H, t, J = 7 Hz)], **19b** [3.0 mg, 0.8% yield; IR ($CHCl_3$) 3400, 1725, 1230, 1020 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 1.05 (3 H, s), 1.19 (3 H, s), 1.25 (3 H, s), 1.60 (3 H, s), 1.71 (3 H, s), 2.05 (3 H, s), 2.76 (1 H, br), 4.56 (2 H, d, J = 7 Hz), 5.08 (1 H, br), 5.32 (1 H, br)], **20a** [33.7 mg, 9.0% yield, mp 148–150 °C; IR ($CHCl_3$) 3600, 3450, 1730, 1240, 1120, 960, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.84 (3 H, s), 1.00 (3 H, s), 1.07 (3 H, s), 1.13 (3 H, s), 1.71 (3 H, s), 2.06 (3 H, s), 2.80 (1 H, dd, J = 12, 5 Hz), 4.58 (2 H, d, J = 7 Hz), 5.33 (1 H, t, J = 7 Hz).], and **20b** [10.9 mg, 2.9% yield, mp 243 °C; IR ($CHCl_3$) 3600, 3450, 1720, 1220, 1100, 1020, 960, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.96 (3 H, s), 1.00 (3 H, s), 1.03 (3 H, s), 1.10 (3 H, s), 1.67 (3 H, s), 2.01 (3 H, s), 2.76 (1 H, dd, J = 13, 6 Hz), 4.53 (2 H, d, J = 7 Hz)].

(±)-(13*E*)-13-Labdene-8α,15-diol (21). A solution of sodium borohydride (38 mg, 1.00 mmol) and sodium hydroxide (80 mg, 2.00 mmol) in water (0.1 mL) was added to a solution of mercuric compound **20a** (63 mg, 0.10 mmol) in dichloromethane (1 mL) and ethanol (1 mL), and the resulting mixture was stirred at room temperature for 30 min. After removal of the precipitates through a cotton-Celite pad, the filtrate was diluted with brine and extracted with dichloromethane. Column chromatography on silica gel (5 g) with a mixture of hexane and ethyl acetate (2:1) gave **21** (26 mg, 85% yield) as a colorless syrup: IR ($CHCl_3$) 3600, 3450, 1160, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.80 (6 H, s), 0.87 (3 H, s), 1.14 (3 H, s), 1.70 (3 H, s), 4.12 (2 H, d, J = 7 Hz), 5.42 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 290.2610 ($M^+ - H_2O$), calcd for $C_{20}H_{34}O$ 290.2609. These spectral properties are identical with those of the natural product.[29]

(±)-(13*E*)-13-Labdene-8β,15-diol (22a). According to the same procedure described above, **20b** (19 mg, 0.0302 mmol) was converted to **22a** (7.7 mg, 83% yield) as a colorless syrup: IR ($CDCl_3$) 3600, 3400, 1650, 980, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.82 (3 H, s), 0.87 (3 H, s), 0.96 (3 H, s), 1.14 (3 H, s), 1.69 (3 H, s), 4.12 (2 H, d, J = 7 Hz), 5.40 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 290.2602 ($M^+ - H_2O$), calcd for $C_{20}H_{34}O$ 290.2609.

Diol 23. According to the same procedure described above, **19a** (58 mg, 0.092 mmol) was converted to **23** (25 mg, 88% yield) as a colorless syrup: IR ($CHCl_3$) 3600, 3450, 1660, 1100, 970, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.82 (3 H, s), 0.95 (3 H, s), 1.16 (3 H, s), 1.63 (3 H, s), 1.70 (3 H, s), 4.12 (2 H, d, J = 7 Hz), 5.10 (1 H, br), 5.39 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 290.2643 ($M^+ - H_2O$), calcd for $C_{20}H_{34}O$ 290.2609.

Diol 24. According to the same procedure described above, **19b** (9 mg, 0.013 mmol) was converted to **24** (2.8 mg. 64% yield) as a syrup: IR ($CHCl_3$) 3600, 3450, 1650, 980, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.87 (3 H, s), 1.17 (3 H, s), 1.63 (3 H, s), 1.70 (3 H, s), 4.15 (2 H, d, J = 7 Hz), 5.10 (1 H, br), 5.39 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 290.2639 ($M^+ - H_2O$), calcd for $C_{20}H_{34}O$ 290.2609.

(±)-Aplysin-20 (22b). The organomercuric compound **20b** (45 mg, 0.0714 mmol) was dissolved in pyridine (1 mL) and the solution was saturated with oxygen. A solution of bromine (12.6 mg, 0.0786 mmol) and lithium bromide (12.4 mg, 0.143 mmol) in pyridine (1.5 mL) also saturated with oxygen was added, and the mixture was stirred in the dark for 20 h under oxygen atmosphere at room temperature. The resulting solution was diluted with 1 N hydrochloric acid and extracted with dichloromethane. The organic phase was washed with sodium hydrogen carbonate. The concentrated extract was subjected to column chromatography on silica gel (5 g) using a 20:1 mixture of hexane and ethyl acetate to give (±)-aplysin-20 acetate (16 mg). This acetate was dissolved in ethanol (0.5 mL) and mixed with a solution of sodium hydroxide (5.0 mg, 0.125 mmol) in ethanol (0.5 mL). The mixture was stirred at 0 °C for 10 min, and then diluted with brine. The dichloromethane extract was subjected to column chromatography on silica gel (2 g) by using a mixture of hexane and ethyl acetate (2:1) to give (±)-aplysin-20 (**22b**) (14 mg, 51% yield) as colorless crystals: mp 168 °C; IR ($CHCl_3$) 3600, 1170, 980, 910 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.96 (3 H, s), 1.00 (3 H, s), 1.08 (3 H, s), 1.16 (3 H, s), 1.70 (3 H, s), 3.96 (1 H, dd, J = 11, 5.5 Hz), 4.16 (2 H, d, J = 7 Hz), 5.41 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 370.1733, 368.1780 ($M^+ - H_2O$), calcd for $C_{20}H_{33}OBr$ 370.1695, 368.1715. These spectral properties were identical with those of the natural product.[30]

Cyclization of (*E,E,E*)-Geranylgeranyl Acetate (4b) in the Presence of Methanol. Methanol (1.14 g, 35.7 mmol) was added to a cooled solution (−20 °C) of **1** prepared by mixing yellow mercuric oxide (774 mg, 3.57 mmol), triflic anhydride (1.01 g, 3.57 mmol), and *N,N*-dimethylaniline (432 mg, 3.57 mmol) in nitromethane (45 mL). To this was added a solution of **4b** (1.00 g, 2.98 mmol) in nitromethane (5 mL), and the mixture was stirred at −20 °C for 2 h. After the addition of saturated potassium bromide solution (50 mL), the mixture was warmed to room temperature and stirred for an additional 3 h. Inorganic precipitate was removed by filtration, and the filtrate was extracted with dichloromethane. Column chromatography on silica gel (100 g) with a mixture of hexane and ethyl acetate (20:1 to 1:1) gave recovery of **4b** (403 mg, 40%), **14** (87 mg, 4.6% yield), and a mixture of mono- and bicyclic organomercuric compounds (389 mg). A solution of the latter mixture in dichloromethane (5 mL) and ethanol (5 mL) was treated with a solution of sodium borohydride (200 mg, 5.26 mmol) and sodium hydroxide (429 mg, 10.5 mmol) in water (0.4 mL) at room temperature for 30 min. After the removal of the precipitate by filtration, the filtrate was diluted with brine and extracted with dichloromethane. Column chromatography on silica gel (30 g) using a 10:1 mixture of hexane and ethyl acetate afforded monocyclic product **25** [68 mg, 7.8% yield, syrup; IR ($CDCl_3$) 3600, 3400, 1660, 1105, 1070, 990 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.85 (3 H, s), 0.96 (3 H, s), 1.12 (3 H, s), 1.61 (3 H, s), 1.68 (3 H, s), 3.14 (3 H, s), 4.14 (2 H, d, J = 7 Hz), 5.11 (1 H, br), 5.41 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 322.2852 (M^+), calcd for $C_{21}H_{38}O_2$ 322.2870] and bicyclic product **26** [110 mg, 12.7% yield, syrup; IR ($CHCl_3$) 3600, 3400, 1660, 1090, 1060, 980 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 0.79 (3 H, s), 0.83 (3 H, s), 0.87 (3 H, s), 1.09 (3 H, s), 1.67 (3 H, s), 3.13 (3 H, s), 4.13 (2 H, d, J = 7 Hz), 5.41 (1 H, t, J = 7 Hz); high-resolution mass spectrum, 322.2848 (M^+), calcd for $C_{21}H_{38}O_2$ 322.2870].

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Registry No. **1**, 88641-99-0; **4a**, 88661-93-2; **4b**, 61691-98-3; (±)-**5**, 82570-46-5; (±)-**6**, 88728-60-3; (±)-**7**, 88728-61-4; (±)-**13**, 100428-28-2; (±)-**14** (isomer 1), 100349-43-7; (±)-**14** (isomer 2), 100349-46-0; (±)-**15**, 100349-44-8; (±)-**16a**, 100349-45-9; (±)-**17**, 100349-50-6; (±)-**17a**, 100349-48-2; (±)-**18**, 100349-49-3; (±)-**18c**, 100349-47-1; (±)-**19a**, 100349-51-7; (±)-**19b**, 100349-52-8; (±)-**20a**, 100298-45-1; (±)-**20b**, 100298-46-2; (±)-**21**, 100349-53-9; (±)-**22a**, 100349-54-0; (±)-**22b**, 94903-98-7; (±)-**22b** (acetate), 100298-48-4; (±)-**23**, 100298-47-3; (±)-**24**, 100349-55-1; (±)-**25**, 100298-49-5; (±)-**26**, 100298-50-8.