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Biomimetic Cyclization of Epoxide Precursors of Indole Mono-, Sesqui- and Diterpene Alkaloids by Lewis Acids

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Cyclization of the synthesized epoxide precursors of indole mono-, sesqui- and diterpene alkaloids was performed to elucidate the mechanism for biomimetic cationic cyclization to polycyclic structures. 3-(6,7-Epoxygeranyl)indole (11), 3-(10,11-epoxyfarnesyl)indole (2) and 3-(14,15-epoxygeranylgeranyl)indole (3) were respectively synthesized from geraniol, farnesol and geranylgeraniol in 6 or 7 steps. Four Lewis acids ($MeAlCl_2$, BF_3•OEt_2, $TiCl_4$ and $SnCl_4$) were applied for biomimetic cyclization of the synthesized epoxide precursors. The cyclization products (one product from 11, four products from 2, and three products from 3) were isolated after separation by chromatography. Their structures were determined by using NMR (COSY, HSQC, HMBC, NOESY, *etc*.) and HRMS analyses. The results show that biomimetic cyclization gave new polycyclic compounds similar to natural indole terpene alkaloids. We conclude that the stability of cation intermediates should determine the preference for product formation by biomimetic cyclization when using a Lewis acid.

Key words: indole alkaloid; monoterpene; sesquiterpene; diterpene; biomimetic cyclization

Indole alkaloids have extraordinarily diverse structures which are produced by the inherent cyclases of various creatures. Many indole alkaloids have complicated frameworks and various bioactivities;[1–4] for example, lolitrem B is the major lolitrem neurotoxin isolated from perennial ryegrass (*Lolium perenne* L.) infected with the endophytic fungus, *Neotyphodium lolii*.[5] Paxilline[6] and paspaline[7] are known as tremorgenic mycotoxins; while emindoles DB and DA[8] are known as the indole diterpene alkaloids produced by the *Emericella* genus (Fig. 1).

Some indole diterpene alkaloids have been studied at the genetic level to analyze the respective functions of biosynthetic genes;[9–12] for example, PaxC (prenyl transferase) is encoded by the *paxC* gene, and has been presumed to function as a cyclase in the biosynthesis of paxilline and paspaline.[12] If recombinant proteins of the cyclases are obtained, they might be applied to the synthesis of cyclic compounds from various acyclic precursors. A combination of the organic synthesis of biosynthetic precursors and subsequent enzymatic cyclization would be a useful method to provide novel compounds which could be expected to have interesting bioactivities. Furthermore, the study of biomimetic cyclization is important to elucidate the basic cyclization mechanism for these classes of compounds.

There are some reports of the indole terpene alkaloids (polyveoline,[13] polyalthenol,[14] petromindole,[15] and emindole SA[16,17] as shown in Fig. 2) which have been assumed to be derived from 2-(10,11-epoxyfarnesyl)indole (**1**), 3-(10,11-epoxyfarnesyl)indole (**2**), 3-(10,11-epoxygeranylgeranyl)indole (**5**) and 3-(14,15-epoxygeranylgeranyl)indole (**3**) as respective biosynthetic intermediates; for example, polyveoline, which exhibits antiparasitic activity, has the 6.6.5-tricyclic framework cyclized from **1**. Petromindole and emindole SA are indole alkaloids possessing the 6.6.6.6-tetracyclic and 6.6-bicyclic framework respectively cyclized from **3** and **5**. A consideration of these reasonable examples leads to the notion that many other polycyclic indole terpene alkaloids would be biosynthesized from such indole epoxypolyenes as **1**, **2**, **3**, **5** and similar intermediates.

Diverse families of indole terpene alkaloids are thought to be biosynthesized *via* the following four steps:[18] (i) recognition of the epoxypolyene and control of its conformation, (ii) generation of the carbocation *via* epoxide-opening, (iii) C-C bond formation and stabilization of resulting carbocation intermediates, and (iv) quenching of the final carbocation. In the case of enzymatic cyclization, C-C bond formation produces not only an energetically stable carbocation, but also a labile carbocation. Furthermore, the hydride shifts and/or alkyl group rearrangements often occur to give other carbocations, the final carbocation being quenched to give the product. Petromindole is biosynthesized *via* the diastereoselective cyclization of enantiopure (*S*)-**3** through epoxide opening. Specific protonation of the epoxide is the most important step, especially in the cyclization of a precursor containing a long terpene chain such as that in the biosynthesis of indole diterpene

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alkaloids, because an epoxide and three double bonds exist together in the precursor. Protonation of an epoxide easily occurs by the action of a Lewis acid to biomimetically generate a carbocation by epoxide opening. The resulted carbocation is attacked by the intramolecular double bond with subsequent hydride shifts and/or alkyl group rearrangements to provide a complex polycyclic skeleton. The biomimetic cyclization mediated by Lewis acids has therefore been studied for a long time and exploited in the total synthesis of natural products;[19–21] for example, biomimetic cyclization with a Lewis acid has been applied for the total synthesis of emindole SA and petromindole.[17,22] These reports indicate that the indole nitrogen was protected as a sulfonamide and *N*-silyl derivative. Since the total syntheses of some natural products has been achieved by biomimetic cyclization using nitrogen-protected precursors, we expected that a natural product could be synthesized by biomimetic cyclization using nitrogen-unprotected precursors. Although indole sesqui- and diterpene alkaloids are popularly known, there have so far been no reports on indole monoterpene alkaloids. We therefore planned to synthesize a new indole monoterpene alkaloid from 3-(6,7-epoxygeranyl)indole (**11**) by biomimetic cyclization, using Lewis acids. It can be expected that the study of biomimetic cyclization with Lewis acids systematically using different chain-length intermediates would be useful in elucidating the cyclization mechanism by cyclases. The products from this study might also be expected to be unknown natural products and new polycyclic compounds similar to natural products which would be useful for studying biological activity. We describe here the biomimetic cyclization of indole terpene precursors **2**, **3**, and **11** by Lewis acids, structural determination of the cyclized products, and elucidation of the cyclization mechanism.

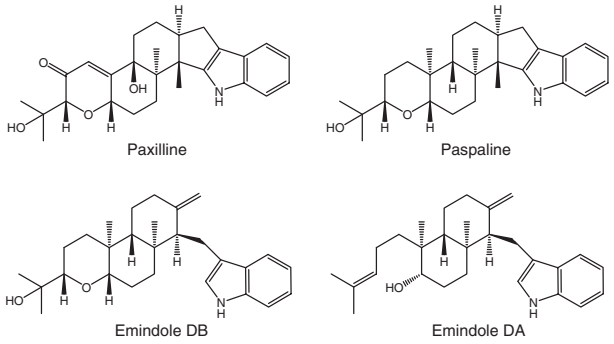


Fig. 1. Indole Diterpene Alkaloids Known as Mycotoxins.

Results and Discussion

The necessary precursors (**11**, **2** and **3**) for biomimetic cyclization were synthesized as shown in Scheme 1. Geraniol was protected with TBDPSCl to give **7** in a 98% yield. Selective epoxidation of **7** with *m*CPBA at 0 °C gave **8** in a 74% yield. This obtained **8** was deprotected with TBAF to give **9** in a 95% yield. Mesylation of **9** with MsCl and subsequent bromination with LiBr gave **10**[23] in a one-pot step. This obtained **10** was coupled with indole to give **11**[23] in a 53% yield in 3 steps.[23] Farnesol was converted to **2**[24] in 6 steps in the same manner as that used for the synthesis of **11** from geraniol.

Geranylgeraniol was protected with TBDPSCl to give **12** in an 89% yield. Obtained **12** was treated with NBS to give bromohydrin **13** in a 35% yield.[25] Obtained **13** was treated with K_2CO_3 in MeOH to give epoxide **14** in an 80% yield. Obtained **14** was converted to **3**[22] in 4 steps in the same manner as that used for the synthesis of **11** from **8**.

Four Lewis acids (1 M $MeAlCl_2$ in a hexane solution, $BF_3 \cdot OEt_2$, 1 M $TiCl_4$ in a CH_2Cl_2 solution and 1 M $SnCl_4$ in a CH_2Cl_2 solution) were used for the cyclization of precursors **2**, **3** and **11**. $BF_3 \cdot OEt_2$[24,26] was used in the biomimetic cyclization of **1**, because it is known as a popular Lewis acid to activate an epoxide, while $MeAlCl_2$ was used for the total synthesis of emindole SA.[17] $SnCl_4$[27] and $TiCl_4$[28] are general Lewis acids used in the synthesis of cyclic compounds for ring-opening cyclization of epoxypolyene and polyene cyclization. In the case of biomimetic cyclization using the same precursor, there was not much difference in the total yield of the reaction with each of these Lewis acids (40–73% from **11**, 29–36% from **2**, and 21–24% from **3**). The total yield decreased with extending terpene chain length, and the number of products increased to

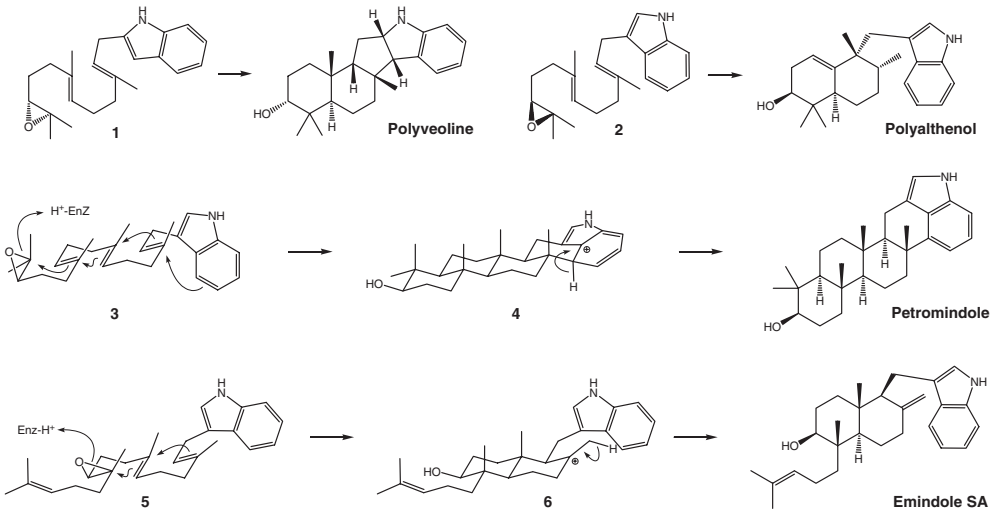
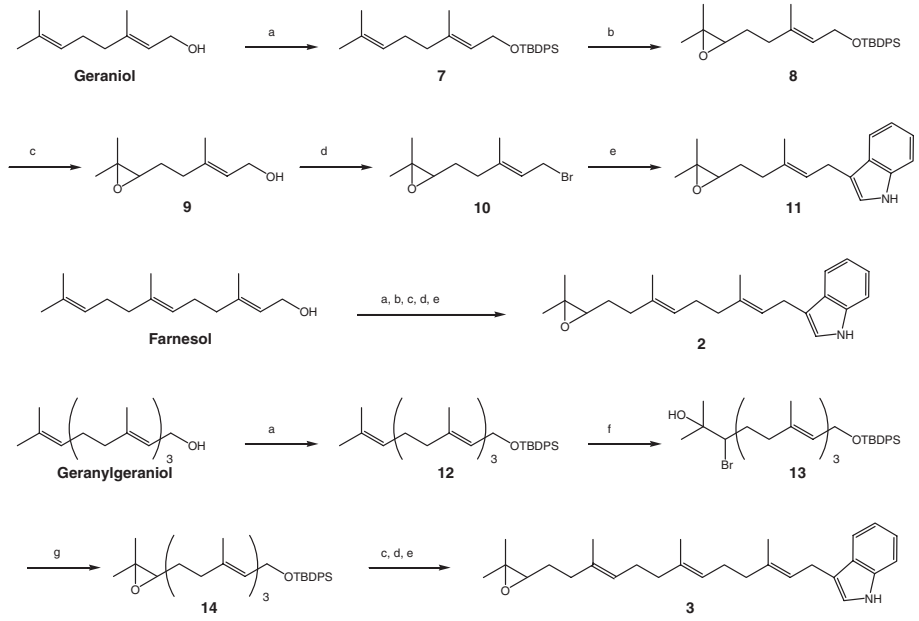


Fig. 2. Plausible Biosynthetic Pathways to Polyveoline, Polyalthenol, Emindole SA and Petromindole.



Scheme 1. Synthesis of the Necessary Precursors (**11**, **2** and **3**) for the Cyclization Reaction.
a) TBDPSCl, imidazole, DMF, **7** (98%), **32** (97%), **12** (89%); b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, **8** (74%), **33** (22%); c) TBAF, THF, r.t, **9** (95%), **34** (91%), **36** (77%); d) MsCl, Et_3N, THF, −40 °C, then LiBr, THF, 0 °C; e) indole, $Zn(OTf)_2$, TBAI, DIEA, toluene, r.t, **11** (53%, 3 steps), **2** (50%, 3 steps), **3** (57%, 3 steps); f) NBS, THF/H_2O, r.t; g) K_2CO_3, MeOH, r.t, 63% (2 steps).

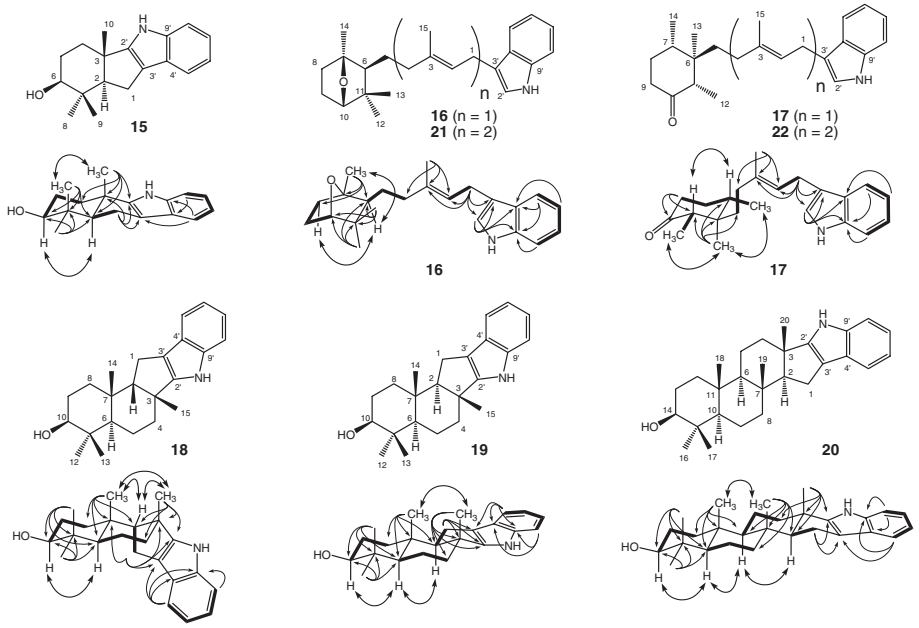


Fig. 3. Cyclic Products from **2**, **3** and **11** by Biomimetic Cyclization with Lewis Acids.
Bold lines denote COSY correlations for the cyclic products. Single-headed arrows denote HMBC correlations, and double-headed arrows denote NOESY correlations.

give different cyclic structures. The structures of the isolated cyclic products were determined with one- and two-dimensional NMR measurements, these structures and NMR data being shown in Fig. 3 and Tables 1–3.

The molecular formula of **15** was established to be $C_{18}H_{23}NO$ by HRMS (calcd. for $C_{18}H_{23}NO$ (M^+), m/z 269.1780; found, 269.1779) coupled with ^{1}H- and ^{13}C-NMR spectral data (Table 1). Three COSY fragments, F15-1 (H-5′, 6′, 7′, 8′), F15-2 (H-1, 2) and F15-3 (H-4, 5, 6), were established by analyzing the COSY correlation peaks (Fig. 3). HMBC correlation peaks were used to connect the COSY fragments and quaternary carbons (Table 1). The aryl portion of the indole moiety was established from F15-1 and the correlation of H-5′/C-9′ and H-8′/C-4′. The remainder of the indole moiety fragment was assigned on the basis of HMBC correlation peaks of H-5′/C-3′, H-1/C-2′ and C-3′, and H-10/C-2′. HMBC correlation peaks from the H-1 methylene proton to C-3′, C-2′ and C-3 led to the connection of the indole moiety and F15-2, while HMBC correlation peaks from the H-10 methyl proton to C-2′, C-2, C-3 and C-4 led to the connection of F15-2, F15-3 and the indole moiety. HMBC correlation peaks from a geminal dimethyl group (H-8 and H-9) to C-2, C-6 and C-7 led to the connection of F15-2 and F15-3. NOESY correlation peaks between H-2 and H-6 indicated the 1,3-

diaxial relationship for H-2 and H-6, while NOESY correlation peaks between C-9 and the C-10 methyl group indicated the 1,3-diaxial relationship for C-9 and the C-10 methyl group. The relative configuration was determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The molecular formula of **16** was established to be $C_{23}H_{31}NO$ by HRMS (calcd. for $C_{23}H_{31}NO$ (M^+), m/z 337.2406; found, 337.2407) coupled with ^{1}H- and ^{13}C-NMR spectral data (Table 2). Four COSY fragments, F16-1 (H-5′, 6′, 7′, 8′), F16-2 (H-1, 2), F16-3 (H-4, 5, 6) and F16-4 (H-8, 9, 10), were established by analyzing the COSY correlation peaks (Fig. 3). HMBC correlation peaks were used to connect the COSY fragments and the quaternary carbons (Table 2). The aryl portion of the indole moiety was established from F16-1, and the correlation of H-5′/C-4′ and C-9′, H-6′/C-4′, and H-8′/C-9′. The remainder of the indole moiety fragment was assigned on the basis of HMBC correlation peaks from the methyne proton at H-2′ to C-3′, C-4′ and C-9′. HMBC correlation peaks from the H-1 methylene proton to C-2′, C-3′, C-2 and C-3 led to the connection of the indole moiety and F16-2, while HMBC correlation peaks from the H-15 methyl proton to C-2, C-3 and C-4 led to the connection of F16-2 and F16-3. HMBC correlation peaks from the H-14 methyl group to C-6, C-7 and C-8 led to the connection of F16-3 and F16-4, and HMBC correlation peaks from a geminal dimethyl group (H-12 and H-13) to C-6, C-10 and C-11 led to the connection of F16-3 and F16-4. It was confirmed that the C-7 quaternary carbon (δ_C 86.7) and C-10 methine carbon (δ_C 86.1) were bound to oxygen by the ^{13}C-NMR spectral data, a bridged framework of C-7 and C-10 therefore being suggested. A NOESY correlation peak between H-6 and H-8 indicated a 1,3-diaxial-like relationship for H-6 and H-8, while a NOESY correlation peak between H-6 and H-14 indicated the *syn*-relationship for H-6 and the C-14 methyl group. The relative configuration was therefore determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The molecular formula of **17** was established to be $C_{23}H_{31}NO$ by HRMS (calcd. for $C_{23}H_{31}NO$ (M^+), m/z 337.2406; found, 337.2407) coupled with the ^{1}H- and

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data for **15**

Carbon no.	**15** (in $CDCl_3$)	
	δ_C (Mult.)	δ_H (Mult., *J* Hz)
(1′)	NH	7.76 (br s)
2′	151.5 (s)	
3′	116.8 (s)	
4′	139.2 (s)	
5′	118.5 (d)	7.45 (dd, 7.3, 3.2)
6′	120.4 (d)	7.09 (m)
7′	119.7 (d)	7.07 (m)
8′	111.6 (d)	7.30 (dd, 7.3, 3.2)
9′	125.2 (s)	
1	22.7 (t)	2.70 (dd, 13.5, 6.1), 2.57 (dd, 13.5, 11.2)
2	62.4 (d)	2.17 (dd, 11.2, 6.1)
3	42.9 (s)	
4	33.6 (t)	2.01 (dt, 11.0, 3.2), 1.76 (m)
5	28.7 (t)	1.90 (m), 1.83 (m)
6	79.5 (d)	3.45 (m)
7	38.7 (s)	
8	16.0 (q)	1.06 (s)
9	28.6 (q)	1.11 (s)
10	20.3 (q)	1.14 (s)

Table 2. ^{1}H- and ^{13}C-NMR Spectral Data for **16–19**

Carbon no.	**16** (in $CDCl_3$)		**17** (in $CDCl_3$)		**18** (in $CDCl_3$)		**19** (in C_6D_6)	
	δ_C (Mult.)	δ_H (Mult., *J* Hz)	δ_C (Mult.)	δ_H (Mult., *J* Hz)	δ_C (Mult.)	δ_H (Mult., *J* Hz)	δ_C (Mult.)	δ_H (Mult., *J* Hz)
(1′)	NH	7.78 (br s)	NH	7.78 (br s)	NH	7.70 (br s)	NH	6.60 (br s)
2′	121.1 (d)	6.94 (br s)	121.1 (d)	6.90 (br s)	152.5 (s)		151.8 (s)	
3′	116.1 (s)		116.0 (s)		113.2 (s)		116.5 (s)	
4′	127.5 (s)		127.5 (s)		139.5 (s)		139.8 (s)	
5′	119.0 (d)	7.58 (d, 8.1)	119.0 (d)	7.58 (d, 8.0)	118.5 (d)	7.42 (dd, 6.2, 1.6)	118.9 (d)	7.64 (dd, 6.8, 1.6)
6′	119.1 (d)	7.09 (t, 8.1)	119.2 (d)	7.10 (t, 8.0)	120.3 (d)	7.07 (m)	120.6 (d)	7.26 (dt, 1.6, 6.8)
7′	121.4 (d)	7.17 (t, 8.1)	122.0 (d)	7.18 (t, 8.0)	119.6 (d)	7.06 (m)	120.0 (d)	7.23 (dt, 1.6, 6.8)
8′	111.0 (d)	7.34 (d, 8.1)	111.1 (d)	7.34 (d, 8.0)	111.4 (d)	7.30 (dd, 6.2, 1.6)	112.0 (d)	7.14 (dd, 6.8, 1.6)
9′	136.5 (s)		136.5 (s)		125.3 (s)		126.1 (s)	
1	24.0 (t)	3.46 (d, 7.1)	24.1 (t)	3.46 (d, 7.0)	26.4 (t)	2.78 (dd, 13.7, 8.3) 2.67 (dd, 13.7, 9.6)	22.3 (t)	2.50 (dd, 13.2, 5.7) 2.38 (dd, 13.2, 11.0)
2	123.2 (d)	5.43 (t, 7.1)	123.2 (d)	5.47 (t, 7.0)	67.0 (d)	2.30 (dd, 9.6, 8.3)	67.9 (d)	1.94 (dd, 11.0, 5.7)
3	135.8 (s)		135.7 (s)		41.4 (s)		43.4 (s)	
4	39.8 (t)	2.00 (m)	32.6 (t)	1.91 (td, 11.6, 5.1) 2.06 (td, 11.6, 5.1)	38.4 (t)	1.86 (dt, 13.1, 1.1) 1.38 (m)	36.6 (t)	1.86 (dt, 11.0, 2.8) 1.43 (m)
5	26.1 (t)	1.43 (m)	35.9 (t)	1.44 (m)	18.1 (t)	1.50 (m)	19.4 (t)	1.66 (m) 1.50 (m)
6	55.2 (d)	1.19 (t, 6.8)	43.5 (s)		47.7 (d)	1.24 (m)	56.5 (d)	0.75 (m)
7	86.7 (s)		36.1 (d)	2.01 (m)	36.9 (s)		37.3 (s)	
8	39.0 (t)	1.46 (m)	31.0 (t)	1.86 (m) 1.62 (m)	35.8 (t)	1.66 (m) 1.44 (dt, 12.6, 3.1)	38.4 (t)	1.38 (m) 0.93 (m)
9	25.8 (t)	1.88 (m) 1.65 (m)	41.6 (t)	2.32 (m)	27.2 (t)	1.70 (m)	27.7 (t)	1.46 (m)
10	86.1 (d)	3.72 (d, 5.3)	214.0 (s)		79.2 (d)	3.29 (dd, 9.7 6.6)	78.8 (d)	3.00 (dd, 11.4, 5.7)
11	45.3 (s)		50.5 (d)	2.48 (q, 6.7)	38.7 (s)		39.1 (s)	
12	25.9 (q)	1.02 (s)	7.6 (q)	0.93 (d, 6.7)	15.7 (q)	0.85 (s)	15.4 (q)	0.83 (s)
13	23.4 (q)	1.01 (s)	15.4 (q)	0.58 (s)	28.3 (q)	1.02 (s)	28.3 (q)	1.03 (s)
14	19.0 (q)	1.32 (s)	15.1 (q)	0.89 (d, 6.7)	23.8 (q)	1.21 (s)	16.9 (q)	0.94 (s)
15	16.0 (q)	1.76 (br s)	16.3 (q)	1.78 (br s)	25.5 (q)	1.53 (s)	21.8 (q)	0.97 (s)

^{13}C-NMR spectral data (Table 2). Five COSY fragments, F17-1 (H-5′, 6′, 7′, 8′), F17-2 (H-1, 2), F17-3 (H-4, 5), F17-4 (H-14, 7, 8, 9) and F17-5 (H-11, 12), were established by analyzing the COSY correlation peaks (Fig. 3). HMBC correlations were used to connect these COSY fragments and the quaternary carbons (Table 2). Since the correlation peaks for the substructure (indole and F17-2) of **17** were consistent with the substructure (indole and F16-2) of **16**, the substructure (indole and F17-2) of **17** was determined in the same manner as that used for the structural determination of **16**. HMBC correlation peaks from the H-15 methyl proton to C-2, C-3, and C-4 led to the connection of F17-2 and F17-3, and HMBC correlation peaks from the H-9 methylene proton to C-10 and C-11 led to the connection of F17-4 and F17-5. HMBC correlation peaks from the H-13 methyl proton to C-5, C-6, C-7 and C-11 led to the connection of F17-3, F17-4, and F17-5. The NOESY correlation peak between H-7 and H-11 indicated the 1,3-diaxial relationship of H-7 and H-11. The NOESY correlation peak between H-13 and H-14 indicated the axial-equatorial relationship of the C-13 and C14 methyl groups, while the NOESY correlation peak between H-12 and H-13 indicated the equatorial-axial relationship of the C-12 and C-13 methyl groups. The relative configuration was determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The molecular formula of **18** was established to be $C_{23}H_{31}NO$ by HRMS (calcd. for $C_{23}H_{31}NO$ (M^+), m/z 337.2406; found, 337.2404) coupled with the ^{1}H- and ^{13}C-NMR spectral data (Table 2). Four COSY fragments, F18-1 (H-5′, 6′, 7′, 8′), F18-2 (H-1, 2), F18-3 (H-4, 5, 6) and F18-4 (H-8, 9, 10), were established by analyzing the COSY correlation peaks (Fig. 3). The HMBC correlation peaks were used to connect the COSY fragments and the quaternary carbons (Table 2). The indole moiety was established from F18-1 and the correlation of H-5′/C-3′, C-4′ and C-9′, and H-8′/C-9′. The HMBC correlation peaks from the H-1 methylene proton to the indole moiety (C-2′ and C-3′), C-3 and C-7 led to the connection of the indole moiety and F18-2. The HMBC correlation peaks from the H-15 methyl proton to C-2′, C-2, C-3 and C-4 led to the connection of F18-3, the indole moiety and F18-2. The HMBC correlation peaks from the H-14 methyl proton to C-2, C-6, C-7 and C-8 led to the connection of F18-2, F18-3 and F18-4. The HMBC correlation peaks from the geminal dimethyl protons (H-12 and H-13) to C-6, C-10 and C-11 led to the connection of F18-3 and F18-4. The NOESY correlation peaks between H-6 and H-10 indicated the 1,3-diaxial relationship for H-6 and H-10, while the NOESY correlation peaks between the H-2 and C-15 methyl groups indicated the *syn*-relationship for the H-2 and C-15 methyl groups. The NOESY correlation peaks between the H-2 and C-14 methyl groups indicated the *syn*-relationship for the H-2 and C-14 methyl groups, and the NOESY correlation peaks between the C-14 and C-15 methyl groups indicated the 1,3-diaxial relationship for the C-14 and C-15 methyl groups. The relative configuration was determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The molecular formula of **19** was established to be $C_{23}H_{31}NO$ by HRMS (calcd. for $C_{23}H_{31}NO$ (M^+), m/z 337.2406; found, 337.2405) coupled with the ^{1}H- and ^{13}C-NMR spectral data (Table 2). Four COSY fragments, F19-1 (H-5′, 6′, 7′, 8′), F19-2 (H-1, 2), F19-3 (H-4, 5, 6) and F19-4 (H-8, 9, 10), were established by analyzing the COSY correlation peaks (Fig. 3). The HMBC correlation peaks were used to connect the COSY fragments and the quaternary carbons (Table 2). The indole moiety was established from F19-1 and the correlation of H-5′/C-3′, C-4′ and C-9′, and H-8′/C-9′ and C-4′. The HMBC correlation peaks from the H-1 methylene proton to the indole moiety (C-2′ and C-3′), C-2 and C-3 led to the connection of the indole moiety and F19-2. The HMBC correlation peaks from the H-15 methyl proton to C-2′, C-2, C-3 and C-4 led to the connection of F19-3, the indole moiety and F19-2. The HMBC correlation peaks from the H-14 methyl proton to C-2, C-6, C-7 and C-8 led to the connection of F19-2, F19-3 and F19-4. The HMBC correlation peaks from the geminal dimethyl protons (H-12 and H-13) to C-6, C-10 and C-11 led to the connection of F19-3 and F19-4. The NOESY correlation peaks between H-2 and H-6 indicated the 1,3-diaxial relationship for H-2 and H-6, and the NOESY correlation peaks between H-6 and H-10 indicated the 1,3-diaxial relationship for H-6 and H-10. The NOESY correlation peaks between the C-14 and C-15 methyl groups indicated the 1,3-diaxial relationship for the C-14 and C-15 methyl groups. The relative configuration was determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The molecular formula of **20** was established to be $C_{28}H_{39}NO$ by HRMS (calcd. for $C_{28}H_{39}NO$ (M^+), m/z 405.3032; found, 405.3050) coupled with the ^{1}H- and ^{13}C-NMR spectral data (Table 3). Five COSY fragments, F20-1 (H-5′, 6′, 7′, 8′), F20-2 (H-1, 2), F20-3 (H-4, 5, 6), F20-4 (H-8, 9, 10) and F20-5 (H-12, 13, 14), were established by analyzing the COSY and HSQC-TOCSY correlation peaks (Fig. 3). The HMBC correlation peaks were used to connect the COSY and HSQC-TOCSY fragments and the quaternary carbons (Table 3). The indole moiety was established from F20-1, and the correlation of H-5′/C-3′, C-4′ and C-9′, H-8′/C-9′ and C-4′. The HMBC correlation peaks from the H-1 methylene proton to the indole moiety (C-2′ and C-3′) and C-3 led to the connection for the indole moiety and F20-2. The HMBC correlation peaks from the H-20 methyl proton to C-2′, C-2, C-3 and C-4 led to the connection for F20-3, the indole moiety and F20-2. The HMBC correlation peaks from the H-19 methyl proton to C-2, C-6, C-7 and C-8 led to the connection for F20-2, F20-3 and F20-4. The HMBC correlation peaks from the H-18 methyl proton to C-6, C-10, C-11 and C-12 led to the connection for F20-3, F20-4 and F20-5, and the HMBC correlation peaks from a geminal dimethyl proton (H-16 and H-17) to C-10, C-14 and C-15 led to the connection for F20-4 and F20-5. The NOESY correlation peaks between H-2 and H-6 indicated the 1,3-diaxial relationship for H-2 and H-6, while the NOESY correlation peaks between H-6 and H-10 indicated the 1,3-diaxial relationship for H-6 and H-10. The NOESY correlation peaks between H-10 and H-14 indicated the 1,3-diaxial relationship for H-10 and H-14, and the NOESY correlation peaks between the C-18 and C-19 methyl groups indicated the 1,3-diaxial relationship for the C-18 and C-19 methyl groups. The NOESY correlation between the C-19 and

Table 3. ^{1}H- and ^{13}C-NMR Spectral Data for **20**–**22**

Carbon no.	**20** (in $CDCl_3$)		**21** (in $CDCl_3$)		**22** (in $CDCl_3$)	
	δ_C (Mult.)	δ_H (Mult., *J* Hz)	δ_C (Mult.)	δ_H (Mult., *J* Hz)	δ_C (Mult.)	δ_H (Mult., *J* Hz)
(1′)	NH	7.75 (br s)	NH	8.09 (br s)	NH	7.88 (br s)
2′	152.3 (s)		121.3 (d)	6.96 (br s)	121.1 (d)	6.94 (d, 1.1)
3′	116.6 (s)		116.1 (s)		116.2 (s)	
4′	139.1 (s)		127.5 (s)		127.6 (s)	
5′	118.4 (d)	7.43 (dd, 6.6, 3.1)	119.0 (d)	7.58 (d, 8.0)	119.1 (d)	7.58 (d, 8.0)
6′	120.3 (d)	7.07 (m)	119.1 (d)	7.08 (t, 8.0)	119.2 (d)	7.09 (t, 7.1)
7′	119.6 (d)	7.05 (m)	121.9 (d)	7.18 (t, 8.0)	122.0 (d)	7.18 (t, 7.0)
8′	111.5 (d)	7.29 (dd, 6.6, 3.1)	111.1 (d)	7.35 (d, 8.0)	111.0 (d)	7.34 (d, 8.0)
9′	125.3 (s)		136.6 (s)		136.6 (s)	
1	22.1 (t)	2.49 (dd, 13.3,11.0) 2.61 (dd, 13.3, 6.0)	23.9 (t)	3.46 (d, 7.1)	24.1 (t)	3.46 (d, 7.1)
2	68.3 (d)	2.18 (dd, 11.0, 6.0)	123.0 (d)	5.47 (t, 7.1)	123.1 (d)	5.45 (t, 7.1)
3	43.4 (s)		135.5 (s)		135.4 (s)	
4	36.4 (t)	1.58 (m) 2.06 (ddd, 8.8, 3.1, 1.6)	39.7 (t)	2.09 (t, 6.4)	39.7 (t)	2.07 (t, 7.0)
5	18.3 (t)	1.65 (m)	26.4 (t)	2.14 (t, 6.4)	26.7 (t)	2.12 (t, 7.0)
6	61.7 (d)	0.97 (m)	124.1 (d)	5.14 (t, 6.4)	124.4 (d)	5.15 (t, 7.0)
7	37.3 (s)		135.3 (s)		135.1 (s)	
8	41.8 (t)	1.16 (m) 1.67 (m)	39.7 (t)	1.92 (m)	32.6 (t)	1.80 (m) 1.95 (m)
9	17.7 (t)	1.53 (m)	26.2 (t)	1.40 (m)	36.0 (t)	1.37 (m)
10	56.1 (d)	0.83 (dd, 11.5, 3.1)	55.3 (d)	1.18 (dd, 8.2, 6.3)	43.5 (s)	
11	37.7 (s)		86.9 (s)		36.1 (d)	1.99 (m)
12	38.4 (t)	1.02 (m) 1.66 (m)	39.0 (t)	1.48 (m)	31.0 (t)	1.85 (m) 1.61 (m)
13	27.4 (t)	1.59 (m)	25.8 (t)	1.88 (m) 1.65 (m)	41.6 (t)	2.33 (m)
14	78.9 (d)	3.21 (dd, 11.2, 5.1)	86.2 (d)	3.73 (d, 5.3)	214.0 (s)	
15	39.1 (s)		45.2 (s)		50.5 (d)	2.45 (q, 6.8)
16	15.2 (q)	0.99 (s)	26.1 (q)	1.04 (s)	7.6 (q)	0.91 (d, 6.8)
17	28.0 (q)	0.81 (s)	23.5 (q)	1.00 (s)	15.4 (q)	0.56 (s)
18	16.1 (q)	0.90 (s)	18.9 (q)	1.31 (s)	15.0 (q)	0.88 (d, 6.8)
19	17.9 (q)	1.10 (s)	16.1 (q)	1.60 (s)	16.2 (q)	1.77 (s)
20	21.6 (q)	1.11 (s)	16.0 (q)	1.76 (br s)	16.1 (q)	1.62 (br s)

C-20 methyl groups was ambiguous due the proximity of their proton signals. No NOESY correlation between the H-2 and C-20 methyl groups was apparent, nor between the H-2 and C-19 methyl groups. The relative configuration was determined in this way by analyzing the NOESY correlation peaks (Fig. 3).

The same bicyclic structure for **21** as that for **16** was confirmed by analyzing the ^{1}H- and ^{13}C-NMR spectral data. Furthermore, the same cyclohexanone structure for **22** as that for **17** was also confirmed by analyzing the ^{1}H- and ^{13}C-NMR spectral data.

Compound **15** would be synthesized from **11** by a cyclization mechanism of the 6.5-bicyclic type in 4 steps: i) epoxide-opening with a Lewis acid, ii) formation of *tert*-cation **23** by nucleophilic attack of C-2, iii) formation of a cation on the indole ring (C-3′) by nucleophilic attack of the indole ring (C-2′), iv) quenching of the carbocation to reproduce the indole ring. Since H-2/H-6 and the C-9 methyl/C-10 methyl were determined to have 1,3-diaxial relationships, the formation of the cyclohexane ring of **15** was presumed to proceed *via* a stable chair conformation. Biomimetic cyclization of **11** gave only **15**, but biomimetic cyclization of **2** and **3** gave several cyclic compounds. It is suggested that biomimetic cyclization of **11** proceeded instantaneously due to the proximity between cation **23** and the indole ring. It is suggested that biomimetic cyclization of **2** and **3** would be difficult to proceed, because of the long distance between the *tert*-cation and the double bond in a flexible conformation based on a longer terpene chain.

The cyclization mechanism for compounds **18** and **19** synthesized from **2** is shown in Fig. 4. These compounds were stereoisomers at C-2. This result suggests that the 6.6-bicyclic framework of **18** and **19** was respectively cyclized through a boat-like and chair-like conformation in the formation at the second ring. The 6.6.5-tricyclic framework of **18** was formed from cation **27** *via* a boat-like conformation (**24**) to give the stereogenic center of **25**, this being followed by quenching of the carbocation to reproduce an indole ring (**26**) and changing to a stable conformation. The 6.6.5-tricyclic framework of **19** was formed from cation **27** *via* a chair-like conformation and quenching of the carbocation to reproduce an indole ring (**28**). The yield of **19** was higher than that of **18**, suggesting that cyclization through the chair-like conformation proceeded more easily than that through a boat-like conformation. The kind of Lewis acid did not affect the total yields of **18** and **19**. Compound **5** had a longer terminal isoprene unit than **2** which was used as a model compound for the synthesis of emindole SA[17] by biomimetic cyclization. Compound **2** is considered to be a biosynthetic precursor of polyalthenol; however, the polyalthenol-type framework and decalin of the emindole-type framework were not synthesized from **2** by biomimetic cyclization.

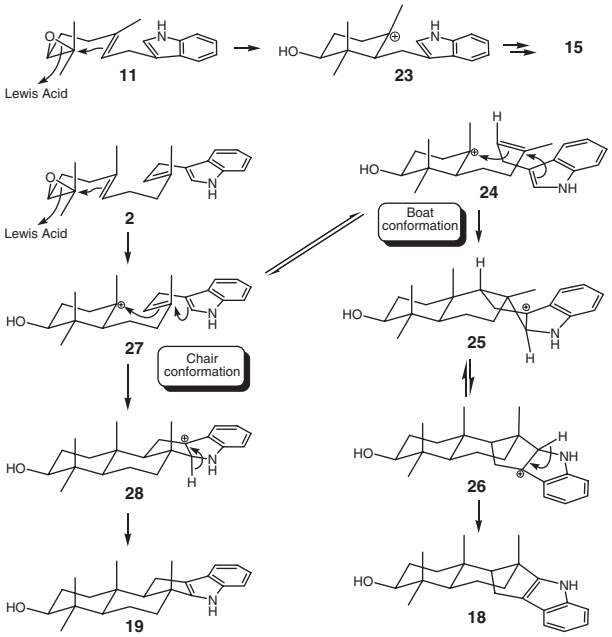


Fig. 4. Cyclization Mechanism for Compounds **15**, **18** and **19**.

Compound **20** would be synthesized from **3** by a cyclization mechanism of the 6.6.6.5-tetracyclic type in 6 steps: i) epoxide- opening with a Lewis acid, ii) formation of a *tert*-cation at C-11 by nucleophilic attack of C-10, iii) formation of a *tert*-cation at C-7 by nucleophilic attack of C-6, iv) formation of a *tert*-cation at C-3 by nucleophilic attack of C-2, v) formation of a cation on the indole ring (C-3′) by nucleophilic attack of the indole ring (C-2′), vi) quenching of the carbocation to reproduce the indole ring. The cyclization of **20** proceeded *via* a chair conformation, because H-2/H-6, H-6/H-10, H-10/H-14, C-18/C-19 and C-19/C-20 each had a 1,3-diaxial relationship.

The cyclization mechanism for compounds **16** and **17** synthesized from **2** is shown in Fig. 5. The bridged framework of **16** was formed from **2** *via* **29** which was in equilibrium with **27**. The framework of **17** was formed from cation **27** *via* the formation of cation **30** by a hydride shift and methyl rearrangement, quenching of the carbocation and subsequent ring-flip of carbonyl compound **31**. It is suggested that biomimetic cyclization easily proceeded not only with cyclization but also with the hydride shift and methyl rearrangement. In the case of biomimetic cyclization, the reaction of the linear side chain of terpene may be difficult, because the olefin in the linear side chain was conformationally away from the cation.

We were interested in the synthesis of natural products by biomimetic cyclization when using a nitrogen-unprotected precursor, because some total syntheses of natural products have been reported by biomimetic cyclization when using a nitrogen-protected precursor. The synthesis in a low yield of petromindole from a nitrogen-protected precursor by biomimetic cyclization when using a Lewis acid has been reported.[22] However, petromindole has not been synthesized from a nitrogen-unprotected precursor. Emindole SA has similarly been synthesized from a nitrogen-protected precursor by biomimetic cyclization when using Lewis acid,[17] but no emindole analogs have been synthesized from a

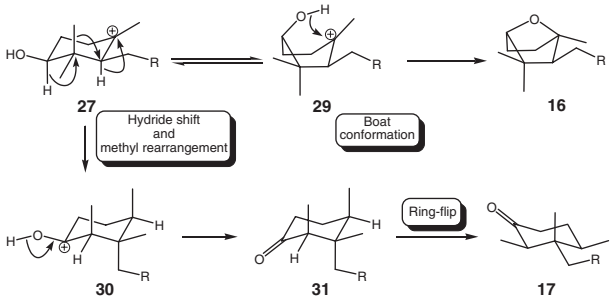


Fig. 5. Cyclization Mechanism for Compounds **16** and **17**.

nitrogen-unprotected precursor by biomimetic cyclization with a Lewis acid. These results suggest that biomimetic cyclization is controlled by the protection of nitrogen: the cyclization mechanism may be controlled to some extent by protecting nitrogen with an electron-withdrawing group such as a sulfonyl.

In conclusion, no natural product was obtained by biomimetic cyclization of a nitrogen-unprotected precursor. However, the many cyclic compounds obtained were new. The results of biomimetic cyclization suggest that the reaction proceeds through a relatively stretched conformation, whereas the enzymatic reaction proceeds through a folded conformation at the reaction site of the cyclase. It would therefore be difficult to synthesize the major or sole product by biomimetic cyclization. Our results suggest that protection of the indole-nitrogen was important in synthesizing the emindole and petromindole framework. Biomimetic cyclization may possibly be controlled to some extent by protecting nitrogen with electron-withdrawing groups. The number of products possessing unknown frameworks would be increased with increasing terpene chain length. Furthermore, all Lewis acids gave the same cyclic compounds. A Lewis acid was enough to initiate the reaction, but insufficient to carry out polycyclization. However, biomimetic cyclization may possibly be used for synthesizing new polycyclic compounds similar to natural indole terpene alkaloids. It is hoped that a useful bioactive compound could be found from these.

Experimental

Instrumentation. IR spectra were measured with a Jasco FT/IR-4100 spectrometer. ^{1}H-NMR spectra were recorded at 400 MHz by a Bruker AVANCE III 400 spectrometer, the peak for TMS (at δ 0.00) being used as the internal standard. ^{13}C-NMR spectra were recorded at 100 MHz by the Bruker AVANCE III 400 spectrometer, the peaks for $CDCl_3$ (at δ 77.0) and C_6D_6 (at δ 128.0) being used as the internal standards. Mass spectra were obtained with a Jeol JMS-BU25 (GCmate II) mass spectrometer in the electron ionization mode at an ionization energy of 70 eV. Column chromatography was carried out on 60 N silica gel (Kanto Chemicals), and PTLC was performed on PLC 60 F_{254} silica gel (Merck, 20 × 20 cm plate, 0.5 mm thickness, 1.05744.0009 or 1.0 mm thickness, 1.13895.0009).

*(*E*)-*tert*-Butyldiphenylsiloxy-3,7-dimethylocta-2,6-diene (**7**).* Imidazole (956 mg, 14.0 mmol) and TBDPSCl (2.31 g, 8.40 mmol) were added to a cooled solution of geraniol (1.08 g, 7.00 mmol) in dry DMF (14 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. After adding aq. NH_4Cl and EtOAc, the reaction mixture was extracted with EtOAc (50 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (hexane/EtOAc 10:1) to give silyl ether **7** (2.69 g,

98%) as a colorless oil. IR υ_{max} (film) cm^{-1}: 3070, 3049, 2961, 2930, 2857, 1472, 1428, 1380, 1111, 1059, 823, 778, 738, 701, 613, 505. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.44 (3H, s), 1.60 (3H, s), 1.68 (3H, s), 1.97 (2H, t, $J = 7.5$ Hz), 2.05 (2H, t, $J = 7.5$ Hz), 4.22 (2H, t, $J = 5.9$ Hz), 5.10 (1H, t, $J = 7.5$ Hz), 5.38 (1H, t, $J = 5.9$ Hz), 7.34–7.42 (6H, m, 6 × Ar*H*), 7.67–7.71 (4H, m, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.3 (CH_3), 17.6 (CH_3), 19.1 (C), 25.7 (CH_3), 26.3 (CH_2), 26.8 (3 × CH_3), 39.4 (CH_2), 61.1 (CH_2), 124.8 (CH), 124.1 (CH), 127.5 (2 × CH), 129.4 (4 × CH), 131.4 (C), 134.5 (2 × C), 135.6 (4 × CH), 137.0 (C). MS *m/z*: 392 (M^+, 16), 335 (98), 257 (41), 230 (16), 198 (100), 181 (39), 135 (57), 121 (24), 105 (14), 93 (11), 77 (32). HRMS *m/z*: calcd. for $C_{26}H_{36}OSi$ (M^+), 392.2535; found, 392.2509.

*(*E*)-*tert*-Butyldiphenylsiloxy-3,7-dimethyl-6,7-epoxyoct-2-ene (**8**).* $NaHCO_3$ (820 mg, 9.76 mmol) and *m*CPBA (77% purity, 1.48 g, 6.59 mmol) were added to a cooled solution of silyl ether **7** (1.96 g, 5.00 mmol) in dry CH_2Cl_2 (51 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. After adding aq. $NaHCO_3$, the reaction mixture was extracted with EtOAc (50 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (hexane/EtOAc 6:1) to give **8** (1.53 g, 74%) as a colorless oil. IR υ_{max} (film) cm^{-1}: 3071, 3049, 2959, 2930, 2857, 1472, 1461, 1428, 1377, 1111, 1058, 823, 786, 739, 702, 613, 505. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.26 (3H, s), 1.30 (3H, s), 1.46 (3H, s), 1.55–1.68 (2H, m), 2.03–2.20 (2H, m), 2.70 (1H, t, $J = 6.4$ Hz), 4.22 (2H, d, $J = 6.0$ Hz), 5.41 (1H, t, $J = 6.0$ Hz), 7.34–7.42 (6H, m, 6 × Ar*H*), 7.67–7.71 (4H, m, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.3 (CH_3), 18.7 (CH_3), 19.1 (C), 24.8 (CH_3), 26.8 (3 × CH_3), 27.2 (CH_2), 36.1 (CH_2), 58.3 (C), 61.0 (CH_2), 64.0 (CH), 124.6 (CH), 127.6 (2 × CH), 129.5 (4 × CH), 134.0 (2 × C), 135.6 (4 × CH), 136.1 (C). MS *m/z*: 351 ($[M - t\text{-Bu}]^+$, 64), 273 (71), 229 (31), 213 (21), 198 (100), 181 (50), 135 (88), 121 (36), 107 (47), 93 (46), 77 (39), 59 (18). HRMS *m/z*: calcd. for $C_{22}H_{27}O_2Si$ $[M - t\text{-Bu}]^+$, 351.1775; found, 351.1790.

*(*E*)-3,7-Dimethyl-6,7-epoxyoct-2-en-1-ol (**9**).* A THF solution of TBAF (1.0 M, 5.60 mL, 5.60 mmol) was added to a cooled solution of **8** (1.53 g, 3.70 mmol) in THF (16 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After adding aq. NH_4Cl and EtOAc, the reaction mixture was extracted with EtOAc (30 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc 1:2.5) to give **9** (597 mg, 95%) as a colorless oil. IR υ_{max} (film) cm^{-1}: 3407, 2962, 2925, 2877, 1666, 1450, 1379, 1248, 1116, 1002, 869, 680. NMR δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, s), 1.30 (3H, s), 1.67 (2H, quintet, $J = 6.4$ Hz), 1.70 (3H, s), 2.10–2.18 (2H, m), 2.71 (1H t, $J = 6.4$ Hz), 4.16 (2H, t, $J = 6.2$ Hz), 5.46 (1H, t, $J = 6.2$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 16.3 (CH_3), 18.7 (CH_3), 24.8 (CH_3), 27.2 (CH_2), 36.2 (CH_2), 58.3 (C), 59.3 (CH_2), 64.0 (CH), 123.9 (CH), 138.8 (C). MS *m/z*: 152 ($[M - H_2O]^+$, 2), 149 (19), 137 (14), 130 (11), 123 (9), 109 (10), 95 (17), 81 (51), 69 (100), 58 (43). HRMS *m/z*: calcd. for $C_{10}H_{16}O$ $[M - H_2O]^+$, 152.1201; found, 152.1203.

*(*E*)-Bromo-3,7-dimethyl-6,7-epoxyoct-2-ene (**10**).* Et_3N (0.98 mL, 7.00 mmol) and MsCl (0.35 mL, 4.55 mmol) were added to a cooled solution of **9** (597 mg, 3.50 mmol) in dry THF (10 mL) in a nitrogen atmosphere at −30 °C. The reaction mixture was stirred at −30 °C for 1 h. To the resulting mesylate solution was added LiBr (1.21 g, 13.9 mmol) in dry THF (10 mL) at −30 °C. The reaction mixture was stirred at 0 °C for 30 min. After adding aq. NH_4Cl and EtOAc, the reaction mixture was extracted with EtOAc (40 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford crude product **10** (820 mg) as a colorless oil. IR υ_{max} (film) cm^{-1}: 2961, 2924, 2860, 1655, 1450, 1377, 1323, 1249, 1202, 1174, 1122, 874, 897, 679, 589. NMR δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, s), 1.31 (3H, s), 1.66 (2H, m), 1.75 (3H, br s), 2.15–2.28 (2H, m), 2.69 (1H t, $J = 6.0$ Hz), 4.01 (2H, d, $J = 8.4$ Hz), 5.58 (1H, t, $J = 8.4$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 18.7 (CH_3), 24.8 (CH_3), 27.0 (CH_2), 29.1 (CH_2), 36.2 (CH_2), 58.4 (C), 63.8 (CH), 121.1 (CH), 142.5 (C). MS *m/z*: 153 ($[M - Br]^+$, 27), 149 (30), 135 (29), 111 (31), 93 (33), 81 (100), 71 (87), 69 (78), 58 (95). HRMS *m/z*: calcd. for $C_{10}H_{17}O$ $[M - Br]^+$, 153.1274; found, 153.1271.

*3-(6,7-Epoxygeranyl)indole (**11**).* DIEA (1.35 mL, 7.75 mmol) was added to a solution of indole (826 mg, 7.05 mmol), $Zn(OTf)_2$ (1.54 g, 4.23 mmol) and TBAI (1.34 g, 3.62 mmol) in dry toluene (21 mL) at room temperature in a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 min. To the reaction mixture was added crude product **10** (820 mg) in dry toluene (14 mL) at room temperature. The reaction mixture was stirred overnight at room temperature. After adding aq. NH_4Cl, the reaction mixture was extracted with EtOAc (35 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc 12:1) to give **11** (497 mg, 53%, 3 steps) as a colorless oil. IR υ_{max} (film) cm^{-1}: 3414, 3342, 3055, 2961, 2923, 2851, 1456, 1378, 1251, 1227, 1125, 1092, 739. NMR δ_H ($CDCl_3$, 400 MHz): 1.25 (3H, s), 1.26 (3H, s), 1.67 (2H, m), 1.78 (3H, br s), 2.12–2.26 (2H, m), 2.72 (1H t, $J = 6.4$ Hz), 3.47 (2H, d, $J = 7.0$ Hz), 5.50 (1H, t, $J = 7.0$ Hz), 6.95 (1H, br s), 7.10 (1H, t, $J = 7.9$ Hz), 7.18 (1H, t, $J = 7.9$ Hz), 7.35 (1H, d, $J = 7.9$ Hz), 7.58 (1H, d, $J = 7.9$ Hz), 7.90 (1H, br s). NMR δ_C ($CDCl_3$, 100 MHz): 16.1 (CH_3), 18.7 (CH_3), 24.0 (CH_2), 24.8 (CH_3), 27.4 (CH_2), 36.3 (CH_2), 58.3 (C), 64.9 (CH), 111.0 (CH), 115.9 (C), 119.0 (CH), 119.1 (CH), 121.1 (CH), 121.9 (CH), 123.6 (CH), 127.4 (C), 134.6 (C), 136.5 (C). MS *m/z*: 269 (M^+, 77), 251 (25), 236 (13), 210 (67), 182 (49), 170 (84), 143 (42), 130 (100), 117 (74), 103 (13), 77 (22), 59 (15). HRMS *m/z*: calcd. for $C_{18}H_{23}NO$ (M^+), 269.1780; found, 269.1756.

*(2*E*,6*E*)-*tert*-Butyldiphenylsiloxy-3,7,11-trimethyldodeca-2,6,10-triene (**32**).* Farnesol (3.89 g, 17.5 mmol) was converted to silyl ether **32** (7.91 g, 97%) as a colorless oil by the same method as that used for the synthesis of **7**. IR υ_{max} (film) cm^{-1}: 3070, 3049, 2959, 2929, 2857, 1472, 1461, 1428, 1387, 1111, 1058, 1006, 822, 738, 700, 613, 505, 739. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.44 (3H, br s), 1.60 (6H, br s), 1.67 (3H, br s), 1.95–2.02 (4H, complex), 2.03–2.11 (4H, complex), 4.22 (2H, d, $J = 6.6$ Hz), 5.09 (1H, t, $J = 7.1$ Hz), 5.11 (1H, t, $J = 6.8$ Hz), 5.38 (1H, t, $J = 6.6$ Hz), 7.32–7.42 (6H, 6 × Ar*H*), 7.65–7.72 (4H, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (CH_3), 16.4 (CH_3), 17.7 (CH_3), 19.2 (C), 25.7 (CH_3), 26.3 (CH_2), 26.8 (CH_2), 26.9 (3 × CH_3), 39.5 (CH_2), 39.7 (CH_2), 61.2 (CH_2), 124.0 (CH), 124.1 (CH), 124.4 (CH), 127.6 (4 × CH), 129.5 (2 × CH), 131.3 (C), 134.1 (2 × C), 135.2 (C), 135.6 (4 × CH), 137.1 (C). MS *m/z*: 403 ($[M - t\text{-Bu}]^+$, 9), 311 (8), 289 (11), 217 (14), 198 (100), 181 (17), 149 (20), 135 (26), 93 (47), 77 (48), 69 (96). HRMS *m/z*: calcd. for $C_{27}H_{35}OSi$ $[M - t\text{-Bu}]^+$, 403.2452; found, 403.2478.

*(2*E*,6*E*)-*tert*-Butyldiphenylsiloxy-10,11-epoxy-3,7,11-trimethyldodeca-2,6-diene (**33**).* Compound **32** (7.91 g, 17.0 mmol) was converted to epoxide **33** (2.11 g, 22%) as a colorless oil by the same method as that used for the synthesis of **8**. IR υ_{max} (film) cm^{-1}: 3070, 3048, 2959, 2930, 2856, 1733, 1590, 1472, 1461, 1445, 1428, 1377, 1111, 1056, 1006, 823, 770, 741, 701, 613, 504. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.25 (3H, br s), 1.29 (3H, s), 1.44 (3H, br s), 1.561.68 (2H, complex), 1.62 (6H, br s), 1.98 (2H, t, $J = 4.0$ Hz), 2.02–2.20 (4H, complex), 2.69 (1H, t, $J = 4.0$ Hz), 4.22 (2H, d, $J = 8.0$ Hz), 5.16 (1H, t, $J = 4.0$ Hz), 5.38 (1H, t, $J = 8.0$ Hz), 7.32–7.42 (6H, 6 × Ar*H*), 7.65–7.72 (4H, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (CH_3), 16.3 (CH_3), 18.7 (CH_3), 19.2 (C), 24.8 (CH_3), 26.3 (CH_2), 26.8 (3 × CH_3), 27.5 (CH_2), 36.3 (CH_2), 39.4 (CH_2), 58.3 (C), 61.2 (CH_2), 64.1 (CH), 124.1 (CH), 124.6 (CH), 127.6 (4 × CH), 129.5 (2 × C), 134.2 (C), 135.1 (C), 135.6 (4 × CH), 137.1 (C). MS *m/z*: 419 ($[M - t\text{-Bu}]^+$, 13), 341 (4), 283 (4), 229 (6), 199 (100), 181 (10), 161 (8), 147 (17), 135 (32), 119 (17), 95 (15), 81 (20), 69 (28). HRMS *m/z*: calcd. for $C_{27}H_{35}O_2Si$ $[M - t\text{-Bu}]^+$, 419.2401; found, 419.2419.

*(2*E*,6*E*)-10,11-Epoxy-3,7,11-trimethyldodeca-2,6-dien-1-ol (**34**).* Epoxide **33** (2.11 g, 4.43 mmol) was converted to the compound **34** (1.14 g, 91%) as a colorless oil by the same method as that used for the synthesis of **9**. IR υ_{max} (film) cm^{-1}: 3414, 2960, 2924, 2857, 1667, 1448, 1378, 1248, 1118, 1066, 871, 678. NMR δ_H ($CDCl_3$, 400 MHz):

1.26 (3H, s), 1.30 (3H, s), 1.62 (3H, br s), 1.62–1.65 (2H, complex), 1.67 (3H, br s), 1.97–2.10 (2H, complex), 2.10–2.19 (4H, complex), 2.70 (1H, t, $J = 6.2$ Hz), 4.15 (2H, t, $J = 6.3$ Hz), 5.16 (1H, t, $J = 6.3$ Hz), 5.41 (1H, t, $J = 6.8$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 16.2 (CH_3), 18.7 (CH_3), 24.8 (CH_3), 26.1 (CH_2), 27.3 (CH_2), 36.3 (CH_2), 39.4 (CH_2), 58.3 (C), 59.3 (CH_2), 64.1 (CH), 123.6 (CH), 124.5 (CH), 134.3 (C), 139.4 (C). MS m/z: 220 ([M-H_2O]$^+$, 5), 199 (25), 189 (10), 177 (9), 159 (25), 153 (26), 143 (33), 135 (71), 121 (56), 109 (75), 93 (84), 85 (86), 81 (100), 69 (69), 59 (59). HRMS m/z: calcd. for $C_{15}H_{24}O$ [M − H_2O]$^+$, 220.1827; found, 220.1864.

*(2*E*,6*E*)-Bromo-10,11-epoxy-3,7,11-trimethyldodeca-2,6-diene (**35**).* Compound **34** (1.14 g, 4.03 mmol) was converted to crude **35** (1.23 g) as a colorless oil by the same method as that used for the synthesis of **10**. IR υ_{max} (film) cm^{-1}: 3458, 2960, 2924, 2853, 2363, 2339, 1654, 1447, 1377, 1202, 1119, 874, 857. NMR δ_H ($CDCl_3$, 400 MHz): 1.25 (3H, s), 1.29 (3H, s), 1.61 (3H, br s), 1.58–1.65 (2H, complex), 1.72 (3H, br s), 2.05–2.15 (6H, complex), 2.69 (1H, t, $J = 7.2$ Hz), 4.08 (2H, d, $J = 7.4$ Hz), 5.13 (1H, t, $J = 6.7$ Hz), 5.52 (1H, t, $J = 7.4$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 16.0 (CH_3), 18.7 (CH_3), 24.9 (CH_3), 26.1 (CH_2), 27.5 (CH_2), 29.6 (CH_2), 36.3 (CH_2), 39.4 (CH_2), 58.3 (C), 64.1 (CH), 120.7 (CH), 124.0 (CH), 134.8 (C), 143.4 (C). MS m/z: 221 ([M − Br]$^+$, 5), 203 (7), 18 (2), 153 (19), 107 (43), 101 (91), 93 (78), 85 (77), 81 (85), 71 (83), 59 (100). HRMS m/z: calcd. for $C_{15}H_{25}O$ [M − Br]$^+$, 221.1900; found, 221.1884.

*3-(10,11-Epoxyfarnesyl)indole (**2**).* Crude **35** (1.23 g) was converted to **2** (677 mg, 50%, 3 steps) as a colorless oil by the same method as that used for the synthesis of **11**. IR υ_{max} (film) cm^{-1}: 3417, 3346, 3055, 2961, 2923, 2852, 1455, 1378, 1351, 1338, 1249, 1225, 1122, 1092, 1045, 1009, 868, 800, 740. NMR δ_H ($CDCl_3$, 400 MHz): 1.24 (3H, s), 1.29 (3H, s), 1.58–1.63 (2H, complex), 1.62 (3H, br s), 1.75 (3H, br s), 2.05–2.20 (6H, complex), 2.70 (1H, t, $J = 6.2$ Hz), 3.46 (2H, d, $J = 7.2$ Hz), 5.18 (1H, t, $J = 6.1$ Hz), 5.46 (1H, t, $J = 7.2$ Hz), 6.93 (1H, d, $J = 2.2$ Hz), 7.09 (1H, t, $J = 7.8$ Hz), 7.17 (1H, t, $J = 7.8$ Hz), 7.34 (1H, t, $J = 7.8$ Hz), 7.58 (1H, t, $J = 7.8$ Hz), 8.03 (1H, br s). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 16.1 (CH_3), 18.7 (CH_3), 23.9 (CH_2), 24.9 (CH_3), 26.4 (CH_2), 27.5 (CH_2), 36.3 (CH_2), 39.6 (CH_2), 58.5 (C), 64.3 (CH), 111.1 (CH), 116.1 (C), 119.0 (CH), 119.1 (CH), 121.3 (CH), 121.9 (CH), 123.2 (CH), 124.8 (CH), 127.5 (C), 134.1 (C), 135.4 (C), 136.6 (C). MS m/z: 337 (M$^+$, 96), 320 (7), 238 (14), 210 (9), 196 (32), 184 (100), 170 (70), 168 (63), 143 (21), 130 (74), 117 (36), 93 (7), 85 (11), 59 (10). HRMS m/z: calcd. for $C_{23}H_{31}NO$ (M$^+$), 337.2406; found, 337.2388.

*(2*E*,6*E*,10*E*,14*E*)*-tert-*Butyldiphenylsiloxy-3,7,11,15-tetramethylhexadeca-2,6,10-tetraene (**12**).* Geranylgeraniol (2.52 g, 8.67 mmol) was converted to silyl ether **12** (4.08 g, 89%) as a colorless oil by the same method as that used for the synthesis of **7**. IR υ_{max} (film) cm^{-1}: 2960, 2929, 2856, 1446, 1428, 1111, 1057, 823, 737, 700, 688, 613, 504, 490. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.44 (3H, br s), 1.59 (3H, br s), 1.90 (6H, complex), 1.67 (3H, br s), 1.95–2.10 (12H, complex), 4.22 (2H, d, $J = 6.3$ Hz), 5.09 (1H, t, $J = 6.9$ Hz), 5.11 (1H, t, $J = 6.6$ Hz), 5.38 (1H, t, $J = 6.3$ Hz), 7.34–7.45 (6H, 6 × Ar*H*), 7.65–7.70 (4H, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (CH_3), 16.1 (CH_3), 16.4 (CH_3), 17.7 (CH_3), 19.2 (C), 25.7 (CH_3), 26.4 (CH_3), 26.7 (CH_2), 26.8 (CH_2), 26.9 (3 × CH_3), 39.6 (CH_2), 39.7 (2 × CH_2), 61.2 (CH_2), 124.0 (2 × CH), 124.3 (CH), 124.4 (CH), 127.6 (4 × CH), 129.5 (2 × CH), 131.3 (C), 134.1 (2 × C), 134.9 (C), 135.2 (C), 135.6 (4 × CH), 137.1 (C). MS m/z: 471 ([M − *t*-Bu]$^+$, 8), 433 (5), 272 (6), 199 (100), 181 (11), 135 (36), 93 (30), 81 (39), 69 (96). HRMS m/z: calcd. for $C_{32}H_{43}OSi$ [M − *t*-Bu]$^+$, 471.3032; found, 471.3034.

*(2*E*,6*E*,10*E*)*-tert-*Butyldiphenylsiloxy-14-bromo-15-hydroxyl-3,7,11,15-tetramethylhexadeca-2,6,10-triene (**13**).* Silyl ether **12** (1.46 g, 2.77 mmol) was converted to bromohydrine **13** (1.37 g, 79%) as a colorless oil According to the method of Ceruti *et al.*[21] IR υ_{max} (film) cm^{-1}: 2960, 2930, 2856, 1428, 1379, 1111, 1055, 701, 502. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.32 (3H, br s), 1.33 (3H, br s), 1.44 (3H, br s), 1.59 (3H, br s), 1.60 (3H, br s), 1.78 (1H, m), 1.92–2.14 (10H, complex), 2.31 (1H, m), 3.96 (1H, d, $J = 11.6$ Hz), 4.22 (2H, d, $J = 6.2$ Hz), 5.12 (1H, t, $J = 6.8$ Hz), 5.20 (1H, t, $J = 6.4$ Hz), 5.38 (1H, t, $J = 6.2$ Hz), 7.34–7.45 (6H, 6 × Ar*H*), 7.65–7.70 (4H, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 16.0 (CH_3), 16.4 (CH_3), 19.2 (C), 25.7 (CH_3), 26.4 (CH_2), 26.6 (CH_2), 26.7 (CH_3), 26.9 (3 × CH_3), 32.2 (CH_2), 38.2 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 61.2 (CH_2), 71.1 (CH), 72.5 (C), 124.0 (CH), 124.2 (C), 126.0 (CH), 127.6 (4 × CH), 129.5 (2 × CH), 133.0 (C), 134.1 (2 × C), 135.0 (C), 135.6 (4 × CH), 137.1 (C). MS m/z: 488 ([M − *t*-Bu − Br]$^+$, 2), 289 (4), 71 (7), 229 (4), 199 (100), 161 (10), 149 (17), 135 (50), 121 (25), 81 (91), 71 (27), 69 (23). HRMS m/z: calcd. for $C_{32}H_{44}O_2Si$ [M − *t*-Bu − Br]$^+$, 488.3105; found, 488.3095.

*(2*E*,6*E*,10*E*)*-tert-*Butyldiphenylsiloxy-14,15-epoxy-3,7,11,15-tetramethylhexadeca-2,6,10-triene (**14**).* Bromohydrine **13** (1.37 g, 2.19 mmol) was converted to **14** (943 mg, 80%) as a colorless oil according to the method of Ceruti *et al.*[21] IR υ_{max} (film) cm^{-1}: 2959, 2930, 2857, 1472, 1461, 1428, 1378, 1111, 1057, 823, 738, 701, 612. NMR δ_H ($CDCl_3$, 400 MHz): 1.04 (9H, s), 1.25 (3H, s), 1.29 (3H, s), 1.44 (3H, br s), 1.60 (3H, br s), 1.61 (br s), 1.60–1.69 (2H, complex), 1.94–2.20 (10H, complex), 2.69 (1H, t, $J = 6.3$), 4.22 (2H, d, $J = 6.1$ Hz), 5.12 (1H, t, $J = 6.9$ Hz), 5.16 (1H, t, $J = 6.6$ Hz), 5.38 (1H, t, $J = 6.1$ Hz), 7.34–7.45 (6H, 6 × Ar*H*), 7.66–7.72 (4H, 4 × Ar*H*). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (CH_3), 16.1 (CH_3), 16.4 (CH_3), 18.8 (CH_3), 24.9 (CH_3), 26.4 (CH_2), 26.9 (3 × CH_3), 27.5 (CH_2), 36.3 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 58.2 (C), 61.2 (CH_2), 64.2 (CH), 124.1 (CH), 124.2 (CH), 124.9 (CH), 127.5 (4 × CH), 129.5 (2 × CH), 133.6 (CH), 134.1 (2 × C), 134.2 (C), 135.1 (C), 135.6 (4 × CH),137.0 (C). MS m/z: 487 ([M − *t*-Bu]$^+$, 9), 351 (3), 271 (13), 199 (100), 181 (12), 164 (14), 135 (65), 121 (34), 93 (53), 77 (35), 69 (31). HRMS m/z: calcd. for $C_{32}H_{43}O_2Si$ [M − *t*-Bu]$^+$, 487.3032; found, 487.3025.

*(2*E*,6*E*,10*E*)-14,15-Epoxy-3,7,11,15-tetramethylhexadeca-2,6,10-trien-1-ol (**36**).* Compound **14** (943 mg, 1.73 mmol) was converted to **36** (408 mg, 77%) as a colorless oil by the same method as that used for the synthesis of **9**. IR υ_{max} (film) cm^{-1}: 3419, 2961, 2923, 2855, 1733, 1668, 1598, 1446, 1379, 1322, 1249, 1121, 1004, 871, 768, 681. NMR δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, s), 1.30 (3H, s), 1.60 (3H, br s), 1.62 (3H, br s), 1.68 (3H, br s), 1.57–1.69 (2H, complex), 1.97–2.20 (10H, complex), 2.70 (1H, t, $J = 6.4$), 4.15 (2H, d, $J = 7.0$ Hz), 5.12 (1H, t, $J = 7.2$ Hz), 5.16 (1H, t, $J = 6.8$ Hz), 5.41 (1H, t, $J = 7.0$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (2 × CH_3), 16.1 (CH_3), 16.3 (CH_3), 18.7 (CH_3), 24.8 (CH_3), 26.3 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 36.3 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 58.3 (C), 59.4 (CH_2), 64.2 (CH), 123.5 (CH), 123.9 (CH), 124.8 (CH), 134.0 (C), 135.2 (C), 139.6 (C). MS m/z: 288 ([M − H_2O]$^+$, 4), 202 (4), 189 (4), 161 (12), 153 (15), 135 (46), 119 (34), 93 (79), 81 (100), 59 (17). HRMS m/z: calcd. for $C_{20}H_{32}O$ [M − H_2O]$^+$, 288.2453; found, 288.2446.

*(2*E*,6*E*,10*E*)-Bromo-14,15-epoxy-3,7,11,15-tetramethylhexadeca-2,6,10-triene (**37**).* Compound **36** (408 mg, 1.33 mmol) was converted to crude **37** (497 mg) as a colorless oil by the same method as that used for the synthesis of **10**. IR υ_{max} (film) cm^{-1}: 2960, 2924, 2854, 1777, 1655, 1449, 1377, 1324, 1248, 1200, 1174, 1121, 897, 872, 793, 5843. NMR δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, s), 1.29 (3H, s), 1.59 (3H, br s), 1.62 (3H, br s), 1.61–1.69 (2H, complex), 1.78 (3H, br s), 1.96–2.20 (10H, complex), 2.69 (1H, t, $J = 6.3$), 4.01 (2H, d, $J = 8.4$ Hz), 5.08 (1H, t, $J = 5.8$ Hz), 5.16 (1H, t, $J = 6.7$ Hz), 5.52 (1H, t, $J = 8.4$ Hz). NMR δ_C ($CDCl_3$, 100 MHz): 16.0 (3 × CH_3), 18.7 (CH_3), 24.8 (CH_3), 26.1 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 29.5 (CH_2), 36.3 (CH_2), 39.5 (CH_2), 39.6 (CH_2), 58.3 (C), 64.2 (CH), 120.6 (CH), 123.5 (CH), 124.8 (CH), 134.1 (C), 135.5 (C), 143.5 (C). MS m/z: 289 ([M − Br]$^+$, 3), 252 (6), 199 (35), 153 (15), 147 (17), 135 (51), 119 (72), 107 (49), 93 (100), 58 (21). HRMS m/z: calcd. for $C_{20}H_{33}O$ [M − Br]$^+$, 289.2526; found, 289.2526.

*3-(14,15-Epoxygeranylgeranyl)indole (**3**).* Crude **37** (497 mg) was converted to **3** (306 mg, 57%) as a colorless oil by the same method as that used for the synthesis of **10**. IR υ_{max} (film) cm^{-1}: 3417, 3343, 3054, 2961, 2920, 2850, 1665, 1618, 1455, 1379, 1351, 1337, 1249, 1224, 1122, 1092, 1009, 867, 739, 423. NMR δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, s), 1.30 (3H, s), 1.60 (3H, br s), 1.61 (3H, br s), 1.59–1.66 (2H, complex), 1.76 (3H, br s), 1.96–2.20 (10H, complex), 2.70 (1H, t, $J = 6.4$), 3.46 (2H, d, $J = 6.8$ Hz), 5.13 (1H, t, $J = 5.6$ Hz), 5.15 (1H, t, $J = 6.0$ Hz), 5.45 (1H, t, $J = 6.8$ Hz), 6.95 (1H, d, $J = 1.2$ Hz), 7.10 (1H, t, $J = 7.7$ Hz), 7.18 (1H, t, $J = 7.7$ Hz), 7.35 (1H, d, $J = 7.7$ Hz),

7.59 (1H, d, $J = 7.7$ Hz), 7.98 (1H, br s). NMR δ_C ($CDCl_3$, 100 MHz): 15.9 (CH_3), 16.0 (CH_3), 16.1 (CH_3), 18.8 (CH_3), 24.0 (CH_2), 24.9 (CH_3), 26.6 (CH_2), 26.7 (CH_2), 27.4 (CH_2), 36.4 (CH_2), 39.6 (CH_2), 39.7 (CH_2), 58.8 (C), 64.3 (CH), 111.0 (CH), 116.1 (C), 119.0 (CH), 119.1 (CH), 121.2 (CH), 121.9 (CH), 123.0 (CH), 124.3 (CH), 125.0 (CH), 127.5 (C), 134.0 (C), 134.9 (C), 135.6 (C), 136.5 (C). MS *m/z*: 405 (M^+, 19), 196 (9), 184 (100), 170 (24), 13 (81), 117 (19), 93 (9). HRMS *m/z*: calcd. for $C_{28}H_{39}NO$ (M^+), 405.3032; found, 405.3020.

*Biomimetic cyclization of indole terpene precursors **11**, **2** and **3** by a Lewis acid.* A Lewis acid (0.12 mmol) was added to the solution of an indole terpene precursor (0.1 mmol) in dry CH_2Cl_2 (1 mL) at $-78\,^\circ C$ in a nitrogen atmosphere. The reaction mixture was stirred at $-78\,^\circ C$ for 1 min. After adding aq. $NaHCO_3$, the reaction mixture was extracted with EtOAc (3×3 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*.

The residue obtained by biomimetic cyclization of **11** was purified by PTLC (hexane/EtOAc 3:1) to give **15** as a colorless oil. The yield of **15** using each Lewis acids was as follows: $MeAlCl_2$, 62%; $BF_3 \cdot OEt_2$, 40%; $TiCl_4$, 73%; and $SnCl_4$, 48%. The ^{1}H- and ^{13}C-NMR data for **15** are shown in Table 1. IR υ_{max} (film) cm^{-1}: 3402, 3304, 2999, 2975, 2933, 2860, 1450, 1370, 1303, 1246, 1216, 1084, 1008, 746. MS *m/z*: 269 (M^+, 73), 254 (100), 236 (83), 182 (32), 146 (29), 130 (46), 120 (93). HRMS *m/z*: calcd. for $C_{18}H_{23}NO$ (M^+), 269.1780; found, 269.1779.

The residue obtained by biomimetic cyclization of **2** was purified by PTLC (hexane/EtOAc 3:1) to give **16**, **17** and a mixture containing **18** and **19** as colorless oils. The mixture containing **18** and **19** was separated by HPLC under the following conditions: column, Inertsil-ODS-3 (ϕ10.0 $\times$ 250 mm, GL Sciences); UV, 210–350 nm; solvent, 85% MeOH; flow rate, 2 mL/min; t_R: **18**, 24.80 min; **19**, 26.25 min. The yields of **16**, **17**, **18** and **19** using each Lewis acid were as follow: $MeAlCl_2$, 7% (**16**), 7% (**17**), 4% (**18**) and 13% (**19**); $BF_3 \cdot OEt_2$, 6% (**16**), 6% (**17**), 7% (**18**) and 16% (**19**); $TiCl_4$, 11% (**16**), 6% (**17**), 6% (**18**) and 13% (**19**); $SnCl_4$, 6% (**16**), 8% (**17**), 3% (**18**) and 12% (**19**). The ^{1}H- and ^{13}C-NMR data for cyclic compounds **16**–**19** are shown in Table 2.

Compound **16**. IR υ_{max} (film) cm^{-1}: 3417, 3299, 2963, 2870, 1455, 1381, 1363, 1351, 1339, 1225, 1192, 1094, 1007, 986, 870, 739. MS *m/z*: 337 (M^+, 91), 210 (20), 196 (33), 184 (57), 170 (100), 168 (27), 143 (19), 130 (90), 117 (36), 95 (14). HRMS *m/z*: calcd. for $C_{23}H_{31}NO$ (M^+), 337.2406; found, 337.2407.

Compound **17**. IR υ_{max} (film) cm^{-1}: 3411, 3295, 2965, 2938, 2874, 1702, 1455, 1377, 1352, 1221, 1091, 1010, 740. MS *m/z*: 337 (M^+, 89), 196 (33), 183 (33), 170 (100), 143 (19), 139 (72), 130 (74), 117 (42), 95 (5). HRMS *m/z*: calcd. for $C_{23}H_{31}NO$ (M^+), 337.2406; found, 337.2407.

Compound **18**. IR υ_{max} (film) cm^{-1}: 3403, 3307, 2938, 2866, 1459, 1452, 1382, 1305, 1027, 1005, 753. MS *m/z*: 337 (M^+, 74), 319 (23), 252 (26), 186 (38), 170 (59), 149 (67), 130 (80), 120 (100), 69 (54), 55 (69). HRMS *m/z*: calcd. for $C_{23}H_{31}NO$ (M^+), 337.2406; found, 337.2404.

Compound **19**. IR υ_{max} (film) cm^{-1}: 3399, 3275, 2999, 2961, 2930, 2851, 1733, 1600, 1540, 1497, 1447, 1215, 1034, 1009, 754. MS *m/z*: 337 (M^+, 22), 322 (21), 273 (15), 252 (11), 188 (25), 149 (49), 135 (60), 120 (100), 69 (64), 57 (94). HRMS *m/z*: calcd. for $C_{23}H_{31}NO$ (M^+), 337.2406; found, 337.2405.

The residue obtained by biomimetic cyclization of **3** was purified by PTLC (hexane/EtOAc 3:1) to give **20**, **21** and **22** as colorless oils. The yields of **20**, **21** and **22** using each Lewis acid were as follow: $MeAlCl_2$, 15% (**20**), 6% (**21**) and 3% (**22**); $BF_3 \cdot OEt_2$, 14% (**20**), 2% (**21**) and 6% (**22**); $TiCl_4$, 12% (**20**), 7% (**21**) and 4% (**22**); $SnCl_4$, 12% (**20**), 5% (**21**) and 4% (**22**). The ^{1}H- and ^{13}C-NMR data for cyclic compounds **20**-**22** are shown in Table 3.

Compound **20**. IR υ_{max} (film) cm^{-1}: 3401, 3311, 2962, 2926, 2852, 1732, 1599, 1463, 1455, 1447, 1417, 1358, 1375, 1302, 1261, 1215, 1101, 1020, 864, 799, 758. MS *m/z*: 405 (M^+, 78), 387 (94), 372 (74), 182 (64), 168 (39), 130 (100), 69 (51), 55 (59). HRMS *m/z*: calcd. for $C_{28}H_{39}NO$ (M^+), 405.3032; found, 405.3050.

Compound **21**. IR υ_{max} (film) cm^{-1}: 3412, 3310, 3054, 2962, 2933, 2870, 1706, 1683, 1618, 1455, 1381, 1092, 1002, 986, 872, 740. MS *m/z*: 405 (M^+, 31), 279 6), 252 (7), 196 (11), 184 (100), 149 (35), 130 (89), 117 (22), 55 (34). HRMS *m/z*: calcd. for $C_{28}H_{39}NO$ (M^+), 405.3032; found, 405.3048.

Compound **22**. IR υ_{max} (film) cm^{-1}: 3407, 3311, 2925, 1703, 1455, 1377, 1261, 1091, 1020, 738. MS *m/z*: 405 (M^+, 45), 238 (7), 196 (10), 184 (100), 170 (33), 139 (39), 130 (92), 117 (229), 69 (47), 55 (61). HRMS *m/z*: calcd. for $C_{28}H_{39}NO$ (M^+), 405.3032; found, 405.3053.

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