Synthetic Photochemistry. XLII.[1] Total Synthesis of Cycloaraneosene, a Fundamental Hydrocarbon of 5-8-5-Membered Tricyclic Diterpenoid from *Sordaria araneosa*[2]

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A 5–8–5-membered tricyclic diterpene, cycloaraneosene, has been totally synthesized via a stereoselective condensation of two units of optically active iridoids, a Cope rearrangement, a chemical reduction of the tetrasubstituted double bond, and the formation of an eight-membered ring. The proposed structure of natural hydroxycycloaraneosene should be revised to 8β-hydroxycycloaraneosene, judging from the NMR spectral data.

In 1975, Borschberg reported the isolation and structure determination of a 5–8–5-membered tricyclic diterpene, cycloaraneosene (**1**),[3] from *Sordaria araneosa* Cain. Obviously, **1** is the biogenetic precursor of the congener diterpenoids of a fungus, such as sordaricin[4] and hydroxycycloaraneosene.[3] In this paper we describe the total synthesis of **1** using the condensation of two functionalized iridoids, in which the synthetic strategy is similar to our previous synthesis of fusicoccatriene.[5] Although several studies on this subject have been appeared, no total synthesis of natural 5–8–5-membered tricyclic compounds has been reported.[6]

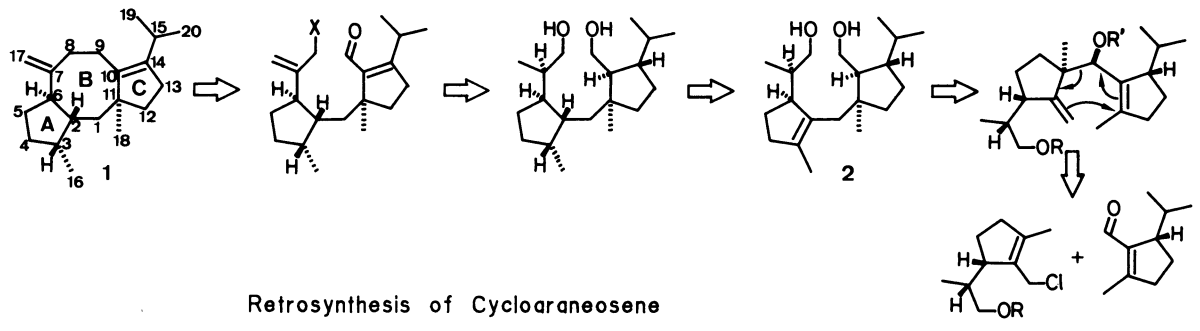
Results and Discussion

Among the natural 5–8–5-membered compounds, the stereochemistry of **1** has two outstanding features: i) the syn-relation between the hydrogen at C-6 and the methyl group C-11 is reverse to that of cotylenins[7] and fusicoccins[8] and ii) the hydrogens at C-2 and C-3 of the saturated ring A have a cis-β-geometry (i.e., (2*R*,3*R*)-structure). The former arrangement can be created by a stereospecific Cope rearrangement of the dimeric condensate of appropriate iridoids.[9] Therefore, in order to synthesize **1**,[10] a stereoselective reduction of the tetrasubstituted double bond, which is indispensable for a Cope rearrangement, is crucial. This reduction must be performed prior to the formation of double bonds and the B-ring.

With the regard to those facts, the key compounds for a reduction must be the diol **2** or its equivalents, the stereochemical framework of which should be inherited from the condensation of (3*S*)-iridenals and (3*S*)-iridenyl chlorides.

In order to obtain **2**, we carried out further conversions of the Cope rearrangement product **3**, prepared from the chromium(II) chloride condensation[11] of (3*S*)-1-iriden-7-al and (3*S*,8*R*)-9-benzyloxy-7-chloro-1-iridene[5] as follows. The hydrolysis of **3** and the epimerization of the resulting aldehyde were consecutively performed with potassium fluoride on silica gel and on Florisil to give thermodynamically stable aldehyde **4** in good yield. The lithium aluminum hydride (LAH) reduction of **4** gave the corresponding primary alcohol **5**. The catalytic hydrogenolysis of **5** with palladium on carbon gave the desired **2**, which was further transformed to diacetate **6** and bis(tetrahydropyranyl) (THP) ether (**7**).

In order to generate the correct stereochemistry of the A-ring, the hydrogenation must occur from the β-side of **2**; this procedure was shown to be promising from observations of the Dreiding's Stereomodels; i.e., the α-side of the A-ring is more hindered than the β-side by substituents on the C-ring. However, all attempts to hydrogenate **2** failed, except for hydrogenation under Adam's conditions, platinum(IV) oxide in acetic acid, which gave a mixture of acetylated dihydro derivatives in low yields. This

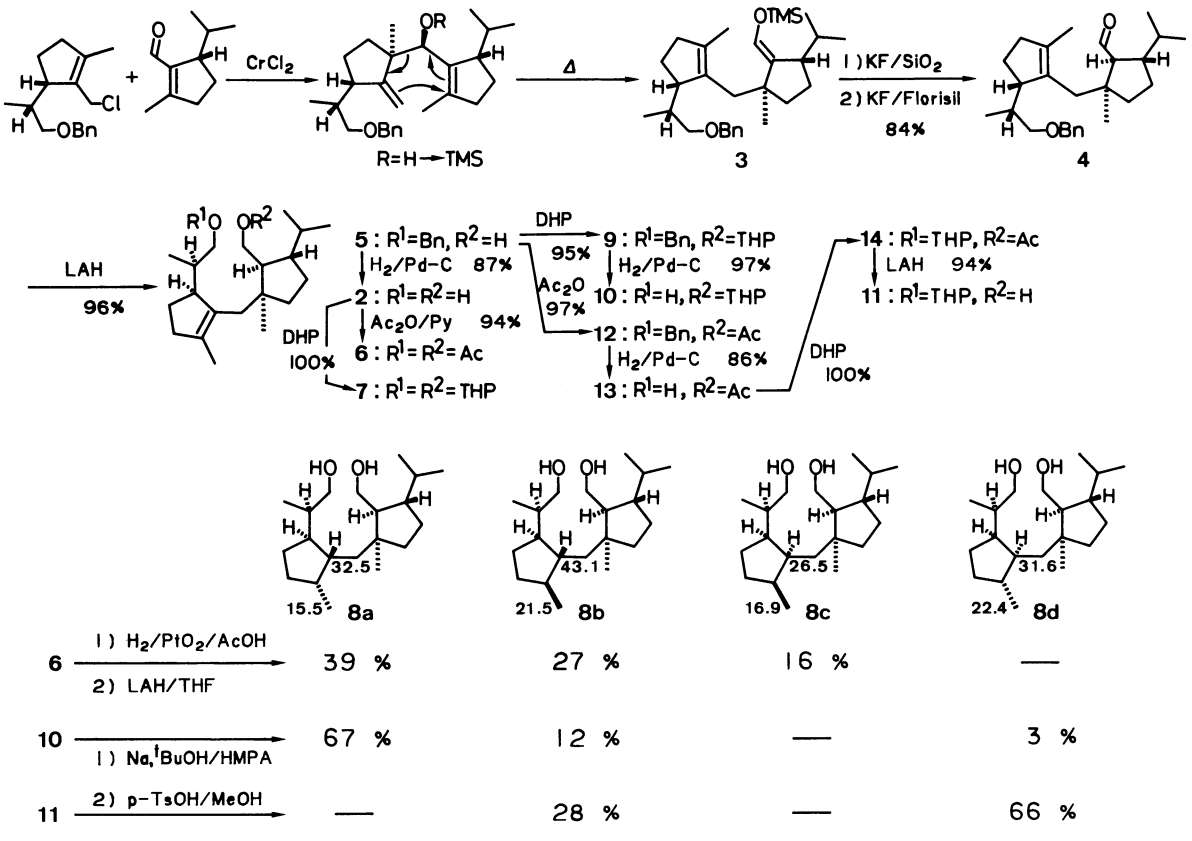


Scheme 1.

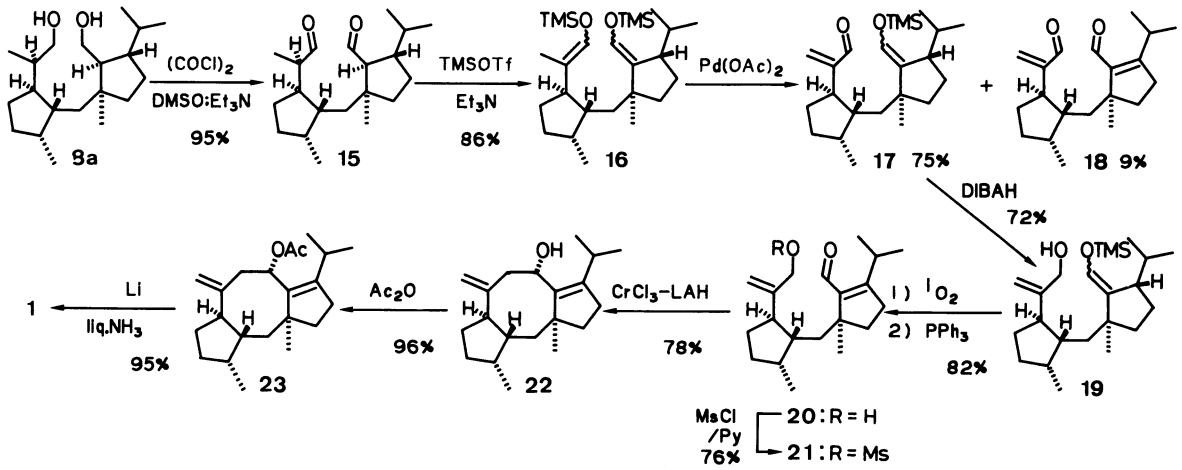
should indicate that the hydrogenation of the acetate might be facile; indeed, when **6** was reduced in acetic acid at 70 °C, three dihydro derivatives were formed. Although this mixture was inseparable, hydrolyzed dihydro diols were fractionated through a silica-gel column chromatography; the yield (39%) of the major dihydro diol (**8a**) was still insufficient for a synthetic purpose. However, a ^{13}C NMR chemical shift comparison of the stereomers, **8b** and **8c** (27 and 16% yields, respectively), disclosed reliable information for selecting the correct isomer for the synthesis.

Interestingly, the catalytic deuteration of **6** under comparable conditions also afforded three products; these reduction products contained more than two deuterium atoms. This finding indicated that the hydrogen (deuterium) exchange via π-allyl complexation is very rapid. Furthermore, the complete disappearance of the signals due to C-2, C-3, and C-16 from the olefinic carbon region indicated the distributions of deuterium; the intactness of the C-6 signal for all isomers assured the original (6*R*)-configuration. According to the well-known relationship of the ^{13}C chemical shift and the stereochemistry, the configurations of the isomers were as follows: **8a** and **8c** having relatively higher secondary methyl signals suggested a cis-configuration between these methyls and the vicinal substituent.[12] The same criteria could be applied to deduce the geometries of C-2 and C-6 from the chemical shifts of C-1 methylene carbons to assign trans and cis, respectively, for **8a** and **8c**. Thus, the major diol, **8a**, is the required (2*R*,3*R*)-isomer, and **8c** is (2*S*,3*S*)-isomer. The remaining **8b**, exhibiting both methyl and methylene signals at a lower field, must be the (2*R*,3*S*)-isomer.

In order to improve the selectivity, an alkali metal reduction of the derivative of **2** in a polar aprotic media under forced conditions seems to be promising.[13] Thus, THP ether **9** prepared from **5** was hydrogenolyzed in order to furnish an alcohol **10**. A sodium metal reduction of **10** in hexamethylphosphoric triamide (HMPA) with added 1,1-dimethylethanol at room temperature yielded **8a** in moderate yield, accompanied by small amounts of **8b** and **8d** (**8a**:**8b**:**8d**=22:4:1). The absence of thermodynamically unstable **8c** was predictable from a mechanistic view point, and the ^{13}C NMR spectrum of **8d** is reasonable as a (2*S*,3*R*)-isomer based on the above-mentioned criteria.[12] These figures are found in illustrations **8a—d**. It is noteworthy that **7**, having no hydroxyl group, did not react under the above conditions. Therefore, a hydrogen-donating hydroxyl group is required in the molecule, and the direction of hydrogenation must be controlled by the orientation of the hydroxyl group. This must be an important factor for an improved selectivity. Further proof for this mechanistic assumption was obtained from a reduction of **11**, which was prepared from **5** in four steps: acetylation of **5** gave **12** which was hydrogeno-



Scheme 2.



Scheme 3.

lyzed to **13**, and etherification of **13** by dihydropyran gave **14**. Finally, an LAH reduction of **14** yielded **11**. The product distributions of the sodium-1,1-dimethylethanol-HMPA reduction of **11** were completely different from the case of **10**. Namely, **8d** was produced as the major product accompanied by **8b** (**8d**:**8b**=7:3), and **8a** was not detected at all. This result can be explained in terms of the directional control of the hydroxyl group, which was conformationally oriented on the α-side of the A ring in **11**. Thus, the dissolving metal reduction of **10** provided the required stereochemistry for the present aim, while the reduction of a compound similar to **11** has been used in our recent synthesis of dictymal.[14]

Subsequently, to construct the tricyclic skeleton with proper functionalities for **1**, **8a** was oxidized to dialdehyde **15**, which was then converted to an isomeric mixture of bis(silyl enol ether)s **16**. Upon palladium(II) acetate-treatment,[15] the less-hindered enol ether of **16** was preferentially oxidized to give **17**; the yield of the accompanying dialdehyde **18** was only 9%. Diisobutylaluminum hydride (DIBAH) reduction gave an allyl alcohol **19**, and its sensitized photooxidation yielded a hydroxy aldehyde **20**. The mesylate **21** derived from **20** was treated with chromium(II) chloride to give a tricyclic compound **22**. The chemical shift of the singlet methyl, δ=1.20, indicated a syn-relationship with the allylic hydroxyl group.

The final transformation was achieved through a reductive elimination of the allylic hydroxyl group via the acetate **23**. The physical properties of **1**, thus obtained, were in accord to those of natural (−)-cycloaraneosene in all respects, including the optical rotation, ($[\alpha]_D$ −37.5° (lit,[3] −38.4°)), and the ^{13}C NMR chemical shifts.[3]

Incidentally, the structure of **22** is same as that proposed for a congener metabolite, hydroxycycloaraneosene (**22A**).[3] However, the physical data of **22** were clearly different from those recorded for the natural product or its epimer derived by chemical transformations.[3] Thus, our **22**, colorless scales, mp 64—65 °C, revealed a negative rotation ($[\alpha]_D$ −21.8°); however, **22A**, a colorless oil, was reported to be positive ($[\alpha]_D$ +7.5°). The reported ^1H NMR chemical shift for the singlet methyl of **22A** was δ=1.02. Presumably, **22A** is 8β-hydroxy derivative of **1**.

Syntheses of other members of terpenoids via this strategy is currently in progress.

Experimental

The elemental analyses were carried out by Miss S. Hirashima, of Institute of Advanced Material Study, Kyushu University. The NMR spectra were measured by a JEOL FX 100 Spectrometer in a $CDCl_3$ solution, unless otherwise specified, and the chemical shifts expressed were in δ units. The mass spectra were measured with a JEOL 01SG-2 Spectrometer. The IR spectra were taken as KBr disks or as a liquid film inserted between NaCl plates using a Jasco IR-A 102 Spectrometer. Optical rotations were measured with a Union Model PM-101 apparatus. The solvents for the reactions were carefully purified by distillation under an N_2 atmosphere immediately before use, and absolutely anhydrous unless otherwise specified. The stationary phase for the column chromatography was Wako Gel C 300 throughout, and elusion systems were mixtures of hexane and ethyl acetate (99:1 to 90:10).

Hydrolysis and Epimerization of 3 to 4. To a tetrahydrofuran (THF) solution (50 cm^3) of **3**[5] (1.69 g), silica gel (11 g), and KF (5.5 g) were added and stirred at 15—25 °C for 2 d. The mixture was then passed through a Florisil column and the residue, obtained by removing the solvent, was dissolved in MeOH (80 cm^3), to which Florisil (6 g) and KF (6 g) were added and kept at 15—25 °C for 1 d. The mixture was filtered on a Florisil column and the residue obtained by removing the solvent was chromatographed on a silica-gel column to give **4** [a colorless oil, 1.27 g; 84%. Found: C, 82.05; H, 10.40%. Calcd for $C_{27}H_{40}O_2$: C, 81.77, H, 10.12%. $[\alpha]_D^{24}$: −20.9° (*C* 2.29, $CHCl_3$). MS *m/z*, 396 (M^+). ^1H NMR δ=0.82 (3H, d, *J*=7 Hz), 0.87 (3H, d, *J*=7 Hz), 1.00 (3H, d, *J*=7 Hz), 1.18 (3H, s), 1.60 (3H, br s), 1.2—2.5 (13H, m), 2.5—2.9 (2H, m), 3.06 (1H, t, *J*=9 Hz), 3.21 (1H, dd, *J*=9, 4 Hz), 4.35 (1H, d, *J*=12 Hz), 4.40 (1H, d, *J*=12 Hz), 7.25 (5H,

br s), and 9.74 (1H, d, J=3 Hz). ^{13}C NMR δ=14.94 (q), 17.00 (q), 20.35 (q), 21.41 (q), 23.35 (t), 27.47 (t), 28.12 (q), 31.47 (t), 33.00 (d), 34.65 (d), 37.36 (t), 38.06 (t), 45.89 (d), 50.30 (s), 52.95 (d), 67.59 (d), 72.12 (t), 73.12 (t), 127.54 (d, 3C), 128.36 (d, 2C), 134.25 (s), 136.25 (s), 139.01 (s), and 205.72 (d). IR ν: 2950, 1715, 1455, 1370, 1100, 730, and 695 cm^{-1}].

LAH Reduction of 4 to 5. To a THF solution (20 cm^3) of **4** (1.18 g), added at 15—25 °C for 2 h was LAH (120 mg). The mixture was then treated with small portions of aq NH_4Cl and the resulting supernatant was dried on $MgSO_4$. After evaporation of the solvent, the residue was purified by silica-gel column chromatography to give **5** [a colorless oil, 1.15 g; 96%. Found: C, 81.24; H, 10.75%. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62%. $[\alpha]_D^{24}$: −39.3° (c 2.16, $CHCl_3$). MS m/z, 398 (M^+). ^{1}H NMR δ=0.84 (3H, d, J=7 Hz), 0.90 (3H, d, J=6 Hz), 1.02 (3H, d, J=7 Hz), 1.09 (3H, s), 1.60 (3H, br s), 1.2—2.0 (11H, m), 2.0—2.3 (4H, m), 2.75 (1H, m), 3.10 (1H, t, J=9 Hz). 3.29 (1H, dd, J=9, 4 Hz), 3.5—3.8 (2H, m), 4.40 (1H, d, J=12 Hz), 4.44 (1H, d, J=12 Hz), and 7.26 (5H, br s). ^{13}C NMR δ=14.94 (q), 17.06 (q), 17.71 (q), 22.30 (q), 23.47 (t), 24.41 (t), 28.53 (q), 29.88 (t), 31.00 (d), 34.71 (d), 37.36 (t), 37.53 (t), 46.53 (s), 47.83 (d), 53.18 (d), 56.24 (d), 63.95 (t), 72.48 (t), 73.18 (t), 127.48 (d), 127.66 (d, 2C), 128.42 (d, 2C), 135.30 (s, 2C), and 139.13 (s). IR ν: 2950, 1450, 1370, 1100, 1030, 730, and 695 cm^{-1}].

Catalytic Hydrogenolysis of 5 to 2. To an ethanol (EtOH) solution (6 cm^3) of **5** (310 mg), Pd/C (5%, 100 mg) was added and the mixture was stirred under an H_2 atmosphere at 15—25 °C for 24 h. After removing the catalyst and the solvent, the residue was chromatographed on a silica-gel column to give **2** [colorless crystals, mp 100—101.5 °C, 209 mg; 87%. Found: C, 77.96; H, 11.97%. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76%. $[\alpha]_D^{20}$: −30.8° (c 2.53, $CHCl_3$). ^{1}H NMR δ=0.83 (3H, d, J=6 Hz), 0.90 (3H, d, J=7 Hz), 0.95 (3H, d, J=7 Hz), 1.12 (3H, s), 1.61 (3H, br s), 1.2—2.4 (15H, m), 2.82 (2H, br s), 3.19 (1H, dd, J=11, 8 Hz), 3.48 (1H, dd, J=11, 5 Hz), and 3.6—3.8 (2H, m). ^{13}C NMR δ=15.06 (q), 16.71 (q), 17.82 (q), 22.18 (q), 23.00 (t), 24.47 (t), 28.83 (q), 29.36 (t), 30.83 (d), 36.47 (d), 37.36 (t), 37.71 (t), 46.59 (s), 47.18 (d), 53.24 (d), 56.30 (d), 63.18 (t), 64.36 (t), 135.48 (s), and 135.78 (s). IR ν: 3610, 2950, 1460, and 1010 cm^{-1}].

Diacetate 6 of 2. A pyridine solution (4 cm^3) of **2** (310 mg) was treated with Ac_2O (1 cm^3), and usual workup afforded a diacetate **6** [a colorless oil, 369 mg; 94%. Found: C, 73.36; H, 10.43%. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27%. MS m/z, 392 (M^+). ^{1}H NMR δ=0.84 (3H, d, J=6 Hz), 0.91 (3H, d, J=7 Hz), 0.97 (3H, d, J=7 Hz), 1.08 (3H, s), 1.61 (3H, br s), 1.3—1.9 (10H, m), 2.01 (3H, s), 2.04 (3H, s), 1.9—2.4 (4H, m), 2.75 (1H, m), 3.69 (1H, dd, J=10, 9 Hz), 3.85 (1H, dd, J=10, 5 Hz), and 4.0—4.2 (2H, m). ^{13}C NMR δ=14.88 (q), 16.65 (q), 17.59 (q), 20.88 (q, 2C), 22.00 (q), 22.88 (t), 24.41 (t), 28.12 (q), 29.59 (t), 30.65 (d), 33.36 (d), 37.24 (t, 2C), 46.47 (s), 47.94 (d), 52.47 (d), 53.00 (d), 65.59 (t), 66.30 (t), 134.36 (s), 136.01 (s), and 171.18 (s, 2C). IR ν: 2950, 1740, 1460, 1365, 1235, and 1030 cm^{-1}].

Bis(tetrahydropyranyl) Derivatives 7 of 2. A CH_2Cl_2 solution (4 cm^3) of **2** (209 mg) was treated with dihydropyran (0.2 cm^3) and pyridinium p-toluenesulfonate (PPTS, 20 mg) at 15—25 °C for 15 h. The mixture was then extracted with ether, washed with aq $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the volatile material, the residue was chromatographed on a silica-gel column to give **7** [a colorless oil, 323 mg; 100%. Found: m/z, 476.3860 (M^+). Calcd for $C_{30}H_{52}O_4$: 476.3863. ^{1}H NMR δ=0.7—1.1 (9H, m), 1.09 (3H, s), 1.58 (3H, br s), 1.3—2.4 (26H, m), 2.75 (1H, m), 3.2—3.6 (4H, m), 3.6—4.0 (4H, m), and 4.4—4.6 (2H, m). IR ν: 2950, 1450, 1195, 1115, 1025, and 970 cm^{-1}].

Catalytic Reduction and Subsequent LAH-Reduction of 6 to 8a, 8b, and 8c. An AcOH solution (15 cm^3) of **6** (889 mg) was reduced with PtO_2 (95 mg) at 15—25 °C for 24 h under an H_2 atmosphere to give an oily stereoisomeric dihydro derivatives (866 mg; 97%), which was dissolved in a THF solution (10 cm^3) and reduced with LAH (250 mg) to give a stereoisomeric mixture. High-pressure liquid chromatography (Micropolasil, hexane-EtOAc (10:1)) of the mixture afforded **8a** [colorless crystals, mp 113—114 °C, 252 mg; 40%. Found:C, 77.31; H, 12.26%. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33%. MS m/z, 310 (M^+). ^{1}H NMR δ=0.82 (3H, d, J=7 Hz), 0.84 (3H, d, J=7 Hz), 0.89 (3H, d, J=7 Hz), 0.99 (3H, d, J=6 Hz), 1.05 (3H, s), 1.1—2.4 (19H, m), 3.35 (1H, dd, J=10, 8 Hz), and 3.5—3.8 (3H, m). ^{13}C NMR δ=15.53 (q), 17.06 (q), 18.06 (q), 22.35 (q), 24.18 (t), 24.88 (t), 27.71 (q), 31.47 (d), 32.47 (t), 33.24 (t), 36.83 (d), 37.41 (d), 38.00 (t), 41.65 (d), 44.89 (s), 47.00 (d), 47.89 (d), 56.06 (d), 64.12 (t), and 65.36 (t). IR ν: 3300, 2950, 1445, 1370, and 1020 cm^{-1}], **8b** [colorless crystals, mp 69—70.5 °C, 188 mg; 28%. Found: m/z, 310.2882 (M^+). Calcd for $C_{20}H_{38}O_2$: 310.2870. ^{1}H NMR δ=0.84 (3H, d, J=6 Hz), 0.90 (3H, d, J=6 Hz), 0.91 (3H, d, J=6 Hz), 1.00 (3H, d, J=6 Hz), 1.06 (3H, s), 1.1—2.2 (19H, m), 3.37 (1H, dd, J=10, 7 Hz), and 3.5—3.8 (3H, m). ^{13}C NMR δ=16.53 (q), 18.06 (q), 21.47 (q), 22.41 (q), 24.83 (t), 27.94 (t), 28.12 (q), 31.41 (d), 33.12 (t), 38.06 (t), 40.12 (d), 41.00 (d), 43.12 (t), 45.36 (s), 45.94 (d), 47.89 (d), 52.42 (d), 56.18 (d), 63.95 (t), and 66.42 (t). IR ν: 3250, 2950, 1460, 1370, and 1030 cm^{-1}], and **8c** [colorless crystals, mp 94—95.5 °C, 119 mg; 17%. Found: m/z, 310.2882 (M^+). ^{1}H NMR δ=0.85 (3H, d, J=6 Hz), 0.90 (3H, d, J=7 Hz), 0.94 (3H, d, J=7 Hz), 1.00 (3H, d, J=6 Hz), 1.04 (3H, s), 1.0—2.2 (19H, m), 3.39 (1H, br dd, J=10, 6 Hz), and 3.5—3.8 (3H, m). ^{13}C NMR δ=16.87 (q), 17.85 (q), 18.44 (q), 22.30 (q), 24.61 (t), 25.47 (t), 26.48 (t), 28.40 (q), 30.51 (t), 31.05 (d), 35.04 (d), 37.58 (t), 39.10 (d), 40.20 (d), 44.49 (s), 47.66 (d), 50.90 (d), 55.82 (d), 63.75 (t), and 67.38 (t)].

Catalytic Deuteration of 6. Similarly, **6** (207 mg) was reduced with deuterium gas in the presence of PtO_2 (20 mg) in AcOD (4 cm^3) and, without isolation, consecutively reduced with LAH to give the deuterio derivatives of **8a**, **8b**, and **8c** in similar product distributions. Silica-gel column chromatography of the mixture afforded analytically pure samples.

THP-Ether 9 from 5. As a manner similar to the formation of **7**, **5** (1.10 g) was treated with dihydropyran (0.5 cm^3) and PPTS (20 mg) to give **9** [a colorless oil, 1.24 g; 95%. Found: C, 79.82; H, 10.56%. Calcd for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44%. MS m/z, 482 (M^+). ^{1}H NMR δ=0.83 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 1.02 (3H, d, J=7 Hz), 1.08 (3H, s), 1.58 (3H, br s), 1.2—2.0 (16H, m), 2.0—2.4 (4H, m), 2.75 (1H, m), 3.09 (1H, t, J=9Hz), 3.27 (1H, dd, J=9.4 Hz), 3.3—3.6 (2H, m), 3.6—4.0 (2H, m), 4.37 (1H, d, J=12 Hz), 4.43 (1H, d, J=12 Hz), 4.54 (1H, m), and 7.25 (5H, br s). IR ν: 2950, 1450, 1365, 1200, 1115, 1025, 730, and 695 cm^{-1}].

Catalytic Hydrogenolysis of 9 to 10. An EtOH solution (12 cm^3) of **9** (1.26 g) was hydrogenated with Pd/carbon (5%, 120 mg) at 15—25 °C for 23 h to give **10** [a colorless oil, 997 mg; 97%. Found: C, 76.29; H, 11.49%. Calcd for

$C_{25}H_{44}O_3$: C, 76.48; H, 11.30%. MS *m/z*, 392 (M^+). ^1H NMR δ=0.8—1.0 (9H, m), 1.08 (3H, s), 1.61 (3H, br s), 1.2—1.9 (16H, m), 1.9—2.4 (5H, m), 2.78 (1H, m), 3.1—3.7 (4H, m), 3.7—4.0 (2H, m), and 4.53 (1H, m). IR ν: 3450, 2950, 1460, 1370, 1200, 1120, 1030, and 980 cm^{-1}].

Na-*t*-BuOH-HMPA-Reduction of 10 to 8a, 8b, and 8d. To HMPA (60 cm^3), metallic Na (350 mg) was added under an N_2 atmosphere. To a blue solution, thus formed, *t*-BuOH (1 cm^3) was added with stirring. Then, **2** (1.30 g) was introduced at 15—25 °C under an N_2 atmosphere and stirring continued for further 15 h. The mixture was then extracted with ether, washed with water, and dried on $MgSO_4$. Silica-gel column chromatography of the organic material gave an oily mixture (1.24 g; 95%), which was subsequently dissolved in MeOH (12 cm^3) containing *p*-TsOH (120 mg) and refluxed for 3 h. The mixture was then extracted with EtOAc and chromatographed on a silica-gel column to give **8a** (660 mg; 70%), **8b** (126 mg; 13%), and **8d** [colorless crystals, mp 142—143 °C, 31.3 mg; 3%. Found: *m/z*, 310.1905 (M^+). Calcd for $C_{20}H_{38}O_2$: 310.2870. ^1H NMR δ=0.84 (3H, d, *J*=6 Hz), 0.91 (3H, d, *J*=7 Hz), 0.94 (3H, d, *J*=7 Hz), 0.97 (3H, d, *J*=6 Hz), 1.06 (3H, s), 2.02 (2H, br s), 1.2—2.2 (17H, m), 3.32 (1H, dd, *J*=10, 7 Hz), and 3.5—3.8 (3H, m). ^{13}C NMR δ=16.64 (q), 18.20 (q), 22.30 (q), 22.38 (q), 25.23 (t), 27.50 (t), 27.81 (q), 31.41 (d), 31.60 (t, 2C), 36.13 (d), 37.85 (t), 39.10 (d), 44.41 (d), 44.80 (s), 45.66 (d), 47.58 (d), 56.21 (d), 64.02 (t), and 67.62 (t). IR ν: 3250, 2950, 1450, 1365, and 1020 cm^{-1}], **8a**, and **8b** were identical with the sample prepared from **2**.

Acetate 12 of 5. A pyridine solution (3 cm^3) of **5** (296 mg) was treated with Ac_2O (0.5 cm^3) to give, after a usual workup, **12** [a colorless oil, 317 mg; 97%. Found: C, 79.15; H, 10.14%. Calcd for $C_{29}H_{44}O_3$: C, 79.04; H, 10.06%. MS *m/z*, 440 (M^+). ^1H NMR δ=0.83 (3H, d, *J*=7 Hz), 0.90 (3H, d, *J*=7 Hz), 1.02 (3H, d, *J*=7 Hz), 1.07 (3H, s), 1.56 (3H, br s), 1.2—1.9 (10H, m), 2.00 (3H, s), 1.9—2.3 (4H, m), 2.71 (1H, m), 3.08 (1H, t, *J*=9 Hz), 3.25 (1H, dd, *J*=9, 4 Hz), 4.10 (2H, br d, *J*=7 Hz), 4.36 (1H, d, *J*=12 Hz), 4.43 (1H, d, *J*=12 Hz), and 7.24 (5H, br s). IR ν: 2950, 1740, 1450, 1360, 1240, 1100, 1025, 730, and 695 cm^{-1}].

Catalytic Hydrogenolysis of 12 and 13. A mixture of **12** (303 mg) and Pd/C (5%, 30 mg) in EtOH (6 cm^3) was stirred under an H_2 atmosphere at 15—25 °C for 24 h. After removing the catalyst and the solvent, the residue was chromatographed on a silica-gel column to give **13** [a colorless oil, 208 mg; 86%. Found: C, 75.48; H, 11.19%. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93%. MS *m/z*, 350 (M^+). ^1H NMR δ=0.83 (3H, d, *J*=6 Hz), 0.90 (3H, d, *J*=7 Hz), 0.94 (3H, d, *J*=7 Hz), 1.07 (3H, s), 1.61 (3H, br s), 2.03 (3H, s), 1.2—2.3 (15H, m), 2.74 (1H, m), 3.23 (1H, dd, *J*=11, 8 Hz), 3.49 (1H, dd, *J*=11, 6 Hz), and 4.13 (2H, br d, *J*=6 Hz). IR ν: 3450, 2950, 1740, 1460, 1370, 1240, and 1030 cm^{-1}].

THP-Ether 14 of 13. A CH_2Cl_2 solution (4 cm^3) of **13** (208 mg) was treated with dihydropyran (0.1 cm^3) and PPTS (20 mg) to give **14** [a colorless oil, 257 mg; 100%. Found: C, 74.63; H, 10.83%. Calcd for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67%. MS *m/z*, 434 (M^+). ^1H NMR δ=0.8—1.1 (9H, m), 1.09 (3H, s), 1.60 (3H, br s), 1.2—2.0 (16H, m), 2.03 (3H, s), 2.0—2.3 (4H, m), 2.74 (1H, m), 2.8—4.0 (4H, m), 4.11 (2H, br d, *J*=6 Hz), and 4.46 (1H, m). IR ν: 2950, 1745, 1460, 1370, 1240, 1125, 1035, and 970 cm^{-1}].

LAH-Reduction of 14 to 11. A THF solution (2 cm^3) of **14** (257 mg) was treated with LAH (23 mg) at 0 °C for 1 h. A small amount of aq NH_4Cl was added, and the resulting supernatant was dried on $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on a silica-gel column to give **11** [a colorless oil, 220 mg; 94%. Found: *m/z*, 392.3288 (M^+). Calcd for $C_{25}H_{44}O_3$: 392.3288. ^1H NMR δ=0.8—1.1 (9H, m), 1.10 (3H, s), 1.56 (3H, br s), 1.1—2.0 (17H, m), 2.0—2.4 (4H, m), 2.76 (1H, m), 2.9—3.9 (6H, m), and 4.50 (1H, m). IR ν: 3450, 2950, 1460, 1370, 1120, 1030, 980, 905, 870, and 810 cm^{-1}].

Na-*t*-BuOH-HMPA-Reduction of 11 to 8b and 8d. Similar to the reduction of **10**, **11** (180 mg) was treated with Na (42 mg) and *t*-BuOH (0.14 cm^3) in an HMPA (6 cm^3). Successive treatments with *p*-TsOH (20 mg) in refluxing MeOH (4 cm^3) afforded a mixture of dihydro-diols. Silica-gel column chromatography of the mixture gave **8b** (40 mg; 28%) and **8d** (94 mg; 66%). Despite careful inspections of every chromatographic fraction, no **8a** was detected.

Swern's Oxidation of 8a to Dial (15). To a CH_2Cl_2 solution (16 cm^3) of $(COCl)_2$ (0.68 cm^3), DMSO (1.10 cm^3) was added drop by drop at −78 °C for 15 min. Then, a THF solution (5 cm^3) of **8a** (801 mg) was added and stirred for another 30 min; after the introduction of Et_3N (7.2 cm^3), the temperature was gradually raised to −10 °C, and treated with aq $NaHCO_3$. The mixture was extracted with EtOAc, and the organic extract was chromatographed on a silica-gel column to give **15** [a colorless oil, 747 mg; 95%. Found: *m/z*, 306.2561 (M^+). Calcd for $C_{20}H_{34}O_2$: 306.2557. ^1H NMR δ=0.80 (3H, d, *J*=7 Hz), 0.82 (3H, d, *J*=7 Hz), 0.87 (3H, d, *J*=7 Hz), 1.11 (3H, d, *J*=7 Hz), 1.17 (3H, s), 1.2—2.5 (17H, m), 9.67 (1H, d, *J*=2 Hz), and 9.70 (1H, br s). ^{13}C NMR δ=13.12 (q), 15.12 (q), 20.41 (q), 21.41 (q), 24.65 (t), 27.24 (q), 27.59 (t), 33.00 (t, 2C), 33.71 (d), 36.65 (d), 38.41 (t), 42.36 (d), 45.77 (d), 45.89 (d), 47.71 (d), 48.94 (s), 67.59 (d), 205.60 (d), and 205.83 (d). IR ν: 2950, 1720, 1460, and 1380 cm^{-1}].

Bis(TMS-Enol Ether) 16 of 15. To a CH_2Cl_2 solution (8 cm^3) of **15** (747 mg), Et_3N (1.7 cm^3) and trimethylsilyl triflate (2.26 cm^3) were added under an N_2 atmosphere, and stirred for 15 h. The mixture was then washed with aq K_2CO_3 and extracted with ether. Florisil-column chromatography of the organic material afforded **16** [a colorless oil, 942 mg; 86%. Found: *m/z*, 450.3368 (M^+). Calcd for $C_{26}H_{50}O_2Si_2$: 450.3338. ^1H NMR δ=0.16 (18H, s), 0.74 (3H, d, *J*=6 Hz), 0.80 (3H, d, *J*=7 Hz), 0.87 (3H, d, *J*=7 Hz), 0.97 (3H, s), 1.2—2.8 (18H, m), and 5.9—6.0 (2H, m). IR ν: 2950, 1665, 1445, 1250, 1155, 870, 840, and 750 cm^{-1}].

$Pd(OAc)_2$-Oxidation of 16. Formation of 17 and 18. To an acetonitrile solution (5 cm^3) of **16** (216 mg) was added $Pd(OAc)_2$ (160 mg) under N_2 atmosphere. After stirring at 15—25 °C for 6 h, the mixture was filtered on a Florisil column, and washed with ether. The residue obtained by removing the solvent was chromatographed on a silica-gel column to give **17** [a colorless oil, 136 mg; 75%. Found: C, 73.17; H, 10.91%. Calcd for $C_{23}H_{40}O_2Si$: C, 73.34; H, 10.70%. MS *m/z*, 376 (M^+). ^1H NMR δ=0.14 (9H, s), 0.73 (3H, d, *J*=7 Hz), 0.86 (6H, d, *J*=7 Hz), 0.96 (3H, s), 1.1—2.8 (15H, m), 5.9—5.95 (2H, m), 6.22 (1H, s), and 9.50 (1H, s). IR ν: 2950, 1690, 1660, 1250, 1150, 865, and 845 cm^{-1}] and **18** [a colorless oil, 13.2 mg; 9%].

DIBAH-Reduction of 17. Formation of 19. To a toluene solution (5 cm^3) of **17** (494 mg), DIBAH dissolved in hexane (1.8 M, 1 cm^3) was added under an N_2 atmosphere and kept at −78 °C for 30 min with stirring. The mixture was then diluted with aq NH_4Cl and extracted with ether. After

removing the solvent, the residue was chromatographed on a silica-gel column to give **19** [a colorless oil, 359 mg; 72%. Found: C, 72.91; H, 11.25%. Calcd for $C_{23}H_{42}O_2Si$: C, 72.95; H, 11.18%. MS *m/z*, 378 (M^+). ^1H NMR δ=0.15 (9H, s), 0.74 (3H, d, *J*=7 Hz), 0.83 (3H, d, *J*=7 Hz), 0.87 (3H, d, *J*=7 Hz), 0.99 (3H, s), 1.1—2.5 (15H, m), 2.65 (1H, br s), 4.04 (2H, br s), 4.86 (1H, br s), 5.04 (1H, q, *J*=1.5 Hz), and 5.98 (1H, d, *J*=2 Hz). IR ν: 3300, 2950, 1660, 1450, 1375, 1250, 1155, 1055, 870, 840, and 750 cm^{-1}].

$^1O_2$-Oxygenation of 19 to 20. An acetone solution (10 cm^3) of **19** (359 mg), pyridine (30 mg), and Rose Bengal (30 mg) was irradiated by means of 500-W tungsten lamp with an air stream at 0—5 °C. After 20 min, the mixture was treated with PPh_3 (373 mg) and kept at 15—25 °C for 15 h. The residue obtained by removing the solvent was then purified with silica-gel column chromatography to give **20** [a colorless oil, 236 mg; 82%. Found: *m/z*, 304.2399 (M^+). Calcd for $C_{20}H_{32}O_2$: 304.2401. $[\alpha]_D^{25}$: −57.8° (*c* 1.28, $CHCl_3$). ^1H NMR δ=0.86 (3H, d, *J*=7 Hz), 1.09 (3H, d, *J*=7 Hz), 1.10 (3H, d, *J*=7 Hz), 1.17 (3H, s), 1.2—2.4 (14H, m), 3.40 (1H, sept, *J*=7 Hz), 3.96 (2H, br s), 4.80 (1H, br s), 5.06 (1H, q, *J*=1.5 Hz), and 9.90 (1H, s). ^{13}C NMR δ=16.00 (q), 21.59 (q, 2C), 26.24 (t), 26.83 (d), 28.94 (q), 30.06 (t), 33.41 (t), 35.59 (t), 36.06 (t), 36.06 (d), 44.71 (d), 48.00 (d), 49.94 (s), 64.42 (t), 108.89 (t), 142.19 (s), 152.30 (s), 172.78 (s), and 188.96 (d). IR ν: 3450, 2950, 1660, 1650, 1450, 1050, 1020, and 890 cm^{-1}].

MsCl-Treatment of 20 to 21. A toluene solution (3 cm^3) of **20** (31.2 mg) was treated with MsCl (0.12 cm^3) and pyridine (0.24 cm^3) at 0 °C under an N_2 atmosphere for 15 h. The mixture was then diluted with aq $NaHCO_3$ and extracted with ether. The extract was chromatographed on a silica-gel column to give **21** [a colorless oil, 29 mg; 76%. Found: *m/z*, 382.2141 (M^+). Calcd for $C_{21}H_{34}O_4S$: 382.2176. ^1H NMR δ=0.88 (3H, d, *J*=7 Hz), 1.10 (6H, d, *J*=7 Hz), 1.19 (3H, s), 1.2—2.6 (13H, m), 3.00 (3H, s), 3.41 (1H, sept, *J*=7 Hz), 4.58 (2H, br s), 5.01 (1H, br s), 5.16 (1H, br s), and 9.94 (1H, s). IR ν: 2950, 1660, 1610, 1460, 1360, 1170, 830, and 730 cm^{-1}].

$CrCl_2$-Cyclization of 21. Formation of 22. A THF solution (5 cm^3) of $CrCl_2$ (prepared from $CrCl_3$, 158 mg, and LAH, 19 mg), was diluted with *N,N*-dimethylformamide (DMF, 30 cm^3) and then **21** (29 mg) in THF (2 cm^3) was added at 0 °C under N_2 atmosphere, and kept stirring for 15 h. The mixture was then diluted with water, extracted with ether, and dried on $MgSO_4$. Silica-gel column chromatography of the organic material gave **22** [colorless scales, mp 64—65 °C, 12.4 mg; 78%. Found: C, 83.27; H, 11.46%. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18%. $[\alpha]_D^{24}$: −21.8° (*c* 2.66, $CHCl_3$). MS *m/z*, 288 (M^+). ^1H NMR δ=0.84 (3H, d, *J*=7 Hz), 0.91 (3H, d, *J*=6 Hz), 0.96 (3H, d, *J*=7 Hz), 1.20 (3H, s), 1.2—2.6 (16H, m), 2.73 (1H, sept, *J*=7 Hz), 4.77 (1H, dd, *J*=8, 7 Hz), 4.79 (1H, br s), and 4.95 (1H, m). ^{13}C NMR δ=17.59 (q), 21.47 (q), 21.94 (q), 27.12 (d), 27.94 (t), 28.65 (t), 29.83 (q), 31.41 (t), 38.18 (d), 38.71 (t), 40.65 (t), 41.00 (d), 45.06 (d), 50.36 (d), 51.53 (s), 69.06 (d), 113.48 (t), 139.30 (s), 148.19 (s), and 148.72 (s). IR ν: 3350, 2950, 1640, 1455, 1380, 1000, 885, and 730 cm^{-1}].

Acetylation of 22 to 23. A pyridine solution (1 cm^3) of **22** (79.1 mg) was treated with Ac_2O (0.2 cm^3) at 15—25 °C to give **23** [a colorless oil, 80.8 mg; 96%. $[\alpha]_D^{26}$: −39.8° (*c* 2.31, $CHCl_3$). Found: C, 80.19; H, 10.39%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.34%. MS *m/z*, 330 (M^+). ^1H NMR δ=0.85 (3H, d, *J*=7 Hz), 0.89 (3H, d, *J*=7 Hz), 0.94 (3H, d, *J*=7 Hz), 1.17 (3H, s), 1.2—2.6 (16H, m), 2.85 (1H, sept, *J*=7 Hz), 1.97 (3H, s), 4.80 (1H, br s), 4.90 (1H, br s), and 5.84 (1H, dd, *J*=10, 7 Hz). ^{13}C NMR δ=17.35 (q), 21.06 (q), 21.47 (q, 2C), 27.30 (d), 27.94 (t, 2C), 30.00 (q), 31.00 (t), 38.36 (t), 38.71 (t), 38.71 (d), 42.77 (t), 45.36 (d), 49.83 (d), 51.12 (s), 71.83 (d), 112.24 (t), 133.60 (s), 147.31 (s), 151.31 (s), and 170.30 (s). IR ν: 2950, 1750, 1650, 1470, 1390, 1255, 1040, 975, and 910 cm^{-1}].

Li-NH_3 Reduction of 23. Formation of 1. At −78 °C, to liq NH_3 containing **23** (11.5 mg), an excess of Li metal, two drops of *t*-BuOH, and THF (1 cm^3) were added. After stirring for 30 min, the mixture was diluted with hexane, and sodium benzoate was added until the solution became yellow. Then, NH_4Cl was added and NH_3 was allowed to vaporize in a hood; the residue, thus obtained, was diluted with hexane, washed with aq $NaHCO_3$, and dried on $MgSO_4$. Silica-gel column chromatography of the organic material gave **1** [9.8 mg; 95%. Found: *m/z*, 272.2527 (M^+). Calcd for $C_{20}H_{32}$: 272.2502. $[\alpha]_D^{27}$: −37.5° (*c* 0.21, $CHCl_3$). ^1H NMR δ=0.82 (3H, d, *J*=7 Hz), 0.87 (3H, s), 0.89 (3H, d, *J*=7 Hz), 0.97 (3H, d, *J*=7 Hz), 1.1—2.5 (17H, m), 2.59 (1H, sept, *J*=7 Hz), 4.67 (1H, m), and 4.76 (1H, d, *J*=2 Hz). ^{13}C NMR δ=16.36 (q), 21.19 (q), 21.34 (q), 24.22 (t), 26.90 (q), 27.10 (t), 27.39 (d), 31.69 (t), 33.06 (t), 35.89 (t), 36.03 (t), 39.16 (d), 40.48 (t), 47.17 (d), 49.32 (d), 50.78 (s), 110.59 (t), 138.91 (s), 142.43 (s), and 155.95 (s). IR ν: 3070, 2955, 2860, 1635, 1450, 1375, 1360, 1330, 1100, and 880 cm^{-1}].

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