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Synthetic Photochemistry. XLVIII.¹⁾ Stereocontrolled Generation of the Ophiobolane Type 5-8-5-Membered Tricyclic Ring System

Nobuo KATO,* Shoji OHBUCHI, and Hitoshi TAKESHITA*

Starting from the chromium (II) chloride-mediated condensation of (3*S*, 8*R*)-9-benzyloxy-1-iriden-7-al and (3*S*)-7-chloro-1,8-iridadiene, ophiobolane type skeleton, was constructed.

Introduction

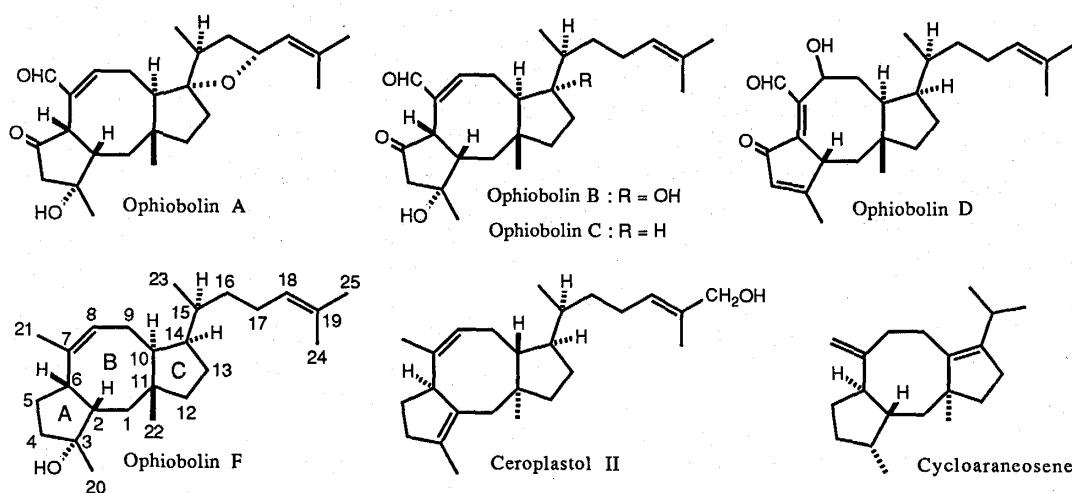
Ophiobolins²⁾ are the first members of sesterterpenoid family and they have the characteristic 5-8-5-membered tricyclic carbon framework. After the discovery, similar tricyclic systems³⁾ have been found as the physiologically active compounds from various organisms. Particularly interesting was that their stereochemistries are mutually different depending on the natural sources, and therefore, their biogenetic modes of cyclization might be different. Since then, the total synthesis of these natural products has attracted a considerable interest.⁴⁾ To our knowledge, however, either total synthesis of natural products, or construction of their exact carbon skeletons has remained unsuccessful until our synthesis of optically active cycloaraneosene,⁵⁾ metabolite of *Sordaria araneosa* Cain.⁶⁾ Herein, we wish to report the synthesis of the ring system, that should be designated as methyl 10,15-diepi-16-hydroxyophiobola-2,7,18-trien-25-oate.⁷⁾

Results and Discussions

First of all, the stereochemistries of natural 5-8-5-membered tricyclic terpenoids differ depending on the origins of compounds. On the stereochemical relation of C-6 hydrogen and C-11 methyl group, the most of such diterpenoids possess anti-relationship, but most of sesterterpenoids possess the syn-relationship. In cases of the sesterterpenoids, stereochemistries of the C₈-side chain on the C-ring between ophiobolanes from microorganisms and ceroplastanes from insects were different. We have already shown that these stereochemically different ring systems can be constructed via reductive condensations of appropriate combinations of two optically active iridoid synthons and subsequent stereochemically controlled Cope rearrange-

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Stereoselective Construction of Ophiobolane Framework

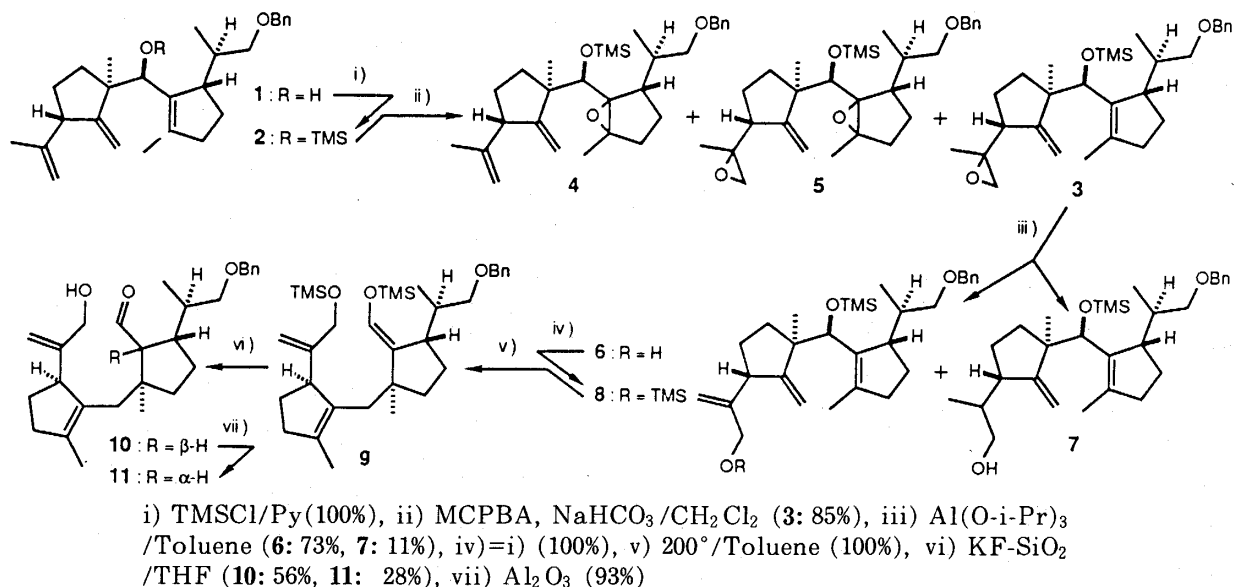


(Fig. 1)

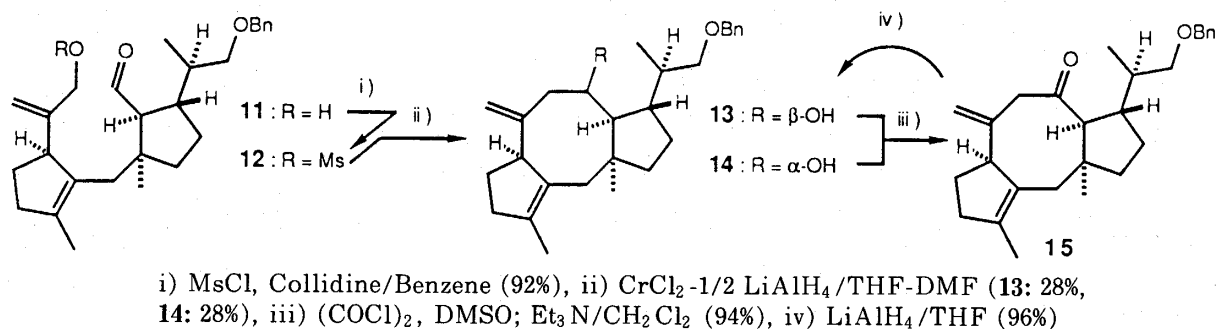
ment; the original *trans*-relationship between the C-14 hydrogen and C-11 methyl is retained during the Cope rearrangement.⁸⁾ On the other hand, if one needs an inverted *cis*-Cope thermolysate, the Cope rearrangement should be performed under "the lactol regulated" conditions as shown in our recent total synthesis of dictymal⁹⁾ and ceroplastol II.¹⁰⁾

Although the most of the ophiobolane natural products were highly oxygenated, following fundamental features should be considered: i) the configurations of C-6 and C-14 indicate the starting iridoids must be a combination of two of (3*R*)-derivatives, ii) the stereochemistry of C-15 relative to C-14 is opposite to the normal hydroboration products of 1,8-iridadiene derivatives, and it must be inverted in the subsequent steps of the synthesis, and iii) the functionalized A ring must be generated by functionalization of the tetrasubstituted double bond after the Cope rearrangement, since it is indispensable for the rearrangement. With these in mind, we have investigated a construction of basic stereostructure, which is seen in ophiobolin F,¹¹⁾ from the adduct (1) prepared previously by the condensation of (3*S*)-1,8-iridadienal and (3*S*, 8*R*)-9-benzyloxy-7-chloro-1-iridene.¹²⁾¹³⁾

Cope Rearrangement. Since the isopropyl side chain should have a functional group for further transformation, 1 was converted to a trimethylsilyl (TMS) ether (2) and further oxidized with *m*-chloroperbenzoic acid (MCPBA) to an epoxy derivative (3) together with two by-products (4 and 5). Subsequent treatment of 3 with aluminum isopropoxide formed an allyl alcohol (6) and a by-product (7). Since the protection of the allylic hydroxyl groups as TMS ethers⁸⁾ is necessary to form the Cope thermolysates, 6 was converted to the TMS ether (8) and heated at 200°C for 17 h to yield a single thermolysate (9). A mild hydrolysis of the TMS-enol ether function of 9 furnished two products (10 and 11); the former, 10, was kinetically-controlled product, since it isomerized to 11 by passing through an alumina column. On the basis of the Dreiding's Stereomolecular Model inspections, kinetical product, 10, might be the correct precursor to ophiobolanes, but, simply due to an availability of the sample, the further



(Scheme 1)



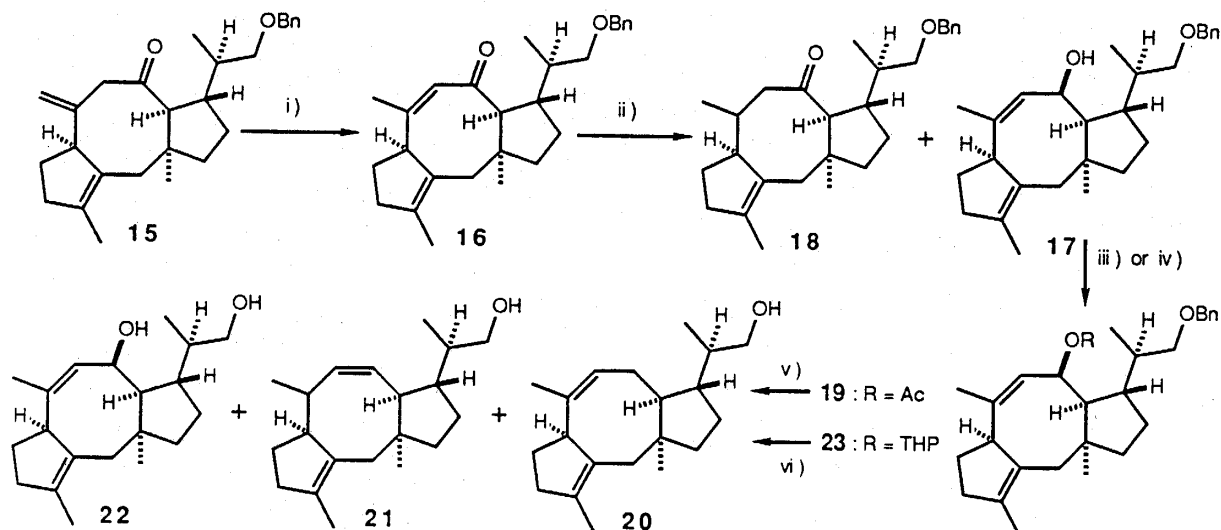
(Scheme 2)

transformations were performed by starting from **11** as a model study for the construction of ophiobolane-type skeleton.

Ring Closure. Treatment of **11** with methanesulfonyl (mesyl) chloride formed a mesylate (**12**), in good yield, and was treated with chromium (II) chloride to give an epimeric mixture of condensates (**13** and **14**), both of which gave the same dehydro ketone (**15**) by Swern's oxidation. Interestingly, the lithium aluminum hydride (LAH) reduction of **15** exclusively gave **14**. Thus, although the stereochemistry was different in respect to that of C-10 of natural products, the carbocyclic framework was prepared, and in view of their highly oxygenated character, the stereochemistry should be adjusted in later desired occasions.

Transformation of Tricyclic Derivatives. A usual acid treatment of dehydro ketone, **15**, despite being β, γ -unsaturated ketone, did not give an α, β -unsaturated ketone (**16**). However, it could be isomerized to **16** by treatment with potassium fluoride supported on Florisil.⁸⁾ The diisobutylaluminum hydride (DIBAH) reduction of **14** gave an allyl alcohol (**17**) in 96% together

Stereoselective Construction of Ophiobolane Framework

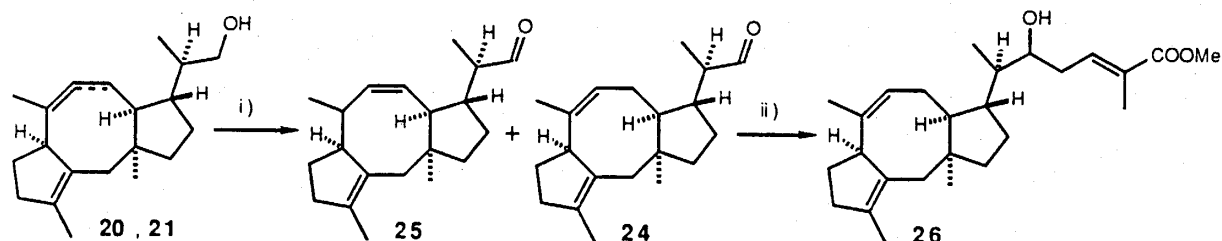


i) KF-Florisil/MeOH (100%), ii) DIBAL/Toluene (**17**: 96%, **18**: 2%), iii) Ac₂O, Et₃N, DMAP/CH₂Cl₂ (**19**: 94%), iv) DPH, PPTS/CH₂Cl₂ (**23**: 100%), v) Li/liq. NH₃ (**20**: 12%, **21**: 12%, **22**: 74%), vi) Li-EtOH/EtNH₂ (**20**: 50%, **21**: 50%)

(Scheme 3)

with a small amount, 2%, of 1,4-reduction product (**18**). After acetylation to **19**, it was reduced under Birch reduction conditions to a mixture of double bond isomers (**20** and **21**), and a hydrolyzed alcohol (**22**), which were separated with high-pressure liquid chromatography (HPLC). However, the predominant product of this reduction was **22**, and in order to obtain **20** or **21** in better yields, the Birch reduction was carried out in tetrahydropyranyl (THP) ether (**23**) derived from **17**; the combined yield of **20** and **21** were nearly quantitative.

Homologation. The mixture of **20** and **21**, obtained from Birch reduction of **23**, was then converted to aldehydes (**24** and **25**) by Swern's oxidation. Thus, the C₅-homologation of **24** should complete the carbon framework of the sesterterpenoid. The dianion species of 2-methyl-2-butenic acid was condensed with **24** to form a secondary alcohol (**26**). Natural ophiobolins are highly oxygenated, and there are many derivatives, of which stereostructures were deviated from the original form; e.g., only the compounds supposed to possess the original stereostructure are ophiobolin C and F, and A/B-ring juncture, the *cis*-form was lost by introduction of C=C bond in ophiobolin D, and C-14 hydrogen was displaced by oxygen functions on ophiobolins



i) (COCl)₂, DMSO; Et₃N/CH₂Cl₂ (**24**: 42%, **25**: 41%), ii) Tiglic acid, LDA; CH₂N₂ (12%)

(Scheme 4)

A and B. Therefore, the most desirable transformation from **26** would be an inversion of B/C-juncture to the *trans*-form. And the related study on this point is currently undergoing.

Conclusion. Beside our recent achievement of synthesizing the tricyclic higher terpenoids, i.e., cycloaraneosene (which also constitutes a formal total synthesis of hydroxycycloaraneosene), ceroplastol II, and albolic acid, as well as dictymal, a B-*seco*-derivative of epoxydictymene, we now added here a construction of basic skeleton of the ophiobolane system. Although we employed the thermodynamically stable aldehyde, **11**, for ring closure to the tricyclic system to result in the formation of *cis*-B/C juncture, there might be no reason to assume that the same reaction with epimeric **10** should not be applicable, and in views of our current findings on the related works, we are confident to get a totally synthesized ophiobolins in near future.

Experimental

Elemental analyses were performed by Miss S. Hirashima, of This Institute. The NMR spectra were measured in CDCl₃ with an FX 100 Model spectrometer, JEOL., and the chemical shift were expressed in δ values. The mass spectra were measured with a O1SG-2 spectrometer, JEOL. IR spectra were measured with a Jasco IR-A 102 Model spectrometer as KBr disks, inserted liquid films, or in CHCl₃ solutions. The optical rotations were measured with a Union Model PM-101 apparatus. The solvents were carefully dehydrated and distilled immediately before the use under N₂ atmosphere; therefore, they were anhydrous unless otherwise stated.

Preparation of 1 by Condensation of Two Iridoid Synthons. For details see the previous paper.¹²⁾

Formation of TMS-Ether (2) from 1. A pyridine solution (100 cm³) of **1** (10.28 g) was treated with TMSCl (2.5 cm³) to give **2** [a colorless oil, 12.58 g; 100%. Found: C, 77.42; H, 9.81%. Calcd for C₃₀H₄₆O₂Si: C, 77.19; H, 9.93%. $[\alpha]_D^{20}$: -87.2° (c 1.89, CHCl₃). ¹H NMR δ =0.06 (9H, s), 1.02 (3H, d, *J*=7 Hz), 1.17 (3H, s), 1.59 (3H, br s), 1.66 (3H, br s), 2.60 (1H, br m), 2.88 (1H, br m), 3.12 (1H, t, *J*=8.5 Hz), 3.18 (1H, br m), 3.45 (1H, dd, *J*=8.5, 3.5 Hz), 4.33 (1H, d, *J*=11.5 Hz), 4.37 (1H, s), 4.49 (1H, d, *J*=11.5 Hz), 4.6-4.8 (4H, m), and 7.27 (5H, br s). ¹³C NMR δ =0.6 (3C, q), 15.2 (q), 18.1 (2C, q), 23.4 (t), 24.1 (q), 28.0 (t), 35.6 (t), 35.9 (d), 37.6 (t), 50.9 (s), 51.7 (d), 53.6 (d), 72.3 (t), 73.3 (t), 74.3 (d), 107.4 (t), 112.7 (t), 127.2 (d), 127.5 (2C, d), 128.2 (2C, d), 136.7 (s), 137.4 (s), 139.1 (s), 146.5 (s), and 159.7 (s). IR ν : 2950, 2875, 1642, 1452, 1370, 1248, 1095, 1063, 1030, 883, 835, 742, 727, and 693 cm⁻¹].

Epoxidation of 2 to 3, 4, and 5. To a CH₂Cl₂ solution (300 cm³) of **2** (11.57 g) added were NaHCO₃ (2.1 g; 1.0 mol eq) and MCPBA (2.2 g; 0.5 mol eq) at 0-5°C and kept in the dark for 15 h. The mixture was then diluted with aq NaHCO₃, extracted with ether, and chromatographed on a silica-gel column, and the recovered **2** was repeatedly oxidized. After repetition with five times, **3** [a colorless oil, 10.18 g; 85%. *m/z*, 482 (M⁺). ¹H NMR δ =0.04 (9H, s), 1.01

(3H, d, $J=7$ Hz), 1.18 (3H, s), 1.21 (3H, s), 1.64 (3H, br s), 2.51 (0.4H, s), 2.70 (1.6H, s), 2.84 (1H, br m), 3.10 (1H, t, $J=8.5$ Hz), 3.43 (1H, dd, $J=8, 3.5$ Hz), 4.29 (1H, s), 4.36 (1H, d, $J=12$ Hz), 4.48 (1H, d, $J=12$ Hz), 4.87 (1.6H, m), 4.92 (0.2H, m), 5.13 (0.2H, m), and 7.27 (5H, br s). IR ν : 2970, 1647, 1458, 1372, 1098, 1035, 901, 879, 839, 745, 732, and 697 cm^{-1}] was obtained together with variable amounts of **4** [a colorless oil. m/z , 347 (M^+-135). ^1H NMR $\delta=0.14$ (9H, s), 1.01 (3H, d, $J=7$ Hz), 1.20 (3H, s), 1.34 (3H, s), 1.62 (3H, br s), 3.10 (1H, br m), 3.21 (1H, t, $J=9$ Hz), 3.38 (1H, s), 3.97 (1H, dd, $J=8.5, 3$ Hz), 4.39 (1H, d, $J=12$ Hz), 4.59 (1H, d, $J=12$ Hz), 4.75 (2H, m), 4.84 (1H, m), 4.96 (1H, m), and 7.29 (5H, br s)] and **5** [a colorless oil. ^1H NMR $\delta=0.13$ (9H, s), 1.00 (3H, d, $J=7$ Hz), 1.21 (3H, s), 1.24 (3H, s), 1.31 (3H, s), 3.50 (1H, s), 3.95 (1H, dd, $J=8.3, 3$ Hz), 4.37 (1H, d, $J=11.5$ Hz), 4.58 (1H, d, $J=11.5$ Hz), 4.91 (1H, m), 5.03 (1H, m), and 7.28 (5H, br s)].

Formation of Allyl Alcohol (6) from 3 by Treatment with Al(O-i-Pr)₃. A toluene solution (280 cm^3) of **3** (10.2 g) and Al(O-i-Pr)₃ (50 fold excess) was refluxed until no starting material was detected on the tlc. The mixture was then extracted with ether, and dried on K₂CO₃. Silica-gel column chromatography of the organic material afforded **6** [a colorless oil, 7.44 g; 73%. Found: C, 74.64; H, 9.60%. Calcd for C₃₀H₄₆O₃Si: C, 74.47; H, 9.74%. $[\alpha]_{\text{D}}^{18} = -97.9^\circ$ (c 2.06, CHCl₃). ^1H NMR $\delta=0.06$ (9H, s), 1.01 (3H, d, $J=7$ Hz), 1.18 (3H, s), 1.65 (3H, br s), 2.60 (1H, br m), 2.86 (1H, br m), 3.11 (1H, t, $J=8.5$ Hz), 3.20 (1H, br m), 3.44 (1H, dd, $J=8.5, 3.5$ Hz), 4.07 (2H, br d, $J=2.5$ Hz), 4.32 (1H, d, $J=12$ Hz), 4.36 (1H, s), 4.48 (1H, d, $J=12$ Hz), 4.73 (1H, br d, $J=2.5$ Hz), 4.82 (1H, br d, $J=2.5$ Hz), 4.92 (1H, br s), 5.16 (1H, m), and 7.27 (5H, br s). ^{13}C NMR $\delta=0.5$ (3C, q), 15.1 (q), 18.0 (q), 23.3 (t), 24.2 (q), 28.5 (t), 35.3 (t), 35.7 (d), 37.4 (t), 50.5 (d), 50.8 (t), 51.5 (d), 63.6 (t), 72.3 (t), 73.2 (t), 74.2 (d), 107.5 (t), 111.5 (t), 127.2 (d), 127.5 (2C, d), 128.2 (2C, d), 136.3 (s), 137.5 (s), 139.0 (s), 150.2 (s), and 160.6 (s). IR ν : 3350, 2950, 2875, 1647, 1500, 1455, 1370, 1250, 1098, 1064, 1032, 900, 875, 839, 747, and 695 cm^{-1}] and **7** [a colorless oil, 1.08 g; 11%. Found: C, 74.33; H, 9.98%. Calcd for C₃₀H₄₈O₃Si: C, 74.07; H, 10.19%. ^1H NMR $\delta=0.05$ (9H, s), 0.75 (3H, d, $J=7$ Hz), 1.01 (3H, d, $J=7$ Hz), 1.13 (3H, s), 1.65 (3H, br s), 2.64 (1H, br m), 2.84 (1H, br m), 3.11 (1H, dd, $J=9, 8$ Hz), 3.3–3.7 (3H, m), 4.32 (1H, d, $J=12$ Hz), 4.44 (1H, s), 4.48 (1H, d, $J=12$ Hz), 4.73 (1H, d, $J=2$ Hz), 4.82 (1H, d, $J=2.5$ Hz), and 7.27 (5H, br s). ^{13}C NMR $\delta=0.5$ (3C, q), 11.0 (q), 15.1 (q), 18.0 (q), 22.8 (t), 23.3 (t), 23.8 (q), 35.1 (t), 35.6 (d), 37.4 (t), 44.4 (d), 51.0 (s), 51.4 (d), 67.5 (t), 72.2 (t), 73.1 (t), 74.2 (d), 105.7 (t), 127.1 (d), 127.1 (2C, d), 128.1 (2C, d), 136.4 (s), 137.3 (s), 139.0 (s), and 160.4 (s). IR ν : 3350, 2960, 2875, 1645, 1455, 1370, 1250, 1095, 1063, 1030, 880, 840, 745, 730, and 695 cm^{-1}].

Cope Rearrangement of 6 to 9. A pyridine solution (50 cm^3) of **6** (7.44 g) was treated with TMSCl (1.5 cm^3) to give **8** [a colorless oil, 8.62 g; 100%. $[\alpha]_{\text{D}}^{18} = -98.7^\circ$ (c 2.48, CHCl₃). Found: C, 71.34; H, 9.75%. Calcd for C₃₃H₅₄O₃Si₂: C, 71.42; H, 9.81%. ^1H NMR $\delta=0.06$ (9H, s), 0.12 (9H, s), 1.02 (3H, d, $J=3$ Hz), 1.18 (3H, s), 1.65 (3H, br s), 2.60 (1H, br m), 2.88 (1H, br m), 3.11 (1H, t, $J=8$ Hz), 3.16 (1H, br m), 3.45 (1H, dd, $J=8, 3.5$ Hz), 4.03 (2H, br s), 4.32

(1H, d, $J=12$ Hz), 4.36 (1H, s), 4.48 (1H, d, $J=12$ Hz), 4.74 (1H, m), 4.82 (1H, m), 4.88 (1H, m), 5.16 (1H, m), and 7.26 (5H, br s). ^{13}C NMR $\delta=-0.4$ (3C, q), 0.6 (3C, q), 15.1 (q), 18.0 (q), 23.3 (t), 24.1 (q), 28.9 (t), 35.3 (t), 35.8 (t), 37.5 (t), 49.9 (d), 50.8 (t), 51.5 (d), 63.1 (t), 72.3 (t), 73.2 (t), 74.2 (d), 107.6 (t), 110.7 (t), 127.2 (d), 127.5 (2C, d), 128.1 (2C, d), 136.5 (s), 137.5 (s), 139.1 (s), 149.6 (s), and 160.0 (s). IR ν : 2950, 2875, 1647, 1500, 1455, 1370, 1250, 1093, 1065, 1032, 875, 838, 745, and 695 cm^{-1}], which was, then, dissolved in toluene (150 cm^3) and heated in an autoclave at 200°C for 17 h. Toluene was removed by evaporation to leave essentially pure **9** [a colorless oil, 8.62 g; 100%. ^1H NMR $\delta=0.12$ (9H, s), 0.15 (9H, s), 1.00 (3H, s), 1.02 (3H, d, $J=7$ Hz), 1.64 (3H, br s), 2.80 (1H, br m), 3.19 (1H, t, $J=9$ Hz), 3.36 (1H, br m), 3.45 (1H, dd, $J=9$, 4 Hz), 3.97 (2H, br s), 4.41 (1H, d, $J=12$ Hz), 4.47 (1H, d, $J=12$ Hz), 4.67 (1H, br s), 5.01 (1H, m), 6.01 (1H, d, $J=2.5$ Hz), and 7.27 (5H, br s)].

KF-Catalyzed Hydrolysis of 9 to 10 and 11. A tetrahydrofuran (THF) solution (60 cm^3) of **9** (2.4 g) was treated with KF-SiO₂ (1: 2, 15 fold excess) at room temperature for 2 d under N₂ atmosphere. The mixture was then filtered on a Florisil column and chromatographed on a silica-gel column to give **10** [a colorless oil, 1.05 g; 56%. m/z , 301 (M^+-109). ^1H NMR $\delta=0.94$ (3H, d, $J=7$ Hz), 0.95 (3H, s), 1.67 (3H, br s), 2.50 (1H, tm, $J=6$ Hz), 3.27 (1H, dd, $J=9$, 5.5 Hz), 3.35 (1H, br m), 3.42 (1H, dd, $J=9$, 4 Hz), 3.93 (2H, br s), 4.41 (1H, d, $J=12$ Hz), 4.47 (1H, d, $J=12$ Hz), 4.69 (1H, br s), 4.97 (1H, m), 7.26 (5H, br s), and 9.65 (1H, d, $J=6$ Hz). ^{13}C NMR $\delta=15.1$ (q), 16.6 (q), 24.2 (q), 28.6 (t), 29.1 (t), 35.6 (d), 36.9 (t), 38.6 (2C, t), 45.4 (d), 47.5 (s), 53.5 (d), 62.0 (d), 63.8 (t), 73.0 (t), 74.6 (t), 108.8 (t), 127.5 (3C, d), 128.2 (2C, d), 133.3 (s), 138.1 (s), 138.4 (s), 151.4 (s), and 205.9 (d). IR ν : 3445, 2935, 2875, 1713, 1645, 1453, 1378, 1111, 1095, 1068, 900, 835, 697, and 677 cm^{-1}] and **11** [a colorless oil, 520 mg; 28%. m/z , 392 (M^+-18). ^1H NMR $\delta=0.86$ (3H, d, $J=7$ Hz), 1.12 (3H, s), 1.67 (3H, br s), 2.60 (1H, qdd, $J=7$, 6.5, 5.1 Hz), 3.25 (1H, dd, $J=9$, 5.1 Hz), 3.32 (1H, dd, $J=9$, 6.5 Hz), 3.35 (1H, br m), 3.97 (2H, br s), 4.41 (2H, br s), 4.66 (1H, m), 4.97 (1H, m), 7.28 (5H, br s), and 9.66 (1H, d, $J=4$ Hz). ^{13}C NMR $\delta=15.0$ (q), 15.3 (q), 27.8 (q), 28.0 (t), 29.1 (t), 31.7 (t), 36.9 (t), 38.1 (d), 38.4 (t), 41.2 (d), 50.1 (s), 53.5 (d), 64.0 (t), 65.9 (d), 72.9 (t), 74.1 (t), 108.6 (t), 127.3 (d), 127.5 (2C, d), 128.2 (2C, d), 133.5 (s), 137.6 (s), 138.3 (s), 150.9 (s), and 205.7 (d). IR ν : 3425, 2955, 2875, 1715, 1455, 1380, 1070, 1029, 900, 735, and 699 cm^{-1}].

Alumina-Catalyzed Isomerization of 10 to 11. The **10** (304 mg) was passed through an Al₂O₃ (neutral, Activity I; 5 g) column by hexane-ether (20:1) to give essentially pure **11** (284 mg; 93%).

Mesylate (12) of 11. To a benzene solution (1.5 cm^3) of **11** (30 mg) and collidine (0.15 cm^3) MsCl (30 mg) was added and kept at room temperature for 1 h. The mixture was then diluted with water, extracted with ether, chromatographed on a silica-gel column to give **12** [a colorless oil, 33 mg; 92%. Found: C, 68.58; H, 8.24%. Calcd for C₂₈H₄₀O₅S: C, 68.82; H, 8.25%. ^1H NMR $\delta=0.87$ (3H, d, $J=7$ Hz), 1.13 (3H, s), 1.68 (3H, br s), 2.61 (1H, qdd, $J=7$, 6.2,

5.3 Hz), 2.98 (3H, s), 3.25 (1H, dd, $J=9$, 5.3 Hz), 3.31 (1H, dd, $J=9$, 6.2 Hz), 3.40 (1H, br m), 4.41 (2H, br s), 4.53 (2H, br s), 4.86 (1H, br s), 5.13 (1H, m), 7.28 (5H, br s), and 9.66 (1H, br d, $J=4$ Hz). ^{13}C NMR $\delta=14.8$ (q), 15.0 (q), 27.6 (q), 27.6 (t), 28.5 (t), 31.4 (t), 36.5 (t), 37.3 (d), 37.8 (q), 38.1 (t), 40.9 (d), 49.9 (s), 53.3 (d), 65.6 (d), 70.6 (t), 72.6 (t), 73.9 (t), 114.7 (t), 127.2 (3C, d), 127.9 (2C, d), 132.5 (s), 138.2 (s), 138.6 (s), 143.9 (s), and 205.2 (d). IR ν : 2950, 2930, 2870, 1715, 1498, 1460, 1455, 1356, 1173, 1098, 998, 963, 925, 840, 738, and 699 cm^{-1}].

CrCl₂-Mediated Cyclization of 12 to 13 and 14. A THF suspension of **12** (300 mg) was treated with CrCl₂ (prepared from CrCl₃, 2 g, and LAH, 260 mg). Silica-gel column chromatography of the mixture afforded **13** [68 mg; 28%. m/z , 394 (M^+). ^1H NMR $\delta=0.73$ (3H, s), 1.00 (3H, d, $J=7$ Hz), 1.60 (3H, br s), 3.07 (1H, br m), 3.23 (1H, dd, $J=9$, 6.5 Hz), 3.51 (1H, dd, $J=9$, 5 Hz), 3.94 (1H, br m), 4.46 (2H, br s), 4.90 (1H, m), 4.94 (1H, br s), and 7.28 (5H, br s). IR ν : 3465, 2950, 2870, 1640, 1498, 1453, 1375, 1099, 1073, 1027, 889, 732, and 698 cm^{-1}] and **14** [67 mg; 28%. ^1H NMR $\delta=0.78$ (3H, s), 1.00 (3H, d, $J=7$ Hz), 1.60 (3H, br s), 2.83 (1H, dd, $J=13.5$, 3.5 Hz), 3.26 (1H, dd, $J=9$, 7 Hz), 3.50 (1H, dd, $J=9$, 5 Hz), 4.47 (2H, br s), 4.83 (1H, m), 4.90 (1H, m), and 7.29 (5H, br s)].

Swern's Oxidation of 13 and 14 to 15. A 1:1-mixture of **13** and **14** (111 mg) was dissolved in CH₂Cl₂ (2 cm^3) and treated with (COCl)₂ (35 mg), dimethyl sulfoxide (DMSO, 70 mg), and Et₃N (0.4 cm^3) to give **15** [a colorless crystals, mp 75–76.5 °C, 104 mg; 94%. $[\alpha]_{\text{D}}^{21}=+139.0^\circ$ (c 1.65, CHCl₃). Found: m/z , 392.2711 (M^+). Calcd for C₂₇H₃₆O₂: 392.2713. ^1H NMR $\delta=0.89$ (3H, d, $J=7$ Hz), 0.94 (3H, s), 1.56 (3H, br s), 2.79 (1H, dm, $J=6$ Hz), 3.04 (1H, d, $J=12$ Hz), 3.10 (1H, dd, $J=9$, 7 Hz), 3.16 (1H, d, $J=12$ Hz), 3.39 (1H, br m), 3.40 (1H, dd, $J=9$, 4.3 Hz), 4.42 (2H, br s), 4.94 (1H, br s), 4.97 (1H, m), and 7.25 (5H, br s). IR ν : 2970, 2930, 2870, 1700, 1642, 1498, 1458, 1378, 1261, 1197, 1100, 1070, 1028, 890, 730, and 697 cm^{-1}].

LAH-Reduction of 15 to 13. A THF solution (2 cm^3) of **15** (38 mg) was reduced with LAH to solely give **13** (36 mg; 96%).

KF-on-Florisil Treatment of 15 to 16. An MeOH solution (2 cm^3) of **15** (48 mg) was treated with KF (170 mg) and Florisil (330 mg) at room temperature for 2 d. The mixture was then filtered and the residue obtained by evaporation of the solvent was chromatographed on a silica-gel column to give **16** [a colorless oil, 48 mg; 100%. Found: m/z , 392.2718 (M^+). Calcd for C₂₇H₃₆O₂: 392.2713. $[\alpha]_{\text{D}}^{20}=305.2^\circ$ (c 1.32, CHCl₃). ^1H NMR $\delta=0.91$ (3H, d, $J=7$ Hz), 0.94 (3H, s), 1.62 (3H, br s), 1.90 (3H, br s), 2.67 (1H, br m), 3.02 (1H, dm, $J=3.5$ Hz), 3.15 (1H, dd, $J=9$, 8 Hz), 3.53 (1H, dd, $J=9$, 4 Hz), 4.18 (1H, br m), 4.44 (1H, d, $J=12$ Hz), 4.50 (1H, d, $J=12$ Hz), 5.97 (1H, m), and 7.28 (5H, br s). IR ν : 2930, 2875, 1730, 1672, 1642, 1613, 1499, 1378, 1100, 732, and 698 cm^{-1}].

DIBAH-Reduction of 16 to 17 and 18. A toluene solution (1.5 cm^3) of **16** (30 mg) was treated with DIBAH (17 mg) at 65 °C for 30 min. The mixture was then extracted with ether,

dried on K_2CO_3 , and chromatographed on a silica-gel column to give **17** [a colorless oil, 29 mg; 96%. Found: m/z , 394.2870 (M^+). Calcd for $C_{27}H_{38}O_2$: 394.2870. 1H NMR $\delta=0.87$ (3H, s), 0.89 (3H, d, $J=7$ Hz), 1.62 (6H, br s), 3.62 (1H, dd, $J=9, 4$ Hz), 3.50 (1H, br m), 3.54 (1H, dd, $J=9, 8$ Hz), 4.44 (1H, d, $J=12$ Hz), 4.54 (1H, d, $J=12$ Hz), 4.77 (1H, dm, $J=8$ Hz), 5.47 (1H, dm, $J=8$ Hz), and 7.29 (5H, br s). IR ν : 3440, 2950, 2870, 1660, 1499, 1453, 1378, 1090, 1071, 1028, 1011, 1001, 732, and 698 cm^{-1}] and **18** [colorless needles, mp $109.5\text{--}111^\circ\text{C}$, 0.7 mg; 2%. Found: C, 82.34; H, 9.64%. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71%. 1H NMR $\delta=0.84$ (3H, s), 0.87 (3H, d, $J=7$ Hz), 0.92 (3H, d, $J=7$ Hz), 1.58 (3H, br s), 2.65 (1H, d, $J=5.3$ Hz), 2.75 (1H, dqd, $J=7.5, 7, 4.5$ Hz), 3.04 (1H, br m), 3.13 (1H, dd, $J=9, 7.5$ Hz), 3.40 (1H, dd, $J=9, 4.5$ Hz), 4.42 (2H, br s), and 7.26 (5H, br s). ^{13}C NMR $\delta=14.0$ (q), 14.6 (q), 16.7 (q), 27.1 (q), 28.9 (t), 29.1 (t), 36.0 (d), 36.5 (t), 36.7 (t), 39.6 (d), 41.8 (t), 47.3 (s), 49.6 (d), 51.7 (d), 53.1 (t), 64.0 (d), 73.0 (t), 74.6 (t), 127.5 (3C, d), 128.2 (2C, d), 133.0 (s), 137.1 (s), 138.6 (s), and 218.0 (s). IR ν : 2960, 2940, 2885, 1685, 1496, 1450, 1373, 1361, 1115, 1095, 735, and 695 cm^{-1}].

Acetylation of 17 to 19. A CH_2Cl_2 solution (4 cm^3) of **17** (360 mg) was treated with *N,N*-dimethylaminopyridine (100 mg), Et_3N (0.5 cm^3), and Ac_2O (1 cm^3) at room temperature for 1 h. The mixture was then chromatographed on silica-gel column to give an acetate, **19** [a colorless oil, 373 mg; 94%. m/z , 376 (M^+-60). 1H NMR $\delta=0.94$ (3H, s), 1.02 (3H, d, $J=7$ Hz), 1.62 (6H, br s), 1.94 (3H, s), 3.25 (1H, dd, $J=9, 7$ Hz), 3.54 (1H, dd, $J=9, 5$ Hz), 3.58 (1H, br m), 4.45 (2H, br s), 5.42 (1H, dm of quint, $J=8, 1.5$ Hz), 5.91 (1H, ddm, $J=8, 2$ Hz), and 7.27 (5H, br s). IR ν : 2960, 2870, 1735, 1662, 1499, 1455, 1370, 1245, 1212, 1095, 958, 732, and 698 cm^{-1}].

Birch Reduction of 19 to 20, 21, and 22. To liq NH_3 (25 cm^3) containing **19** (50 mg), Li (45 mg) was added. An ordinary workup of the mixture gave **20** [a colorless oil, 4 mg; 12%. m/z , 288 (M^+). 1H NMR $\delta=0.88$ (3H, br s), 1.02 (3H, br d, $J=7$ Hz), 1.61 (6H, br s), 3.41 (1H, ddm, $J=11.5, 7$ Hz), 3.67 (1H, ddm, $J=11.5, 4$ Hz), and 5.40 (1H, tm, $J=8$ Hz)], **21** [a colorless oil, 4 mg; 12%. 1H NMR $\delta=0.79$ (3H, s), 0.83 (3H, d, $J=7$ Hz), 1.02 (3H, dm, $J=6$ Hz), 1.61 (3H, s), 3.38 (1H, dd, $J=11.5, 7$ Hz), 3.42 (1H, br m), 3.66 (1H, ddm, $J=11.5, 3$ Hz), 4.96 (1H, ddd, $J=12.5, 5.5, 2.5$ Hz), and 5.34 (1H, ddd, $J=12.5, 3, 2$ Hz)], and hydrolyzed **22** [a colorless oil, 26 mg; 74%. Found: m/z , 304.2402 (M^+). Calcd for $C_{20}H_{32}O_2$: 304.2401. 1H NMR $\delta=0.89$ (3H, d, $J=7$ Hz), 0.90 (3H, s), 1.63 (6H, br s), 3.41 (1H, dd, $J=12, 4$ Hz), 3.70 (1H, dd, $J=12, 8$ Hz), 4.83 (1H, dm, $J=8$ Hz), and 5.49 (1H, dm, $J=8$ Hz). IR ν : 3350, 2950, 2875, 1447, 1375, 1033, 1012, 860, and 802 cm^{-1}].

THP Ether (23) of 17. An anhydrous CH_2Cl_2 solution of **19** (325 mg) was refluxed with dihydropyran (0.15 cm^3) and PPTS (6 mg) for 3 h. Then, aq $NaHCO_3$ was added and extracted with ether. Silica-gel column chromatography of the extract gave **23** [a colorless oil, 395 mg; 100%. Found: m/z , 478.3482 (M^+). Calcd for $C_{32}H_{46}O_3$: 478.3445. 1H NMR $\delta=0.86$ (3H, s), 1.00 (3H, d, $J=7$ Hz), 1.61 (6H, br s), 3.2–4.0 (5H, m), 4.3–4.9 (4H, m), 5.57 (1H, br d, $J=8$

Hz), and 7.28 (5H, br s) for isomer-a; $\delta=0.90$ (3H, s), 1.03 (3H, d, $J=7$ Hz), 1.61 (6H, br s), 3.2–4.0 (5H, m), 4.3–4.9 (4H, m), 5.33 (1H, br d, $J=8$ Hz), and 7.28 (5H, br s) for isomer-b (a: b=3: 2). IR ν : 2949, 2875, 1660, 1475, 1379, 1200, 1135, 1110, 1075, 1020, 1001, 865, 810, 731, and 695 cm^{-1}].

Birch Reduction of 23 to and 21. Anhydrous EtNH_2 (25 cm^3) was trapped in a cold vessel, to which an anhydrous THF solution of **23** (37 mg) containing EtOH (0.05 cm^3) was introduced and reduced with Li metal. Ordinary workup of the mixture afforded **20** and **21** in a quantitative amount.

Swern's Oxidation of 20 and 21 (a mixture) to 24. A CH_2Cl_2 solution (2.5 cm^3) of **20** and **21** (40 mg) and $(\text{COCl})_2$ (30 mg) was treated with DMSO (60 mg) and Et_3N (55 mg) to give **24** [a colorless oil, 17 mg; 42%. Found: m/z , 286.2271 (M^+). Calcd for $\text{C}_{20}\text{H}_{30}\text{O}$: 286.2295. ^1H NMR $\delta=0.86$ (3H, s), 1.21 (3H, d, $J=7$ Hz), 1.61 (6H, br s), 5.42 (1H, m), and 9.54 (1H, d, $J=3$ Hz). IR ν : 2950, 2925, 2875, 1727, 1455, 1377, 1260, 1095, 1075, 1020, and 800 cm^{-1}] and **25** [a colorless oil, 16 mg; 41%. ^1H NMR $\delta=0.81$ (3H, s), 0.82 (3H, d, $J=7$ Hz), 1.22 (3H, d, $J=7$ Hz), 1.61 (3H, br s), 4.9–5.4 (2H, m), and 9.73 (1H, d, $J=3$ Hz)].

Homologation of 24 to 26. A THF solution (10 cm^3) of $(i\text{-Pr})_2\text{NH}$ (0.5 cm^3) added was BuLi (2.2 cm^3 , 1.5M) at -78°C under an N_2 atmosphere. After stirred for 30 min, a THF solution (2 cm^3) of tiglic acid (190 mg) was introduced gradually. While cooling at -78°C , a THF solution (1.5 cm^3) of **24** (30 mg) was added in drop by drop. After 30 min, N,N -dimethylformamide (DMF, 4 cm^3) was introduced and stirred for another 30 min, and kept room temperature for 15 h, and finally heated to 75°C for 2.5 h. The mixture was then diluted with aq NaHCO_3 , extracted with ether, and dried on K_2CO_3 . The organic layer was evaporated, dissolved in ether, and treated with ethereal CH_2N_2 . Silicagel column chromatography of the mixture afforded **26** [a colorless oil, 5 mg; 12%, Found: m/z , 400.2977. Calcd for $\text{C}_{26}\text{H}_{40}\text{O}_3$: 400.2975. ^1H NMR $\delta=0.88$ (3H, s), 0.94 (3H, d, $J=7$ Hz), 1.62 (6H, br s), 1.87 (3H, d, $J=1$ Hz), 3.72 (3H, s), 3.6–3.9 (1H, m), 5.45 (1H, m), and 6.79 (1H, tm, $J=8$ Hz). IR ν : 3460, 2870, 1715, 1647, 1452, 1473, 1377, 1281, 1247, 1125, 1099, and 742 cm^{-1}].

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