The Total Synthesis of 8β-Hydroxycycloaraneosene by Means of an Eight-Membered Ring-Formation via a Lewis Acid-Catalyzed Ene Reaction. Confirmation of Its Natural Occurrence

Nobuo KATO,* Xue WU, Shinya TANAKA,† and Hitoshi TAKESHITA*
Institute of Advanced Material Study, 86, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816
†Graduate School of Engineering Sciences, 39, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816
(Received January 22, 1990)

An improved eight-membered ring closure by means of a Lewis-acid-catalyzed ene reaction was applied to the synthesis of cycloaraneosene and its congener, "hydroxycycloaraneosene." Comparisons of the NMR spectral data of the synthetic and natural compounds established that the natural product possesses an 8β-hydroxy structure, not the originally proposed 9α-hydroxy one.

In the last decade, the total synthesis of di- and sester-terpenoids of the 5-8-5-membered tricyclic systems, such as ophiobolins,[1] ceroplastols,[2] fusicoccins,[3] cotylenins,[4] and cycloaraneosene,[5] has attracted much attention because of their unique biological activities and the presence of the eight-membered ring, a medium-sized ring being regarded difficult to make.[6] Only recently several papers describing successful syntheses of natural products have appeared; cycloaraneosene,[7a] ceroplastol II and albolic acid,[7b] ophiobolin C,[7c] and ceroplastol I.[7d] Also dictymal, a biogenetically related *seco*-derivative of epoxydictymene,[8] has been totally synthesized.[9] During our synthetic study of cycloaraneosene (**1**),[7a] a metabolite from *Sordaria araneosa*, 5-8-5-membered tricyclic diterpene isolated by Borschberg[5] we have prepared 9α-hydroxycycloaraneosene (**2**),[7a] whose structure corresponds to the proposed structure of a congener, "hydroxycycloaraneosene" (**A**). However, the ^{1}H NMR spectra of **2** and **A** were not identical with each other, and so the **A** structure should be revised. Originally reported spectral data have suggested that **A** might be 8β-hydroxycycloaraneosene (**3**).[7a] That is, the ^{1}H NMR spectrum of **2** showed signals ascribable to a methyl group on C-11 at δ=1.20, while the reported figure for the corresponding methyl of **A** was at 1.02, which suggested that the configuration of the allylic alcohol might be epimeric. However, the epimer of **A**, prepared by Borschberg,[5] was not identical to **2**, either. Therefore, the hydroxyl must not be substituted on C-9. To obtain concrete evidence, we have now carried out an independent total synthesis of hydroxycycloaraneosene, **3**. At the same time, we have also tried to develop an alternative eight-membered ring formation by the use of a Lewis-acid-catalyzed intramolecular ene reaction[10] of the appropriate precursor, which would be an 8,9-*seco*-enal derivative obtained from a chromium(II) chloride condensation product derived from two iridoid synthons.[11]

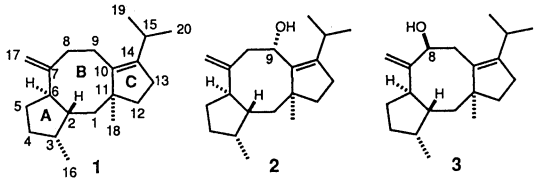
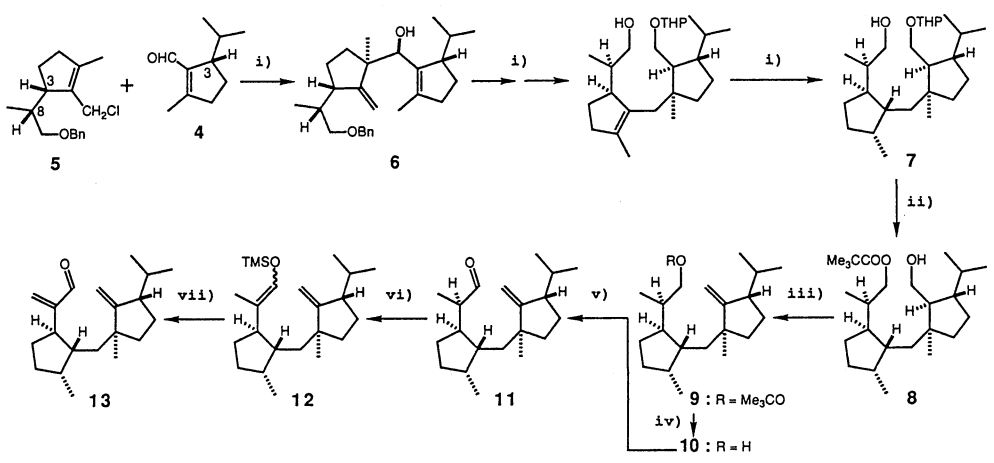
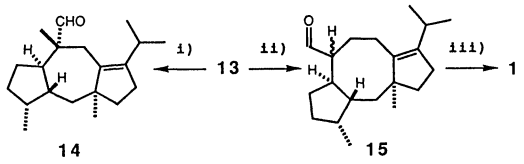


Fig. 1.



Scheme 1. i) See, Ref. 7a; ii) Pivaloyl chloride/pyridine; TsOH/MeOH, 98%; iii) *o*-nitrophenyl selenocyanate-tributylphosphine/THF; H_2O_2, 97%; iv) $LiAlH_4$/THF, 99%; v) $(Cl_3CCO)_2O$-DMSO, Et_3N, 99%; vi) F_3CSO_3TMS-Et_3N/CH_2Cl_2, 98%; vii) $Pd(OAc)_2$/MeCN, 51% or O_2-Rose Bengal/acetone, 70%.

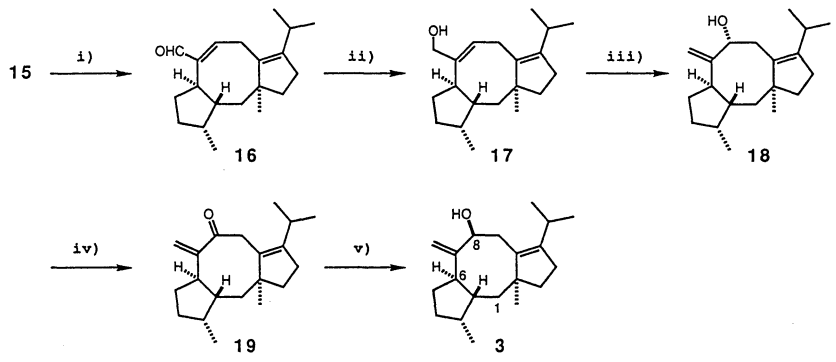
When (3*S*)-1-iriden-7-al (**4**) and (3*S*,8*R*)-9-benzyloxy-7-chloro-1-iridene (**5**) were condensed by the use of chromium(II) chloride in a mixture of tetrahydrofuran and *N*,*N*-dimethylformamide in the presence of 2-propanol, a stereoselective formation of the desired condensate (**6**) was observed, as was reported in former studies.[7a,12] From this epimer, **6**, a series of transformations described in connection with the previous synthesis of **1** was repeated to obtain a suitable substrate for the intramolecular ene reaction. 8,9-*seco*-(2*R*,3*R*,6*R*,7*R*,10*S*,11*S*,14*S*)-8-Hydroxy-9-(2-tetrahydropyranyloxy)-cycloaraneosane (**7**), obtained from the dissolving metal reduction of Δ^2-precursor,[7a] was then treated with pivaloyl chloride in pyridine and with *p*-toluenesulfonic acid in methanol to afford 9-hydroxy-8-pivaloyloxy derivative (**8a**), which was contaminated by an epimer (**8b**). After the separation of the isomers by means of silica-gel column chromatography, **8a** was treated with Grieco's reagent,[13] *o*-nitrophenyl selenocyanate, and tributylphosphine in tetrahydrofuran and subsequently oxidized with hydrogen peroxide to afford an elimination product (**9**), which was then hydrolyzed by lithium-aluminum-hydride reduction to an alcohol (**10**). The Swern oxidation[14] of **10** afforded an aldehyde (**11**) in a good yield. The treatment of **11** with trimethylsilyl trifluoromethanesulfonate and triethylamine gave an trimethylsilyl enol ether (**12**). The conversion of **12** to an α,β-unsaturated aldehyde (**13**), the precursor for the intramolecular ene reaction, was achieved by the use of palladium(II)acetate[15] or by singlet-oxygen oxidation.



Scheme 2. i) 200 °C/toluene, 97%; ii) $SnCl_4$/THF, 85%; iii) $NaBH_4$/MeOH; *o*-nitrophenyl selenocyanate-tributylphosphine/THF; H_2O_2, 50%.

The ene reaction of **13** in toluene by just heating at 200 °C in a sealed tube, however, afforded a seven-membered ring compound (**14**) as the single product. The stereochemistry of the product was assumed to be as depicted from the mechanistic point of view. The formation of the seven-membered ring derivative, **14**, can be explained in terms of the preference for the smaller ring formation under the sterically crowded circumstances in the transition state; the π-system of the enal moiety might not be coplanar. The mechanism of the formation of **14** indicated that, for the desired eight-membered ring closure, the carbonyl group of the aldehyde must be sufficiently polarized by the aid of acidic species. Therefore, the Lewis acid-mediated reaction was then attempted by adding tin(IV) chloride to a THF solution of **13**; the products, formed as a mixture in an 85% yield, were indeed the desired compounds (**15**). The epimeric nature of the products and their tricyclic ring system were proven by their conversion to the previously synthesized cycloaraneosene, **1**, in the following manner:

Thus, the sodium borohydride reduction of this aldehyde mixture, **15**, gave an epimeric mixture of alcohols, which, when treated with Grieco's reagent followed by hydrogen peroxide oxidation, afforded **1** as a single product. The identity of the sample with the previously prepared compound was cofirmed by direct comparisons. Therefore, the ene reaction products possess the proper ring system, with proper stereochemistries, for further transformations. An isomeric mixture of trimethylsilyl enol ethers prepared from **15** was oxidized to α,β-unsaturated aldehyde (**16**) by means of palladium(II) acetate oxidation, and **16** was reduced with sodium borohydride and cerium(III) chloride[16] to give an allylic alcohol (**17**). The treatment of **17** with Grieco's reagent, followed by hydrogen peroxide oxidation, caused a smooth [2,3]sigmatropic rearrangement[17] to give secondary allylic alcohol (**18**) stereoselectively. The NMR spectral data of **18** were identical with the *epi*-hydroxycycloaraneosene which had previously been



Scheme 3. i) F_3CSO_3TMS-Et_3N/CH_2Cl_2; $Pd(OAc)_2$/MeCN, 85%; ii) $NaBH_4$-$CeCl_3$/MeOH, 99%; iii) *o*-nitrophenyl selenocyanate-tributylphosphine/THF; H_2O_2; 77%; iv) $(Cl_3CCO)_2O$-DMSO, Et_3N/CH_2Cl_2, 94%; v) $NaBH_4$-$CeCl_3$/MeOH, 92%.

prepared in the structural study of **A**. Moreover, in a formal sense, this accomplishes a total synthesis of **3**; our transformation from **18** to **3** is actually the same as in the original manner.[5] Thus, the Swern oxidation of **18** afforded a ketone (**19**), which was identical with the dehydro derivative of **A**, as predicted, while the reduction with sodium borohydride and cerium(III) chloride gave **3** stereoselectively. The ^1H and ^{13}C NMR spectra of **3** were essentially identical with the data reported for the natural product, **A**, although some discrepancies were observed within the range of instrumental error; e.g., δ=1.00 was observed for the methyl group on C-11, which had previously been reported to be δ=1.02. Since model inspections clearly show that the convex face around C-8 of the cycloaraneosane ring system is α-face, the stereoselective formations of both **18** and **3** strongly suggested that the hydroxyl of the former is α-oriented, while that of the latter is β-oriented. This conclusion was confirmed spectroscopically by the nuclear Overhauser effect (NOE) experiment. Thus, in **3**, distinct NOE's were observed on H-6 (δ=2.09, br td, J=10, 8 Hz) and H-1α (δ=1.44, dd, J=15, 8 Hz) by irradiation at the frequency of H-8 (δ=4.46, dd, J=8, 6 Hz).

Consequently, the results described herein constituted the total synthesis of hydroxycycloaraneosene, as well as its structure proof. It is worthy of comment that the intramolecular ene reaction is excellently applied for eight-membered ring formation. This became feasible by taking advantage of our intermediates having two cyclopentane rings; this apparently reduces the entropic factor in the ring-formation reactions. Three different methods are now available; the first is a low-valent titanium chloride-mediated reductive cyclization of dialdehyde to 1,2-diols,[7b] the second, a low-valent chromium chloride-mediated condensation of allyl halide to aldehyde to give allylic alcohol,[7a] and the third, the ene reaction. The yields are all high. Certainly, one can select an appropriate method depending on the types of the target molecules.

Related studies of the synthesis of the tricyclic higher terpenoids will be reported in the future.

Experimental

The elemental analyses were performed by Miss S. Hirashima, of this Institute, Kyushu University. The mps were measured with a Yanagimoto Micro mp apparatus and are not corrected. The NMR spectra were measured by means of JEOL FX 100 and GSX 270H spectrometers in $CDCl_3$, unless otherwise specified, and the chemical shifts were expressed in δ units. The mass spectra were measured with a JEOL 01SG-2 spectrometer. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily materials, using a JASCO IR-A 102 spectrometer. The optical rotations were measured with a Union Model PW-101 apparatus. The solvents for the reactions were carefully purified by distillation in the presence of appropriate dehydrating agents and in an N_2 atmosphere immediately prior to use; therefore, they were anhydrous, unless otherwise stated. The stationary phase for the column chromatography was Wakogel C-300, and the elution solvents were mixtures of hexane and ethyl acetate, unless otherwise stated.

Pivalate 8a and its Stereoisomer (8b). According to our previous results,[7a] the starting tetrahydropyranyl ether **7** was obtained as a mixture with its stereoisomer by the reduction of the Δ^2-precursor (1.07 g) by the dissolving-metal reduction in hexamethylphosphoric triamide. The stereoisomeric mixture of the reduction products (ca. 1 g), thus obtained was then dissolved into pyridine (15 cm^3) and treated with an excess of pivaloyl chloride (1 cm^3) at 20—25 °C for 12 h. The reaction mixture was then diluted with an aq. $NaHCO_3$ solution and extracted with a 2:1 mixture of hexane and ethyl acetate. The residue (ca. 1.3 g) obtained from an organic extract was then dissolved in methanol (20 cm^3) and treated with *p*-toluenesulfonic acid (80 mg) at 25 °C for 4 h. The mixture was diluted with H_2O and extracted with a 1:1-mixture of hexane and ethyl acetate. Silica-gel column chromatography of the extract gave **8a** [a colorless oil, 775 mg; 72% (98% when started from pure **7**). Found: C, 76.07; H, 11.72%. Calcd for $C_{25}H_{46}O_3$: C, 76.09; H, 11.75%. $[\alpha]_D^{21}$ −73.8° (*c* 2.05, $CHCl_3$). MS *m/z*, 394 (M^+), 81 (base peak). ^1H NMR δ=0.84 (3H, d, J=7 Hz), 0.85 (3H, d, J=6.5 Hz), 0.91 (3H, d, J=6.5 Hz), 1.01 (3H, d, J=7 Hz), 1.07 (3H, s), 1.20 (9H, s), 1.86 (1H, m), 2.12 (1H, m), 3.65 (1H, dd, J=11, 5 Hz), 3.73 (IH, dd, J=11, 4 Hz), 3.84 (1H, dd, J=11, 8.5 Hz), and 4.12 (1H, dd, J=11, 4 Hz). ^{13}C NMR δ=15.58 (q), 17.64 (q), 17.90 (q), 22.27 (q), 23.79 (t), 24.55 (t), 27.21 (3C, q), 27.49 (q), 31.24 (d), 32.09 (t), 33.09 (t), 33.99 (d), 36.69 (d), 37.90 (t), 38.82 (s), 41.74 (d), 44.88 (s), 47.23 (d), 47.64 (d), 56.04 (d), 64.06 (t), 66.97 (t), and 178.77 (s). IR ν: 3450, 2950, 2870, 1735, 1715, 1450, 1285, 1160, 1030 cm^{-1}], and its stereoisomer, (2*R*,3*S*)-isomer, **8b** [colorless needles, mp 47—48 °C, 218 mg; 20%. Found: C, 75.90; H, 11.67%. $[\alpha]_D^{17}$ −37.5° (*c* 1.79, $CHCl_3$). MS *m/z*, 394 (M^+), 57 (base peak). ^1H NMR δ=0.85 (3H, d, J=6.5 Hz), 0.91 (3H, d, J=7 Hz), 0.94 (3H, d, J=7 Hz), 1.00 (3H, d, J=6.5 Hz), 1.08 (3H, s), 1.20 (9H, s), 1.80 (2H, m), 3.62 (1H, dd, J=11, 5 Hz), 3.70 (1H, dd, J=11, 7 Hz), 3.83 (1H, dd, J=10.5, 7.5 Hz), and 4.08 (1H, J=10.5, 4.5 Hz). ^{13}C NMR δ=17.09 (q), 17.96 (q), 21.35 (q), 22.29 (q), 24.64 (t), 27.24 (3C, q), 27.49 (t), 28.01 (q), 31.30 (d), 33.09 (t), 36.64 (d), 37.94 (t), 38.85 (s), 41.08 (d), 42.79 (t), 45.27 (s), 46.06 (d), 47.67 (d), 52.70 (d), 56.17 (d), 64.07 (t), 67.86 (t), and 178.71 (s). IR ν: 3440, 2950, 2865, 1730, 1715, 1480, 1460, 1285, 1160, and 1030 cm^{-1}].

Dehydration of 8a to a Terminal Olefin (9). Into a tetrahydrofuran (THF) solution (10 cm^3) of **8a** (452 mg), *o*-nitrophenyl selenocyanate (310 mg) and tributylphosphine (0.34 cm^3) were added successively. After it had then been stirred for 20 min at 20 °C, the reaction mixture was diluted with H_2O and extracted with ether. The yellow oil (633 mg) obtained from the extract was dissolved into THF (5 cm^3), and the mixture was treated with 35% H_2O_2 (0.2 cm^3) at 20—25 °C for 6 h. The reaction mixture was then diluted with H_2O and extracted with a 3:1 mixture of hexane and ethyl acetate. The residue obtained from the extract was chromatographed on a silica-gel column to give **9** [a colorless oil, 418 mg; 97%. Found: C, 79.68; H, 11.62%. Calcd for $C_{25}H_{44}O_2$: C, 79.73; H, 11.78%. $[\alpha]_D^{18}$ −110.7° (*c* 1.83,

$CHCl_3$). MS m/z, 376 (M^+), 95 (base peak). ^1H NMR δ=0.77 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 0.97 (3H, d, J=7 Hz), 0.98 (3H, s), 0.99 (3H, d, J=6.5 Hz), 2.15 (1H, m), 2.41 (1H, m), 3.83 (1H, dd, J=10.5, 8.5 Hz), 4.06 (1H, dd, J=10.5, 4 Hz), 4.73 (1H, d, J=2.5 Hz), and 4.81 (1H, d, J=2.5 Hz). ^{13}C NMR δ=15.77 (q), 16.46 (q), 17.60 (q), 21.96 (q), 23.04 (t), 23.74 (t), 27.24 (3C, q), 27.95 (q), 28.78 (d), 33.17 (t), 33.65 (d), 36.41 (d), 37.29 (t), 38.82 (s), 40.11 (t), 41.97 (d), 46.52 (s), 47.46 (d), 51.20 (d), 66.92 (t), 103.24 (t), 163.36 (s), and 178.73 (s). IR ν: 3060, 2950, 2860, 1735, 1645, 1480, 1460, 1155, and 875 cm^{-1}].

LAH-Reduction and Subsequent Swern Oxidation of 9 to 11 via 10. A THF solution (8 cm^3) of **9** (338 mg) was treated with $LiAlH_4$ (20 mg) at 0 °C for 30 min. A small portion of aq NH_4Cl was then added, and the resulting supernatant was dried over $MgSO_4$. Silica-gel chromatography of the residue afforded a corresponding alcohol **10** [a colorless oil, 260 mg; 99%. Found: C, 82.10; H, 12.28%. Calcd for $C_{20}H_{36}O$: C, 82.13; H, 12.40%. $[\alpha]_D^{17}$ −120.2° (c 1.61, $CHCl_3$). MS m/z, 292 (M^+), 95 (base peak). ^1H NMR δ=0.77 (3H, d, J=6.5 Hz), 0.84 (3H, d, J=7 Hz), 0.97 (3H, d, J=6.5 Hz), 0.98 (3H, s), 1.00 (3H, d, J=7 Hz), 1.97 (1H, sept of d, J=7, 4.5 Hz), 2.15 (1H, m), 2.41 (1H, m), 3.36 (1H, dd, J=10.5, 8 Hz), 3.69 (1H, dd, J=10.5, 4 Hz), 4.76 (1H, d, J=2.5 Hz), and 4.83 (1H, d, J=3 Hz). ^{13}C NMR δ=15.72 (q), 16.44 (q), 17.26 (q), 21.99 (q), 23.05 (t), 23.90 (t), 27.93 (q), 28.75 (d), 33.23 (t), 36.46 (d), 37.03 (d), 37.32 (t), 40.16 (t), 41.90 (d), 46.58 (s), 47.33 (d), 51.26 (d), 65.37 (t), 103.11 (t), and 163.82 (s). IR ν: 3330, 3060, 2950, 2860, 1645, 1455, 1380, 1370, 1030, and 880 cm^{-1}]. To a CH_2Cl_2 solution (15 cm^3) of trichloroacetic anhydride (0.25 cm^3) we added a CH_2Cl_2 solution (0.5 cm^3) of dimethyl sulfoxide (0.2 cm^3) at −80 °C. After the mixture had been stirred at −70—−80 °C for 30 min, a CH_2Cl_2 solution (5 cm^3) of **10** (260 mg) was added at −80 °C; stirring was then continued for another 1 h at −75—−65 °C. The reaction temperature was then lowered again to −80 °C, and Et_3N (1.5 cm^3) was introduced. The mixture was gradually warmed to −20 °C, diluted with an aq. $NaHCO_3$ solution, and extracted with a 5:1 mixture of hexane and ether. Silica-gel column chromatography of the extract gave **11** [a colorless oil, 256 mg; 99%. ^1H NMR δ=0.77 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 0.99 (3H, s), 1.08 (3H, d, J=7 Hz), 2.21 (1H, m), 2.40 (1H, m), 2.49 (1H, m), 4.76 (1H, d, J=2.5 Hz), 4.81 (1H, d J=3 Hz), and 9.75 (1H, d, J=2 Hz). ^{13}C NMR δ=13.23 (q), 15.38 (q), 16.44 (q), 21.96 (q), 23.04 (t), 24.85 (t), 27.89 (q), 28.77 (d), 33.09 (t), 36.44 (d), 37.31 (t), 39.88 (t), 42.48 (d), 46.18 (d), 46.48 (s), 47.59 (d), 51.22 (d), 103.45 (t), 163.25 (s), and 206.06 (d). IR ν: 3110, 2980, 2910, 2760, 1730, 1650, 1460, 1390, and 905 cm^{-1}].

Conversion of 11 to α,β-Unsaturated Aldehyde (13). Into a CH_2Cl_2 solution (5 cm^3) of saturated aldehyde **11** (168 mg) we added Et_3N (0.24 cm^3) and trimethylsilyl trifluoromethanesulfonate (0.17 cm^3), after which the mixture was stirred for 14 h at 20—25 °C. Then the mixture was diluted with an aq K_2CO_3 solution and extracted with a 5:1 mixture of hexane and ether. The organic extract was washed successively with a very dilute aq $KHSO_3$ solution, an aq $NaHCO_3$ solution, and brine. The residue obtained from the extract was quickly passed through a Florisil column to give trimethylsilyl enol ether of **12** (206 mg; 98%), which was subsequently oxidized to an unsaturated aldehyde by the following two methods.

a) $Pd(OAc)_2$ Oxidation. An CH_3CN solution (5 cm^3) of **12** (290 mg) was treated with $Pd(OAc)_2$ (198 mg) at 20—25 °C for 3 h. The reaction mixture was then passed through a short Florisil column with ether. The elutant was washed successively with an aq. $NaHCO_3$ solution, H_2O, and brine. Silica-gel column chromatography of the residue gave **13** [a colorless oil, 120 mg; 52%. ^1H NMR δ=0.75 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=7 Hz), 0.94 (3H, s), 0.96 (3H, d, J=7 Hz), 1.14 (1H, dd, J=14.5, 2 Hz), 2.2—2.45 (2H, m), 2.63 (1H, br td, J=9.5, 7.5 Hz), 4.69 (1H, d, J=3 Hz), 4.71 (1H, d, J=3 Hz), 5.99 (1H, s), 6.24 (1H, br s), and 9.54 (1H, br s). ^{13}C NMR δ=16.08, 16.67, 22.20, 23.21, 27.99, 29.02, 29.69, 33.69, 36.41, 37.43, 39.42, 42.90, 44.99, 46.52, 51.30, 103.55, 134.30, 154.10, 163.30, and 195.28].

b) $^1O_2$ Oxidation. A mixture of **12** (191 mg), pyridine (0.03 cm^3), and Rose Bengal (1 mg) was irradiated by means of a 500-W tungsten lamp under an oxygen stream for 40 min at 0 °C. Then triphenylphosphine (165 mg) was added, and the reaction mixture was stirred for 3 h at 20—25 °C. Acetone was removed under reduced pressure, and the residue was chromatographed on a silica-gel column to give **13** (108 mg; 71%).

Thermal Ene Reaction of 13 to 14. A toluene solution (5 cm^3) of **13** was heated at 200 °C for 24 h in a sealed tube. The subsequent evaporation of the solvent and chromatographic purification of the residue afforded **14** [a colorless oil, 29 mg; 97%. $[\alpha]_D^{23}$ +32° (c 1.32, $CHCl_3$). MS m/z, 288 (M^+), 137 (base peak). ^1H NMR δ=0.81 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 0.90 (3H, s), 0.92 (3H, s), 1.02 (3H, d, J=6.5 Hz), 2.58 (1H, sept, J=7 Hz), and 9.47 (1H, s). ^{13}C NMR δ=12.46 (q), 14.61 (q), 20.63 (q), 21.58 (q), 25.53 (t), 25.56 (q), 26.85 (t), 27.18 (d), 30.50 (t), 33.48 (t), 37.59 (t), 39.87 (d), 43.07 (t), 49.52 (s), 49.75 (s), 51.23 (s), 135.46 (s), 144.92 (s), and 207.08 (d). IR ν: 2950, 2860, 1725, 1695, 1455, 1380, and 1200 cm^{-1}].

Lewis-Acid-Catalyzed Ene Reaction of 11 to 13. Into a THF solution (8 cm^3) of the enal **11** (53 mg) we added $SnCl_4$ (0.022 cm^3) at 0 °C, after which the mixture was stirred for 16 h at 20—25 °C. The reaction mixture was then diluted with an aq. $NaHCO_3$ solution and extracted with a 4:1 mixture of hexane and ethyl acetate. The residue obtained from the organic extract was chromatographed on a silica-gel column to give **13** (a colorless oil, 45 mg; 85%), which was an epimeric mixture at C-7. The separation and characterization of the epimers were not attempted at this stage.

Formation of 1 from 15. A MeOH solution (2 cm^3) of **15** (45 mg) was treated with $NaBH_4$ (10mg) at 0 °C for 30 min. The reaction mixture was then diluted with H_2O and extracted with ether. The crude isomeric mixture of alcohols (45 mg) obtained from the extract was then treated with *o*-nitrophenyl selenocyanate (43 mg) and tributylphosphine (0.046 cm^3) in THF at 20—25 °C for 30 min; then the mixture was directly treated with H_2O_2 (0.025 cm^3) at 20—25 °C for 6 h. Extraction with a 1:1 mixture of EtOAc and hexane and chromatography on a silica-gel column gave **1** (a colorless oil, 21 mg; 50%). This compound was confirmed to be cycloaraneosene by a direct comparison with a previously prepared sample.[7a]

Formation of α,β-Unsaturated Aldehyde (16) from 15. Into a CH_2Cl_2 solution (8 cm^3) of **15** (51 mg) we added Et_3N (0.075 cm^3) and trimethylsilyl trifluoromethanesulfonate (0.055 cm^3), after which the mixture was stirred for 12 h. Then, the mixture was diluted with an aq K_2CO_3 solution

and extracted with ether. The residue obtained from the extract was quickly passed through a Florisil column to give an isomeric mixture of the corresponding silyl enol ethers (57 mg), which was then treated with $Pd(OAc)_2$ (40 mg) in CH_3CN (5 cm^3) at 20—25 °C for 6 h. The reaction mixture was then passed through a short Florisil column with ether. The elutant was washed successively with an aq $NaHCO_3$ solution, H_2O, and brine. Silica-gel column chromatography of the residue gave **16** [a colorless oil, 43 mg; 85%. ^1H NMR δ=0.84 (3H, d, J=7 Hz), 0.87 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=7 Hz), 0.90 (3H, s), 2.51—2.62 (2H, m), 2.75 (1H, dd, J=14, 8.5 Hz), 3.00 (1H, ddt, J=14, 8.5, 1.5 Hz), 6.61 (1H, td, J=8.5, 1 Hz), and 9.24 (1H, d, J=1 Hz)].

1,2-Reduction of 16 to Allyl Alcohol (17). Into a MeOH solution (3 cm^3) of **16** (30 mg), $CeCl_3 \cdot 7H_2O$ (47 mg) was added at 0 °C, after which the mixture was stirred for a while. Then it was treated with $NaBH_4$ (6 mg) for 20 min. The reaction mixture was diluted with 0.5 M HCl and extracted with ether. Silica-gel column chromatography of the extract gave the desired alcohol, **17** [a colorless oil, 30 mg; 99%. ^1H NMR δ=0.84 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 0.87 (3H, s), 0.90 (3H, d, J=6.5 Hz), 2.48 (1H, dd, J=14, 8.5 Hz), 2.58—2.77 (3H, m), 4.03 (1H, d, J=12 Hz), 4.07 (1H, d, J=12 Hz), and 5.85 (1H, br t, J=8.5 Hz)]. Although the full characterization of this compound was not carried out, a clean 1,2-reduction of the enal moiety of **16** to **17** obviously occurred judging from the ^1H NMR spectrum.

Reaction of 17 with *o*-Nitrophenyl Selenocyanate and Subsequent 2,3-Sigmatropic Rearrangement to Give Unsaturated Alcohol, *epi*-Hydroxycycloaraneosene (18). Into a THF solution (4 cm^3) of **17** (30 mg) we added *o*-nitrophenyl selenocyanate (28.5 mg) and tributylphosphine (0.031 cm^3). The mixture was then stirred at 20—25 °C for 20 min, diluted with H_2O, and extracted with ether. The chromatographic purification of the residue gave a yellow oil (47 mg), which was then treated with H_2O_2 (0.13 cm^3) in THF (2.5 cm^3) in the presence of Et_3N (0.1 cm^3) for 20 h. After the usual work-up, the residue was chromatographed on a silica-gel column to give **18** [colorless needles, mp 128.5—130 °C (lit.[5] 129—130 °C), 23 mg; 77%. $[\alpha]_D^{23}$ −14° (c 0.43, $CHCl_3$) (lit.[5] −10°). ^1H NMR δ=0.84 (3H, d, J=7 Hz), 0.84 (3H, s), 0.91 (3H, d, J=6.5 Hz), 0.97 (3H, d, J=7 Hz), 1.94 (1H, dd, J=13.5, 10.5 Hz), 2.37 (1H, br td, J=9.5, 5.5 Hz), 2.52—2.70 (2H, m), 4.31 (1H, dd, J=10.5, 7 Hz), 4.84 (1H, br s), and 4.94 (1H, br s). ^{13}C NMR δ=14.81 (q), 20.55 (q), 21.18 (q), 26.50 (t), 26.99 (q), 27.99 (d), 29.56 (t), 34.15 (t), 34.59 (t), 34.72 (t), 41.37 (d), 42.14 (t), 42.52 (d), 50.04 (d), 50.24 (s), 76.98 (d), 112.54 (t), 135.15 (s), 143.14 (s), and 159.02 (s). IR ν: 3440, 2980, 2950, 1640, 1010, 1000, and 900 cm^{-1}].

Oxidation of 18 to Ketone 19. Into a CH_2Cl_2 solution (4 cm^3) of trichloroacetic anhydride (0.029 cm^3) we added a CH_2Cl_2 solution (0.05 cm^3) of dimethyl sulfoxide (0.022 cm^3) at −80 °C. After the mixture had then been stirred at −70—−80 °C for 30 min, a solution (0.5 cm^3) of **18** (30 mg) was added at −80 °C and stirring was continued for another 1 h at −75—−65 °C. The reaction temperature was then lowered again to −80 °C, and Et_3N (0.15 cm^3) was introduced. The mixture was gradually warmed to −20 °C, diluted with an aq $NaHCO_3$ solution, and extracted with a 5:1 mixture of hexane and ether. Silica-gel column chromatography of the extract gave **19** [colorless needles, mp 72.5—74 °C (lit.[5] 75—76 °C), 28 mg; 94%. $[\alpha]_D^{24}$ +132° (c 0.75, $CHCl_3$) (lit.[5] +53°). ^1H NMR δ=0.87 (3H, d, J=7 Hz), 0.88 (3H, d, J=6.5 Hz), 0.90 (3H, d, J=7 Hz), 0.96 (3H, s), 2.42 (1H, br q, J=8.5 Hz), 2.61 (1H, sept, J=7 Hz), 3.08 (1H, br d, J=14.5 Hz), 3.24 (1H, br d, J=14.5 Hz), 5.13 (1H, br s), and 5.34 (1H, br s). ^{13}C NMR δ=15.76 (q), 19.98 (q), 20.86 (q), 26.93 (q), 27.18 (d), 27.45 (t), 29.90 (t), 33.31 (t), 35.11 (t), 38.72 (t), 40.10 (d), 42.39 (t), 47.19 (d), 48.12 (d), 50.81 (s), 113.51 (t), 130.39 (s), 147.66 (s), 155.89 (s), and 206.97 (s). IR ν: 2970, 2890, 1685, 1650, 1630, 1450, 1375, 1260, 1100, 935, and 800 cm^{-1}].

Reduction of 19 to 3, Hydroxycycloaraneosene. To an MeOH solution (3 cm^3) of **19** (28 mg) $CeCl_3 \cdot 7H_2O$ (47 mg) was added at 0 °C, after which the mixture was stirred for a while, and then treated with $NaBH_4$ (6 mg) for 20 min. The reaction mixture was diluted with 0.5 M HCl and extracted with ether. Silica-gel column chromatography of the extract gave **3** [a colorless oil, 26 mg; 92%. $[\alpha]_D^{23}$ +16° (c 0.94, $CHCl_3$) (lit.[5] +7.5°). ^1H NMR δ=0.83 (3H, d, J=7 Hz), 0.89 (3H, d, J=7 Hz), 0.91 (3H, J=7 Hz), 1.00 (3H, s), 1.26 (1H, dddd, J=13, 9, 6, 3 Hz; H-4α), 1.34 (1H, ddd, J=10, 8, 7 Hz; H-2), 1.44 (1H, dd, J=15, 8 Hz; H-1α), 1.50 (1H, ddd, J=13, 9, 6 Hz; H-12α), 1.58 (1H, ddd, J=13, 9, 8 Hz; H-12β), 1.62 (1H, br d J=15 Hz; H-1β) 1.63 (1H, dtd, J=13, 10, 6 Hz; H-5β), 1.69 (1H, br s; OH), 1.78 (1H, dddd, J=13, 9, 8, 5 Hz; H-5α), 1.87 (1H, dddd, J=13, 10, 7, 5 Hz; H-4β), 2.03 (1H, sext of d, J=7, 3; H-3), 2.09 (1H, br td, J=10, 8 Hz; H-6), 2.1—2.2 (2H, m; H-13's), 2.39 (1H, ddt, J=14, 6, 2 Hz; H-9α), 2.51 (1H, dd, J=14, 8 Hz; H-9β), 2.72 (1H, sept, J=7 Hz; H-15), 4.46 (1H, dd, J=8, 6 Hz; H-8), 4.93 (1H, br s; H-17), and 5.09 (1H, br s; H-17). ^{13}C NMR δ=16.70 (q), 21.17 (q), 21.23 (q), 27.29 (d; C-15), 27.85 (t; C-13), 27.86 (q; C-18), 29.60 (t; C-5), 31.81 (t; C-4), 33.90 (t; C-9), 36.70 (t; C-12), 39.36 (d; C-3), 42.53 (t; C-1), 46.46 (d; C-2), 48.74 (d; C-6), 50.79 (s; C-11), 73.24 (d; C-8), 107.09 (t; C-17), 134.23 (s), 144.64 (s), and 157.67 (s). IR ν: 3360, 2950, 1640, 1375, 1360, 1020, and 895 cm^{-1}].

References

1) S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Takahashi, S. Tamura, K. Ishibashi, and M. Shirasaka, *J. Am. Chem. Soc.*, **87**, 4968 (1965); L. Canonica, A. Fiecchi, M. G. Kienle, and A. Scala, *Tetrahedron Lett.*, **1966**, 1329.

2) T. Ríos and L. Quijano, *Tetrahedron Lett.*, **1969**, 1317; T. Ríos and F. Gómez G., *ibid.*, **1969**, 2929.

3) K. D. Barrow, D. H. R. Barton, E. B. Chain, U. F. W. Ohonsorge, and R. Thomas, *Chem. Commun.*, **1968**, 1198; A. Ballio, M. Brufani, C. G. Casinovi, S. Fedeli, R. Pellicciari, B. Santurbano, and A. Vaciago, *Experientia*, **24**, 631 (1968).

4) T. Sassa, *J. Agr. Biol. Chem.*, **36**, 2037 (1972).

5) H. J. Borschberg, Ph. D. Dissertation, Eidgenössischen Technischen Hochschule, Zurich (1975).

6) H. Takeshita and N. Kato, *Yuki Gosei Kagaku Kyokai Shi (J. Synth. Org. Chem., Jpn.)*, **44**, 1081 (1986), and the references cited therein.

7) a) N. Kato, S. Tanaka, and H. Takeshita, *Chem. Lett.*, **1986**, 1989; *Bull. Chem. Soc. Jpn.*, **61**, 3231 (1988); b) N. Kato, H. Kataoka, S. Ohbuchi, S. Tanaka, and H. Takeshita, *J. Chem. Soc., Chem. Commun.*, **1988**, 354; *J. Chem. Soc., Perkin Trans. 1*, **1989**, 165; c) M. Rowley, M. Tsukamoto, and Y. Kishi, *J. Am. Chem. Soc.*, **111**, 2735 (1989); d) R. K. Boeckman, Jr., A. Arvanitis, and M. E. Voss,

ibid., **111**, 2737 (1989).

8) N. Enoki, A. Furusaki, K. Suehiro, R. Ishida, and T. Matsumoto, *Tetrahedron Lett.*, **24**, 4341 (1983); M. Segawa, N. Enoki, M. Ikura, K. Hikichi, R. Ishida, H. Shirahama, and T. Matsumoto, *ibid.*, **28**, 3703 (1987).

9) N. Kato, S. Tanaka, H. Kataoka, and H. Takeshita, *Chem. Lett.*, **1987**, 2295; *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1833.

10) N. H. Andersen and F. F. Golec, Jr., *Tetrahedron Lett.*, **1977**, 3783; W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, **17**, 476 (1978), and the references cited therein.

11) For a preliminary account of this paper, see N. Kato, X. Wu, S. Tanaka, and H. Takeshita, *Chem. Lett.*, **1989**, 91.

12) N. Kato, X. Wu, S. Ohbuchi, H. Miyagawa, S. Tanaka, H. Kataoka, T. Imaoka, and H. Takeshita, *Kyushu Daigaku Kinou Bussitsu Kagaku Kenkyusho Hokoku (Rep. Inst. Advanced Material Study, Kyushu Univ.)*, **2**, 115 (1988).

13) P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1481 (1976); K. B. Sharpless and M. W. Young, *ibid.*, **40**, 947 (1975).

14) K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976); E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).

15) Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978).

16) J.-L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978).

17) D. L. J. Clive, G. Chittattu, N. J. Curtis, and S. M. Menchen, *J. Chem. Soc., Chem. Commun.*, **1978**, 770.