[Chem. Pharm. Bull. 31(2) 414—422 (1983)]

Synthetic Studies on Pseudoguaianolides. II.[1] A Total Synthesis of (±)-Carpesiolin[2]

KEISHIRO NAGAO, MASATO CHIBA, and SANG-WON KIM*

Faculty of Pharmaceutical Sciences, Josai University,
1-1, Keyakidai, Sakado, Saitama 350-02, Japan

(Received July 17, 1982)

A total synthesis of (±)-carpesiolin (**3**) is reported starting from the hydroazulenone (**2**), which is a key intermediate of helenanolide synthesis. For the introduction of the C_6 to C_8 functionalities, **2** was converted to the epoxy-alcohol (**5**). Its structure was confirmed by chemical and spectroscopic evidence. After construction of the γ-lactone ring, the *tert*-butyl protective group was removed from the ester (**15**) by acid-catalyzed thermolysis. However, this reaction was unexpectedly accompanied by concomitant 1,3-acyl migration with inversion of the configuration at C_4 to yield the hydroxy-ester (**16**), whose structure was established by analysis of its proton magnetic resonance spectrum and some chemical reactions. After manipulation of the protective group to give the tetrahydropyranyl ether (**18**), its conversion to (±)-carpesiolin was achieved by (i) introduction of the *exo*-methylene group onto the lactone ring, (ii) oxidation to the cyclopentanone (**24**), and (iii) deprotection of the C_6 hydroxyl group.

Keywords——pseudoguaianolide; helenanolide; carpesiolin; total synthesis; 1,3-acyl migration; α-methylene-γ-lactone

The pseudoguaianolides are one of the most interesting sesquiterpene lactones and have inspired much synthetic interest because of (i) their widespread occurrence in plants, (ii) their characteristic structures based on the angularly methylated *trans* perhydroazulene skeleton, and (iii) promising biological activities associated with some of them. Consequently several synthetic strategies have been reported for helenanolides and ambrosanolides (pseudoguaianolides with a C_{10} α- and β-methyl group, respectively) and were successfully applied in total syntheses of many of them.[3]

In the preceding paper, we reported the regio- and stereospecific preparation of the key intermediate (**2**) for the synthesis of helenanolides from the readily available enone (**1**) using the ring expansion reaction as the key step.[1] In this paper we report full details of a total synthesis of (±)-carpesiolin starting from **2**.[2]

Carpesiolin (**3**) was isolated from *Carpesium abrotanoides* L. by Maruyama and Omura as an antibiotic substance.[4] Though they did not elucidate its structure completely, it was finally established through the total synthesis by Vandewalle in 1979.[5] The same compound, named 6α-hydroxy-2,3-dihydroaromaticin, was also isolated from *Telekia speciosa* (Schreber) Baumg by Bohlmann and Mahanta.[6]

Our initial goal was to establish the correct stereochemistry of functionalities at C_6 to C_8.[7] Reduction of **2** with lithium aluminum hydride (LAH) gave the alcohol (**4**) as the sole product, whose oxidation with peracid proceeded smoothly to give the epoxide (**5**). Though similar stereoselectivity was observed by two groups in similar systems, no conclusive evidence for the structure assignments was presented except for an X-ray diffraction study of a further elaborated compound by one of them.[8] We can now confirm the structures of **4** and **5** on the basis of the following chemical and spectroscopic evidence.

Oxidation of **5** with Jones reagent gave the epoxy-ketone (**6**) in good yield; **6** thus obtained was identical with the sample obtained on treatment of **2** with *tert*-butyl hydroperoxide in the presence of Triton B. Reduction of **6** with sodium borohydride afforded the new epoxy-alcohol (**7**), isomeric with **5** in the configuration of the hydroxyl group.[8b,9] It is quite rational to assume that the bulky hydroperoxide anion would attack the enone (**2**) from the less hindered α-side of the molecule, to give the α-epoxide (**6**).[10] The configuration of the hydroxyl groups in **5** and **7** was initially inferred from their proton magnetic resonance (PMR) spectra. In the PMR spectrum of **7**, the C_6- and C_7-protons are observed as a doublet (J=4 Hz at δ 3.02) and a triplet (J=4 Hz at δ 3.23), respectively. On the other hand, the splitting patterns of these signals in **5** are difficult to define in the 60 MHz PMR spectrum. However, they were conclusively assigned as two doublets (J=5 Hz at δ 3.11 for the C_6-proton, and at δ 3.32 for the C_7-proton) by means of an induced shift experiment with tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctandionato(4,6)]-europium[$Eu(FOD)_3$]. The zero coupling constant between the C_7- and the C_8-protons in **5** indicated that the dihedral angle subtended by these protons is nearly 90°. The molecular model revealed two equilibrating conformations, (A) and (B), for these alcohols. In view of the steric repulsions apparent in A and B, the α-alcohol isomer (R_1=H, R_2=OH) should exist in the conformation (A) in which the dihedral angle between the C_7- and C_8- protons is about 110°. The β-alcohol isomer (R_1=OH, R_2=H), on the other hand, should exist in the conformation (B), in which the angle in question is about 150°. The two angles cited above are consistent with the coupling constants in **5** and **7**, respectively. These analyses supported the assignments that **5** is the α-alcohol isomer and **7** the β-alcohol isomer.

In order to confirm this, **5** was converted to the *cis*-1,3-diol acetonide (**9**) as follows. Nucleophilic epoxide ring opening of **5** should occur specifically at C_7 due to the strong steric congestion of the β-face at C_6. Indeed, reduction of **5** with LAH produced the 1,3-diol (**8**) as the sole product. This could be cleanly converted to the acetonide (**9**) on treatment with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate. Thus the structures of **4** to **7** were firmly established.[5,11]

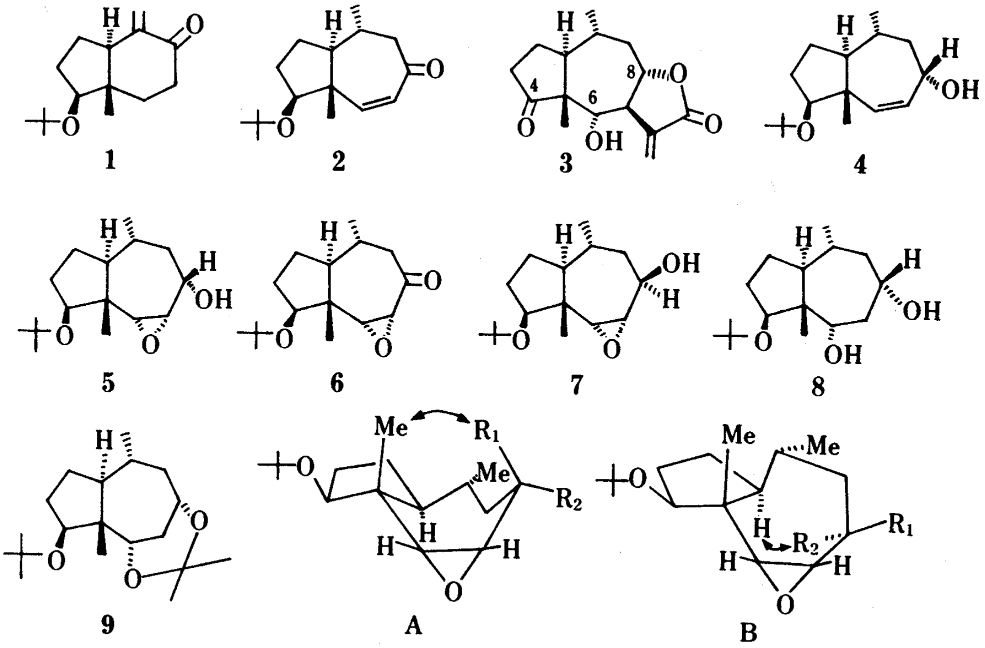

Chart 1

Conversion of **5** to the γ-lactone (**10**) required nucleophilic opening of the epoxide ring at C_7 by an acetic acid equivalent. Our initial efforts were centered on the possibility of intramolecular epoxide opening, using the *cis*- and *trans*-2,3-epoxy-cycloheptanol esters (**11**; X=H, $CO_2C_2H_5$, $COCH_3$, SC_6H_5) as model compounds.[12] In spite of the favorable stereoelectronic environment in these molecules, the enolate anions of these esters only decomposed to give the original epoxy-cycloheptanol or complex mixtures.[13] The Lewis acid treatment of the enol trimethylsilyl ethers of the acetoacetates (in order to suppress the ketene elimination) also met with little success.

Reaction of **5** with the conventional dilithioacetate, however, provided the desired γ-lactone (**10**), mp 143—144.5 °C, in moderate yield, though a large excess of the reagent was required. In the infrared (IR) spectrum **10** shows an intense absorption at 1770 cm^{-1} due to the γ-lactone carbonyl group, while in its PMR spectrum the C_6-proton is observed as a doublet ($J=8$ Hz) at δ 3.52. The signal of the C_8-proton is observed at lower field as a multiplet overlapped by that of the C_4-proton (δ 3.83—4.43). On the basis of these data, the structure of **10** was confirmed, and the regioisomeric γ-lactone (in which the lactone ring was closed with the C_6-hydroxyl group) could not be isolated.[8,11a)] Attempted reaction of **5** with the allyl Gringnard reagent as a more convenient nucleophilic equivalent to dilithioacetate was rather disappointing, giving the desired 1,3-diol in only 34% crude yield.

With the γ-lactone (**10**) in hand, the remaining problems are (i) introduction of the α-methylene group onto the γ-lactone ring and (ii) removal of the *tert*-butyl group in a manner that permits the differentiation of the hydroxyl groups at C_4 and C_6. The preferred method of removing the protective group would be acid-catalyzed thermolysis. Model experiments with α-methylene-γ-butyrolactone itself, however, showed that this functionality is vulnerable to the reaction conditions required. Therefore our attention was focused on the introduction of the *exo*-methylene group in a masked form. The arylselenomethyl group was chosen because of its stability to acid and ease of preparation as well as oxidative elimination.

Treatment of **10** with lithium diisopropylamide (LDA) followed by introduction of gaseous formaldehyde gave the diol (**12**) in high yield. Its reaction with *o*-nitrophenylselenenyl cyanide and tributylphosphine[14)] provided the selenide (**13**) in moderate yield, the remainder being polar by-products of unknown structure. The hydroxyl group of **13** was protected as the trifluoroacetate in the usual manner and the crude ester was subjected to thermolysis catalyzed by *p*-toluenesulfonic acid (TsOH) in boiling toluene. The product, however, was rather unstable to chromatography on silica gel, and the hydroxy-ester (**14**) was obtained in 46% yield (see "Experimental" and the following discussions). Such difficulties in this route prompted us to remove the *tert*-butyl group before introduction of the C_1 unit onto the lactone ring.

Acidic thermolysis of the trifluoroacetate (**15**) [PMR δ: 4.33—4.80 (1H, m, C_4-proton), 5.10 (1H, d, $J=8$ Hz, C_6-proton)], which was easily prepared from **10**, unexpectedly provided the hydroxy-ester (**16**) in high yield as stable crystals, mp 162—166 °C, resulting from a 1,3-shift of the acyl group in addition to debutylation as discussed below.

(a) In the PMR spectrum of **16**, the C_6-proton is observed at δ 3.50 [t, $J=8$ Hz (d, $J=8$ Hz upon D_2O addition)], a value consistent with a proton adjacent to the hydroxyl group (as in **10**) but not with a proton adjacent to the trifluoroacetoxy group (as in **15**). Furthermore the C_4-proton is observed as a multiplet at δ 5.40—5.83, a significant downfield shift from that of **15**.

(b) The oxidation product of **16** with pyridinium chlorochromate (PCC) showed absorption at 1700 cm^{-1} in the IR spectrum due to the carbonyl group of a cycloheptanone derivative. These observations unambiguously showed that the acyl group had migrated to the hydroxyl group at C_4 from C_6. Inspection of the molecular model indicated that this rearrangement may proceed through the transition state (C) with inversion of the configuration at C_4.[15)] Indeed, hydrolysis of **16** gave a diol which was smoothly converted to the acetonide (**17**) on treatment with 2,2-dimethoxypropane and TsOH. The β-configuration of the hydroxyl group at C_4 and/or C_6 makes the acetonide formation impossible. Thus the structure of **16** was firmly established.

Reaction of **16** with dihydropyran (DHP) cleanly yielded the corresponding tetrahydropyranyl (THP) ether, which was hydrolyzed with alkali to give the desired alcohol (**18**), mp 155—156 °C, in high yield. As expected, oxidation of **18** with PCC gave a

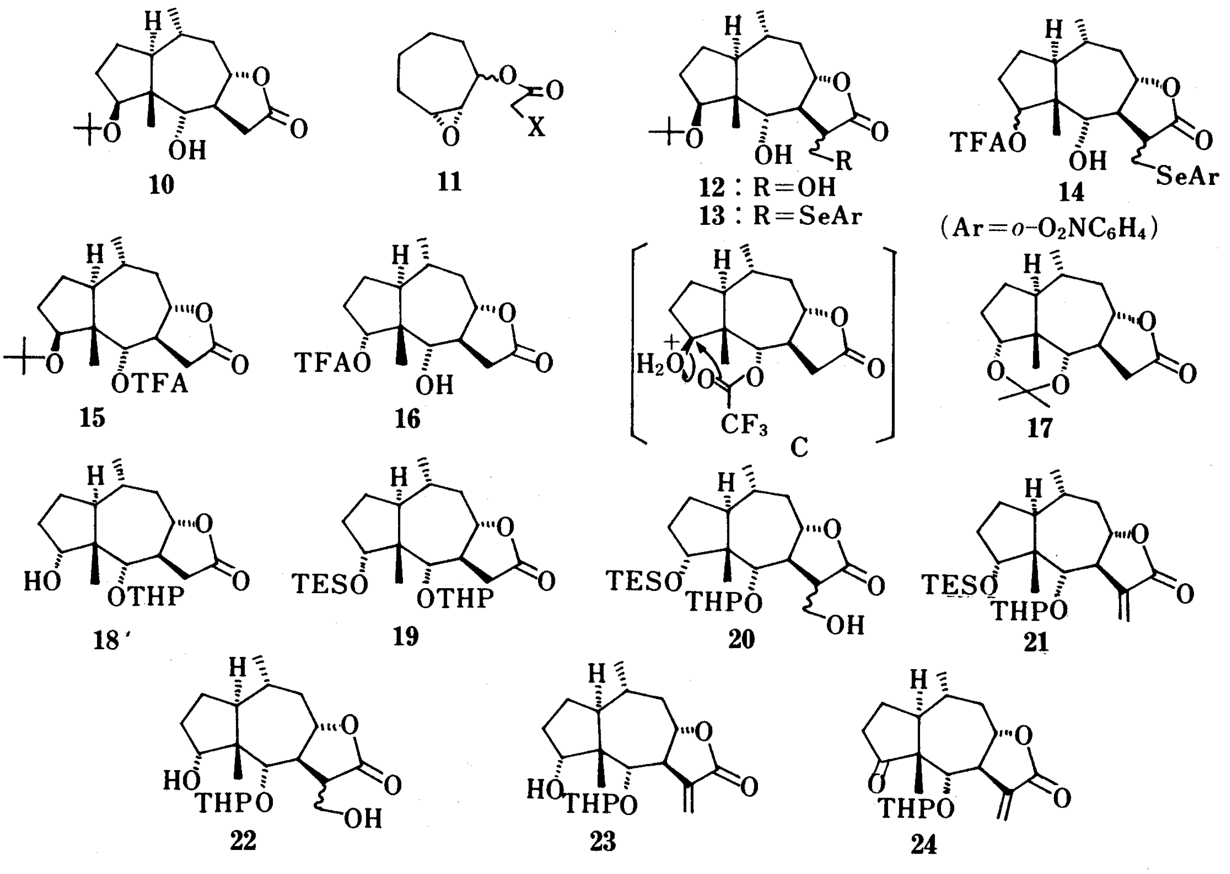

Chart 2

cyclopentanone derivative (IR: 1740 cm^{-1}). The arrangement of functionalities in **18** was ideal for subsequent conversion to the target compound.

In order to facilitate introduction of the *exo*-methylene group into **18**, its alcohol function was initially protected as the triethylsilyl ether (**19**). Reaction of **19** with LDA followed by introduction of gaseous formaldehyde afforded the alcohol (**20**) in 67% yield. Mesylation of **20** followed by elimination of methanesulfonic acid (MsOH) gave the desired α-methylene lactone (**21**) in good yield. However, to our great surprise, removal of the silyl group with tetrabutylammonium fluoride[16] was always accompanied by hydrolysis of the THP ether to give the corresponding diol.[17] Moreover, treatment of the mesylate of **20** with *N*-bromosuccinimide in dimethylsulfoxide–water (10:1)[18] also furnished the same diol, resulting from removal of two hydroxyl protective groups and MsOH.

At this stage, the direct hydroxymethylation of **18** was examined. Reaction of the enolate of **18** with gaseous formaldehyde furnished the diol (**22**) in 60% yield after chromatography on silica gel. Mesylation of **22** at room temperature was rather inappropriate, producing a substantial amount of the undesired dimesylate, but lowering of the reaction temperature to −40 to −50 °C proved successful, giving the primary monomesylate of **22** (PMR δ: 3.00 and 3.05, total 3H, each s) cleanly. Subsequent elimination of MsOH afforded the α-methylene lactone (**23**) in good yield, and oxidation of **23** with PCC in dichloromethane buffered with sodium acetate gave the cyclopentanone (**24**) in 50% yield. Finally removal of the THP ether with TsOH in benzene–water (12:1) furnished (±)-carpesiolin (**3**), mp 197—200 °C, in quantitative yield. The racemic specimen thus obtained showed IR and PMR spectra identical with those of natural carpesiolin.[19,20]

Application of the present successful strategy to other helenanolides is being investigated.

Experimental

All melting points and boiling points are uncorrected. Gas-chromatographic (GC) analysis was performed on a Hewlett Packard 5710A gas chromatograph using a column of OV-1 (1%) on Chromosorb W (DMCS). IR spectra were measured with a Hitachi 285 spectrometer. PMR spectra were measured with a JEOL PMX 60, a Hitachi R-24B, or a JEOL PS-PFT 100 [for (±)-carpesiolin] spectrometer using TMS as an internal standard. Mass spectra (MS) were measured with a Shimadzu LKB-9000 GC-MS spectrometer. High-resolution MS were measured with a JEOL JMS-01SG spectrometer. All extracts were dried over anhydrous $MgSO_4$.

1β-*tert*-Butoxy-1,2,3,3aα,4,5,6,8a-octahydro-4α,8aβ-dimethyl-6α-azulenol (4)——A solution of **2** (3.90 g, 15.6 mmol) in dry tetrahydrofuran (THF) (30 ml) was added to a suspension of LAH (570 mg, 15 mmol) in dry THF (50 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min and at room temperature for 15 min, then the excess hydride was destroyed by addition of AcOEt with ice cooling. After addition of aq. sodium potassium tartrate and removal of the precipitate by filtration, the product was extracted with Et_2O. The extract was washed with brine, and dried. Evaporation of the solvent and distillation of the remaining oil gave **4** (3.21 g). Column chromatography of the residue (652 mg) on silica gel, eluting with Et_2O–hexane, gave a further crop of **4** (40 mg); total yield, 3.25 g (90%), bp 114—118 °C (0.15 Torr). IR ($CHCl_3$): 3400, 1080 cm^{-1}. PMR ($CDCl_3$) δ: 0.83 (3H, s), 1.17 (9H, s), 4.30—4.70 (1H, m), 5.50—5.80 (2H, m). MS m/e: 252 (M^+). An analytical sample was obtained as the acetate, bp 135—140 °C (bath) (0.5 Torr) on bulb-to-bulb distillation. *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.13; H, 10.00.

1β-*tert*-Butoxy-7α,8α-epoxy-1,2,3,3aα,4,5,6,7,8,8a-decahydro-4α,8aβ-dimethyl-6α-azulenol (5)——A solution of **4** (4.076 g, 16.2 mmol) in dry CH_2Cl_2 (120 ml) was treated with *m*-chloroperbenzoic acid (5.92 g of 70% purity, 24.0 mmol), and stirring was continued overnight. The excess peracid was destroyed by addition of aq. $NaHSO_3$, and the organic phase was washed with sat. aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent and column chromatography of the residue on sdilica gel, eluting with Et_2O–hexane, gave **5** (3.086 g, 71%). IR ($CHCl_3$): 3400, 1090 cm^{-1}. PMR ($CDCl_3$) δ: 0.75 (3H, s), 1.15 (9H, s), 3.11 (1H, d, $J=5$ Hz), 3.32 (1H, d, $J=5$ Hz), 3.53—4.30 (2H, m). MS m/e: 268 (M^+). High-resolution MS m/e: 268.2033 (M^+) Calcd for $C_{16}H_{28}O_3$ 268.2038.

1β-*tert*-Butoxy-7α,8α-epoxy-2,3,3aα,4,5,7,8,8a-octahydro-4α,8aβ-dimethyl-6(1*H*)-azulenone (6)——i) From **2**: Triton B (3.8 ml of 35% solution in MeOH, 8.58 mmol) and purified *tert*-butyl hydroperoxide[21] (0.38 ml, 3.97 mmol) were added in that order to a solution of **2** (953 mg, 3.81 mmol) in dry THF (30 ml) at room temperature under N_2, and the mixture was stirred overnight. The excess hydroperoxide was destroyed by addition of aq. $NaHSO_3$, and the volatiles were removed *in vacuo*. Brine was added to the residue, and the product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent and column chromatography of the residue on silica gel, eluting with Et_2O–hexane, gave pure **6** (788 mg, 79%). IR ($CHCl_3$): 1695, 1100 cm^{-1}. PMR ($CDCl_3$) δ: 0.70 (3H, s), 0.93 (3H, d, $J=6$ Hz), 1.20 (9H, s), 3.27—3.58 (2H, m), 3.70—4.14 (1H, m). MS m/e: 210 ($M^+-C_4H_8$). High-resolution MS m/e: 210.1242 ($M^+-C_4H_8$) Calcd for $C_{12}H_{18}O_3$ 210.1254.

ii) From **5**: A sample of **5** (47 mg, 0.175 mmol) was oxidized with Jones reagent in the usual manner, and the product was purified by column chromatography on silica gel, eluting with Et_2O–hexane, to give pure **6** (42 mg, 90%). The product was identified by thin-layer chromatography (TLC), GC, IR, and PMR in comparison with an authentic sample.

1β-*tert*-Butoxy-7α,8α-epoxy-1,2,3,3aα,4,5,7,8,8a-decahydro-4α,8aβ-dimethyl-6β-azulenol (7)——A solution of **6** (102mg, 0.38 mmol) in dry EtOH (7 ml) was treated with $NaBH_4$ (8 mg, 0.21 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The excess hydride was destroyed by addition of acetone, and the volatiles were removed *in vacuo*. Brine was added to the residue, and the product was extracted with CH_2Cl_2. The extract was washed with brine, and dried. Evaporation of the solvent gave pure **7** (108 mg, quant.). IR ($CHCl_3$): 3450, 1100, 1085 cm^{-1}. PMR ($CDCl_3$) δ: 0.95 (3H, s), 1.17 (9H, s), 3.02 (1H, d, $J=4$ Hz), 3.23 (1H, t, $J=4$ Hz), 3.60—4.03 (1H, m), 4.23—4.50 (1H, m). MS m/e: 268 (M^+). High-resolution MS m/e: 268.2019 (M^+) Calcd for $C_{16}H_{28}O_3$ 268.2037.

1β-*tert*-Butoxy-1,2,3,3aα,4,5,6,7,8,8a-decahydro-4α,8aβ-dimethyl-6α,8α-azulenediol Acetonide (9)——A solution of **5** (54 mg, 0.20 mmol) in dry THF (10 ml) was treated with LAH (12 mg, 0.32 mmol), and the mixture was refluxed overnight. The excess hydride was destroyed by addition of AcOEt, and a solution of aq. sodium potassium tartrate was added. The precipitate was removed by filtration, and the product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent and chromatography of the residue on silica gel, eluting with Et_2O–hexane and CH_2Cl_2–MeOH, gave pure **8** (33 mg, 60.7%). IR ($CHCl_3$): 3400, 1100, 1020 cm^{-1}. PMR ($CDCl_3$) δ: 0.75 (3H, s), 1.13 (9H, s), 2.63 (2H, br s, disappeared upon D_2O addition), 3.60—4.30 (3H, m). MS m/e: 214 ($M^+-C_4H_8$). A mixture of **8** (26 mg, 0.096 mmol), 2,2-dimethoxypropane (0.4 ml, 3.25 mmol), and a catalytic amount of pyridinium *p*-toluenesulfonate in dry C_6H_6 (4 ml) was refluxed for 6 h. The mixture was washed with sat. aq. $NaHCO_3$ and brine, then dried. After evaporation of the solvent, the residue was purified by column chromatography on silica gel, eluting with

Et$_2$O–hexane, to give pure **9** (13 mg, 43.5%). IR (CHCl$_3$): 2095, 1380, 1362 cm^{-1}. PMR (CDCl$_3$) δ: 0.70 (3H, s), 1.13 (9H, s), 1.35 (3H, s), 1.50 (3H, s), 3.75—4.55 (3H, m). High-resolution MS *m/e*: 295.2271 (M$^+$ −CH$_3$) Calcd for C$_{18}$H$_{31}$O$_3$ 295.2272.

5β-*tert*-Butoxy-3aα,4,4a,5,6,7,7aα,8,9,9aβ-decahydro-4α-hydroxy-4aβ,8α-dimethyl-azuleno[6,5-*b*]furan-2(3*H*)-one (10)———Butyllithium (265 ml of 1.5 M solution in hexane, 398 mmol) was added to a solution of diisopropylamine (60 ml, 429 mmol) in dry DME (130 ml) under Ar at −45—−55 °C, and the mixture was stirred for 30 min. To this was added a solution of dry AcOH (11.26 ml, 197 mmol) in dry DME (20 ml)–dry hexamethylphosphoric triamide (80 ml) at the same temperature. The mixture was warmed to room temperature, and finally heated at 50—55 °C for 1.5 h. To the resulting warm suspension was added a solution of the crude epoxide (**5**) [3.60 g, obtained from **4** (3.25 g, 12.9 mmol) and *m*-chloroperbenzoic acid (4.763 g of 70% purity, 19.3 mmol) in dry CH$_2$Cl$_2$ (100 ml)] in dry DME (35 ml), and heating was continued for 16 h. After cooling to room temperature, the mixture was poured into water (300 ml) and the aq. phase was extracted with Et$_2$O to remove neutral contaminants; TLC examination revealed that no **5** was recovered. The aq. phase was acidified with conc. HCl with ice cooling, then saturated with NaCl, and the product was extracted with Et$_2$O. The extract was washed with 50% brine and brine, then dried. The volatiles were removed, and the residue was dissolved in AcOEt, washed with water and brine, then dried (to remove traces of the triamide). The solvent was removed, and the residue was chromatographed on silica gel, eluting with Et$_2$O–hexane, Et$_2$O–MeOH, and CH$_2$Cl$_2$–MeOH, to give crude **10** (2.82 g). Recrystallization from hexane and chromatography of the mother liquor on silica gel were repeated several times to obtain pure **10** (1.77 g, 44% from **4**), mp 143—144.5 °C (from hexane). IR (CHCl$_3$): 3420, 1770 cm^{-1}. PMR (CDCl$_3$) δ: 0.95 (3H, s), 1.22 (9H, s), 3.52 (1H, d, J=8 Hz), 3.83—4.43 (2H, m). MS *m/e*: 310 (M$^+$). *Anal.* Calcd for C$_{18}$H$_{30}$O$_4$: C, 69.64; H, 9.74. Found: C, 69.41; H, 9.75.

5β-*tert*-Butoxy-3aα,4,4a,5,6,7,7aα,8,9,9aβ-decahydro-4α-hydroxy-4aβ,8α-dimethyl-3-(*o*-nitrophenylselenomethyl)-azuleno[6,5-*b*]furan-2(3*H*)-one (13)———Butyllithium (7.3 ml of 1.5 M solution in hexane, 11.0 mmol) was added to a solution of diisopropylamine (1.7 ml, 12.2 mmol) in dry THF (5 ml) under Ar at −20—−30 °C, and the mixture was stirred for 30 min. To the resulting solution was added a solution of **10** (680 mg, 2.19 mmol) in dry THF (15 ml) at −78 °C. The whole was stirred at −78 °C for 15 min and at −35 °C for 15 min, gaseous formaldehyde [generated by pyrolysis of dry paraformaldehyde (4 g) at 170 °C] was introduced into the mixture at −30—−40 °C. After being stirred for 15 min, the mixture was warmed to 0 °C and 10% HCl was added. After saturation of the aq. phase with NaCl, the product was extracted with Et$_2$O. The extract was washed with sat. aq. NaHCO$_3$ and brine, then dried. The solvent was removed, and column chromatography of the residue on silica gel, eluting with CCl$_4$–CH$_2$Cl$_2$ and CH$_2$Cl$_2$–MeOH, gave the diol (**12**) (715 mg, 96%). IR (CHCl$_3$): 3400, 1760 cm^{-1}. PMR (CDCl$_3$) δ: 0.96 (3H, fused d), 0.97 (3H, s), 1.17 (9H, s), 3.37—4.30 (5H, m). MS *m/e*: 238 (M$^+$−C$_4$H$_8$), 265, 247. The diol (**12**) (715 mg, 2.43 mmol) was mixed with a solution of *o*-nitrophenylselenenyl cyanide (645 mg, 2.84 mmol) and tributylphosphine (0.95 ml, 3.81 mmol) in dry THF (70 ml) under Ar, and the mixture was stirred for 1 h. A further portion of *o*-nitrophenylselenenyl cyanide (60 mg, 0.26 mmol) was added and stirring was continued for a further 2 h. The solvent was removed, and the product was taken up in CCl$_4$, then chromatographed on silica gel, eluting with CCl$_4$–CH$_2$Cl$_2$ and CH$_2$Cl$_2$–MeOH, to give **13** (472 mg, 43%), mp 200—210 °C (from hexane). IR (CHCl$_3$): 3400, 1760, 1335 cm^{-1}. PMR (CDCl$_3$) δ: 0.93 (3H, s), 1.23 (9H, s), 3.23—4.43 (3H, m), 7.10—7.65 (3H, m), 8.15 (1H, d, J=8 Hz). MS *m/e*: 322 (M$^+$−ArSeH). *Anal.* Calcd for C$_{25}$H$_{34}$NO$_6$Se: C, 57.36; H, 6.55; N, 2.68. Found: C, 57.46; H, 6.47; N, 2.45.

3aα,4,4a,5,6,7,7a a,8,9,9aβ-Decahydro-4α-hydroxy-4a b,8α-dimethyl-3-(*o*-nitrophenylselenomethyl)-5-trifluoroacetyloxy-azuleno[6,5-*b*]furan-2(3*H*)-one (14)———A solution of **13** (423 mg, 0.81 mmol) in dry pyridine (10 ml) was treated with trifluoroacetic anhydride (0.3 ml, 2.12 mmol) at room temperature, and the mixture was left for 1.5 h. The mixture was diluted with AcOEt, washed with 10% HCl, sat. aq. NaHCO$_3$ and brine, then dried. Evaporation of the solvent gave the trifluoroacetate of **13** (470 mg, 91.5%), mp 193—197 °C (from C$_6$H$_6$–hexane). IR (CHCl$_3$): 1770, 1320 cm^{-1}. PMR (CDCl$_3$) δ: 0.97 (3H, s), 1.07 (9H, s), 5.30 (1H, d, J= 6 Hz), 7.37—7.80 (3H, m), 8.24 (1H, d, J=8 Hz). A solution of the trifluoroacetate (390 mg, 0.61 mmol) was refluxed with a catalytic amount of TsOH in dry toluene (30 ml) for 3.5 h under Ar. The mixture was cooled, washed with sat. aq. NaHCO$_3$ and brine, then dried. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel, eluting with CCl$_4$–CH$_2$Cl$_2$ and CH$_2$Cl$_2$–MeOH, to give **14** (164 mg, 46%). IR (CHCl$_3$): 1765, 1335 cm^{-1}. PMR (CDCl$_3$) δ: 1.00 (3H, s), 3.40 (1H, d, J=8 Hz), 5.00—5.50 (1H, m), 7.30—7.83 (3H, m), 8.26 (1H, d, J=8 Hz). MS *m/e*: 344 (M$^+$−ArSeH—H$_2$O). High-resolution MS *m/e*: 344.1232 (M$^+$−ArSeH—H$_2$O) Calcd for C$_{17}$H$_{19}$F$_3$O$_4$ 344.1234.

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-4α-hydroxy-4aβ,8α-dimethyl-5α-trifluoroacetyloxy-azuleno[6,5-*b*]-furan-2(3*H*)-one (16)———A solution of **10** (700 mg, 2.26 mmol) in dry pyridine (10 ml) was treated with trifluoroacetic anhydride (0.5 ml, 3.54 mmol) with ice cooling, and the mixture was left at room temperature overnight. The mixture was poured into ice-cold water. This solution was acidified with conc. HCl, and after saturation of the aq. phase with NaCl, the product was extracted with AcOEt. The extract was washed with sat. aq. NaHCO$_3$ and brine, then dried. Evaporation of the solvent gave crude **15**. IR (CHCl$_3$): 1780, 1155 cm^{-1}. PMR (CDCl$_3$) δ: 1.03 (3H, s), 1.08 (9H, s), 3.70—4.17 (1H, m), 4.33—4.80 (1H, m), 5.10 (1H, d,

J=8 Hz). The crude ester (**15**) was pyrolyzed with a catalytic amount of TsOH in boiling toluene (30 ml) under Ar for 3 h. The mixture was diluted with C_6H_6, washed with sat. aq. $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo*, and trituration of the residue with Et_2O gave pure **16**. The Et_2O-soluble fraction was subjected to the above thermolysis–trituration sequence several times to give a further crop of **16**; total yield, 704 mg (89% from **10**), mp 162—166 °C (from C_6H_6–hexane). IR ($CHCl_3$): 3450, 1780 cm^{-1}. PMR ($CDCl_3$) δ: 1.03 (3H, s), 3.50 [1H, t, J=8 Hz (d, J=8 Hz upon D_2O addition)], 4.28—4.62 (1H, m), 5.40—5.83 (1H, m). MS m/e: 350 (M$^+$). *Anal.* Calcd for $C_{16}H_{21}F_3O_5$: C, 54.86; H, 6.04. Found: C, 54.64; H, 6.02. Oxidation to a cycloheptanone derivative was performed as follows. A solution of **16** (100 mg, 0.285 mmol) in dry CH_2Cl_2 (10 ml) was treated with PCC (250 mg, 1.16 mmol), and the mixture was stirred at room temperature for 6 h. Dilution of the mixture with Et_2O, filtration through celite, and evaporation of the solvent gave a crude ketone, which was purified by column chromatography on silica gel, eluting with Et_2O–hexane and Et_2O–MeOH. IR ($CHCl_3$): 1780, 1700 cm^{-1}. MS m/e: 348 (M$^+$).

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-4α,5α-dihydroxy-4aβ,8α-dimethyl-azuleno[6,5-*b*]furan-2(3*H*)-one Acetonide (17)———A solution of **16** (82 mg, 0.234 mmol) in THF (10 ml) was mixed with 5% aq. K_2CO_3 (10 ml) at room temperature, and the mixture was stirred for 1 h, then saturated with NaCl. The product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent gave the crude diol (51 mg), which, without further purification, was mixed with 2,2-dimethoxypropane (1 ml, 8.15 mmol) and a catalytic amount of TsOH in dry acetone (8 ml). The mixture was refluxed for 4 h, quenched with sat. aq. $NaHCO_3$, and concentrated *in vacuo*. Brine was added to the residue, and the product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent gave pure **17** (71 mg, quant.), mp 130—132 °C (from hexane). IR ($CHCl_3$): 1775, 1120 cm^{-1}. PMR ($CDCl_3$) δ: 0.95 (3H, s), 1.32 (3H, s), 1.41 (3H, s). MS m/e: 294 (M$^+$). High-resolution MS m/e: 279.1583 (M$^+$$-$$CH_3$) Calcd for $C_{16}H_{23}O_4$ 279.1594.

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-5α-hydroxy-4aβ,8α-dimethyl-4α-(2-tetrahydropyranyloxy)-azuleno[6,5-*b*]furan-2(3*H*)-one (18)———Pyridinium *p*-toluenesulfonate (23 mg) and DHP (0.53 ml, 5.80 mmol) were added to a solution of **16** (1.357 g, 3.76 mmol) in dry CH_2Cl_2 (45 ml) at room temperature under Ar, and stirring was continued overnight. The mixture was washed with 50% brine and brine, then dried. Evaporation of the solvent and chromatography of the residue on silica gel, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave the corresponding THP ether (1.600 g, 95%). IR ($CHCl_3$): 1775, 1155 cm^{-1}. PMR ($CDCl_3$) δ: 1.00 (3H, fused d), 1.07 (3H, s), 3,52 (1H, d, J=6 Hz). MS m/e: 332 (M$^+$$-DHP-$$H_2O$). A solution of K_2CO_3 (1.0 g, 7.23 mmol) in H_2O (150 ml) was added to a solution of the THP ether (1.600 g, 3.66 mmol) in THF (150 ml) at room temperature, and the mixture was stirred for 30 min. After saturation with NaCl, the product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent gave pure **18** (1.246 g, quant.), mp 155—156 °C (from C_6H_6–hexane). IR ($CHCl_3$): 3400, 1775 cm^{-1}. PMR ($CDCl_3$) δ: 0.93 (3H, s), 3.20—4.10 (2H, m), 4.10—4.80 (2H, m). MS m/e: 320 (M$^+$$-$$H_2O$). *Anal.* Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.77; H. 8.79. Oxidation to a cyclopentanone derivative was performed as follows. PCC (70 mg, 0.32 mmol) and anhydrous AcONa (100 mg, 1.22 mmol) were added to a solution of **18** (21 mg, 0.062 mmol) in dry CH_2Cl_2 (7 ml), and the mixture was stirred at room temperature for 4 h. Dilution with Et_2O, filtration through celite, and evaporation of the solvent gave the crude ketone. IR ($CHCl_3$): 1775, 1740 cm^{-1}. MS m/e: 336 (M$^+$), 252 (M$^+$$-$DHP).

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-4aβ,8α-dimethyl-4α-(2-tetrhydropyranyloxy)-5α-triethylsilyloxy-azuleno[6,5-*b*]furan-2(3*H*)-one (19)———4-Dimethylaminopyridine (108 mg, 0.884 mmol) and triethylchlorosilane (0.15 ml, 0.89 mmol) were added to a solution of **18** (100 mg, 0.296 mmol) in dry pyridine (5 ml) at room temperature, and the mixture was stirred at room temperature for 2.5 h then at 80 °C overnight. The mixture was diluted with AcOEt, washed with cold 10% HCl, sat. aq. $NaHCO_3$ and brine, then dried (with addition of $NaHCO_3$). Evaporation of the solvent and column chromatography of the residue on Florisil, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave **19** (133 mg, quant.). IR ($CHCl_3$): 1775, 1070 cm^{-1}. PMR ($CDCl_3$) δ: 0.42—1.23 (21H, complex set of sharp signals), 3.37—4.10 (2H, m), 4.10—4.73 (2H, m). MS m/e: 368 (M$^+$$-$DHP), 350. High-resolution MS m/e: 368.2346 (M$^+$$-$DHP) Calcd for $C_{20}H_{36}O_4Si$ 368.2381.

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-4aβ,8α-dimethyl-3-methylene-4α-(2-tetrahydropyranyloxy)-5α-triethylsilyloxy-azuleno[6,5-*b*]furan-2(3*H*)-one (21)———Butyllithium (3.15 ml of 1.5 M solution in hexane, 4.73 mmol) was added to a solution of diisopropylamine (0.7 ml, 5.00 mmol) in dry THF (10 ml) under Ar at −50 °C. The mixture was stirred for 20 min, then the temperature was lowered to −74—−79 °C and a solution of **19** (678 mg, 1.50 mmol) in dry THF (25 ml) was added. The whole was stirred at the same temperature for 20 min, at −50 °C for 20 min, and finally at −30 °C for 20 min. Gaseous formaldehyde [generated by pyrolysis of dry paraformaldehyde (2 g) at 190 °C] was introduced at −25 °C. The mixture was stirred for 10 min, then sat. aq. NH_4Cl was added. The product was extracted with Et_2O, and the extract was washed with brine, and dried (with addition of $NaHCO_3$). Evaporation of the solvent and chromatography of the residue on Florisil, eluting with CCl_4–CH_2Cl_2, gave pure **20** (484 mg, 67%). IR ($CHCl_3$): 3400, 1775 cm^{-1}. PMR ($CDCl_3$) δ: 0.43—1.27 (21H, complex set of sharp signals), 3.37—4.17 (4H, m), 4.23—4.83 (2H, m). MS m/e: 482 (M$^+$), 464, 398. A solution of **20** (125 mg, 0.259 mmol) in dry pyridine (2 ml) was treated with methanesulfonyl chloride (0.022 ml, 0.28 mmol) at room temperature, and the mixture was stirred for

3.5 h. The mixture was diluted with AcOEt, washed with cold 10% HCl, sat. aq. $NaHCO_3$ and brine, then dried (with addition of $NaHCO_3$). Evaporation of the solvent gave the crude mesylate (130 mg). Next, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (43 mg, 0.28 mmol) was added to a solution of the crude mesylate (130 mg) in dry C_6H_6 (5 ml) at room temperature, and stirring was continued for 3 h. The mixture was diluted with C_6H_6, washed with cold 10% HCl, sat. aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent and chromatography of the residue on Florisil, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave pure **21 (76 mg, 63% from 20)**. IR ($CHCl_3$): 1760, 1120, 1070 cm^{-1}. PMR ($CDCl_3$) δ: 0.50—1.25 (21H, complex set of sharp signals), 5.83, 6.03, 6.14 (total 2H, each d, $J=3$ Hz). MS *m/e*: 464 (M^+). High-resolution MS *m/e*: 380.2368 (M^+-DHP) Calcd for $C_{21}H_{36}O_4Si$ 380.2381.

3aα,4,4a,5,6,7,7aα,8,9,9aβ-Decahydro-5α-hydroxy-4aβ,8α-dimethyl-3-methylene-4α-(2-tetrahydropyranyloxy)-azuleno[6,5-*b*]furan-2(3*H*)-one (23)———Butyllithium (2.3 ml of 1.5 M solution in hexane, 3.45 mmol) was added to a solution of diisopropylamine (0.63 ml, 4.5 mmol) in dry THF (5 ml) at −50 °C under Ar. The mixture was stirred for 20 min, then the temperature was lowered to −78 °C and a solution of **18** (340 mg, 1.00 mmol) in dry THF (10 ml) was added. The mixture was stirred at −78 °C for 30 min, at −40 °C for 20 min, and finally at −25 °C for 15 min. Gaseous formaldehyde [generated by pyrolysis of dry paraformaldehyde (1 g) at 180 °C] was introduced at −25 °C, and the reaction was quenched by addition of sat. aq. NH_4Cl. The product was extracted with Et_2O, and the extract was washed with 50% brine and brine, then dried. Evaporation of the solvent and chromatography of the residue on Florisil, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave **22** (221 mg, 60%). IR ($CHCl_3$): 3400, 1755 cm^{-1}. PMR ($CDCl_3$) δ: 1.00 (3H, s), 3.17—4.80 (6H, m). MS *m/e*: 266 (M^+-DHP$-H_2O$), 248. A solution of **22** (221 mg, 0.60 mmol) and Et_3N (0.13 ml, 0.93 mmol) in dry CH_2Cl_2 (10 ml) was treated with a solution of methanesulfonyl chloride (76 mg, 0.66 mmol) in dry CH_2Cl_2 (5 ml) at −40—−50 °C under Ar, and the mixture was stirred for 2 h. A solution of methanesulfonyl chloride (30 mg, 0.26 mmol) and Et_3N (0.65 ml, 4.66 mmol) in dry CH_2Cl_2 (5 ml) was further added and stirring was continued for 1 h. This process was repeated twice more, by which time TLC analysis indicated complete consumption of **22**. The mixture was washed with 10% HCl, sat. aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent gave the crude mesylate (280 mg). IR ($CHCl_3$): 3400, 1775, 1360 cm^{-1}. PMR ($CDCl_3$) δ: 1.00 (3H, s), 3.00, 3.05 (total 3H, each s), 4.10—4.83 (4H, m). MS *m/e*: 446 (M^+). DBU (0.13 ml, 0.86 mmol) was added to a solution of the crude mesylate (280 mg) in C_6H_6 (10 ml) at room temperature. After being stirred for 3 h, the mixture was washed with 10% HCl, sat. aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent and chromatography of the residue on Florisil, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave pure **23** (164 mg, 78% from **22**), mp 151—156 °C (from Et_2O). IR ($CHCl_3$): 3400, 1760 cm^{-1}. PMR ($CDCl_3$) δ: 0.93 (3H, s), 3.75 (1H, d, $J=8$ Hz), 5.67, 6.18, 6.26 (total 2H, each d, $J=3$, 4, and 3 Hz, respectively). MS *m/e*: 266 (M^+-DHP). High-resolution MS *m/e*: 266.1513 (M^+-DHP) Calcd for $C_{15}H_{22}O_4$ 266.1516.

(±)-Carpesiolin (3)———Anhydrous AcONa (200 mg, 2.44 mmol) and PCC (98 mg, 0.45 mmol) were added to a solution of **23** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (7 ml) at room temperature. The mixture was stirred for 1 h, then further portions of PCC (196 mg, 0.90 mmol) and anhydrous AcONa (400 mg, 4.88 mmol) were added. After being stirred for 100 min, the mixture was diluted with Et_2O and filtered through celite. Evaporation of the solvent and chromatography of the residue on silica gel, eluting with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH, gave pure **24** (25 mg, 50%). IR ($CHCl_3$): 1765, 1740 cm^{-1}. PMR ($CDCl_3$) δ: 1.00 (3H, s) 4.07, 4.20 (total 1H, each d, $J=5$ Hz), 6.17, 6.22 (total 2H, each d, $J=2$ Hz). Excess TsOH was added to a solution of **24** (25 mg, 0.07 mmol) in C_6H_6 (6 ml)–H_2O (0.5 ml), and the mixture was stirred at room temperature for 5 h. The mixture was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was taken up in AcOEt, and the solution was washed with sat. aq. $NaHCO_3$ and brine, then dried. Evaporation of the solvent and chromatography of the residue on SILIC AR CC-7, eluting with CCl_4–CH_2Cl_2, gave pure carpesiolin (16 mg, quant.), mp 197—200 °C (from $CHCl_3$–hexane) [lit.[5] 145—148 °C (from $CHCl_3$–hexane) (sublimes)]. IR ($CHCl_3$): 3470, 1765, 1730, 1660 cm^{-1}. PMR ($CDCl_3$) δ: 1.03 (3H, s), 1.09 (3H, d, $J=6.1$ Hz), 2.94 (1H, d, $J=3.0$ Hz, disappeared upon D_2O addition), 4.01 [1H, dd, $J=3.0$, 8.8 Hz (d, $J=8.8$ Hz upon D_2O addition)], 4.38 (1H, ddd, $J=2.9$, 9.8, 10.7 Hz), 5.99 (1H, d, $J=3.2$ Hz), 6.22 (1H, d, $J=3.6$ Hz). MS *m/e*: 264 (M^+), 246, 97. *Anal.* Calcd for $C_{15}H_{22}O_4$: C, 68.16; H, 7.63. Found: C, 68.21; H, 7.84.

Acknowledgment The authors are grateful to Prof. Maruyama for providing copies of the IR and PMR spectra of natural carpesiolin. Thanks are also due to Prof. Bohlmann and Prof. Vandewalle for the identification of our PMR spectra as those of 6α-hydroxy-2,3-dihydroaromaticin and racenic carpesiolin, respectively.

References and Notes

1) Part 1: K. Nagao, I. Yoshimura, M. Chiba, and S-W. Kim, *Chem. Pharm. Bull.*, **31**, 114 (1983).
2) Preliminary communication: K. Nagao, M. Chiba, I. Yoshimura, and S-W. Kim, *Chem. Pharm. Bull.*, **29**, 2733 (1981).
3) See refs. 1, 2, and 3 of Part 1.
4) M. Maruyama and S. Omura, *Phytochemistry*, **16**, 782 (1977).
5) P. Kok, P.J. De Clercq, and M.E. Vandewalle, *J. Org. Chem.*, **44**, 4553 (1979).

6) F. Bohlmann and P.K. Mahanta, *Phytochemistry,* **18**, 887 (1979).
7) In this text, the numbering of the natural product is used.
8) *a*) P.A. Grieco, Y. Ohfune, and G. Majetich, *J. Org. Chem.,* **44**, 3092 (1979); *b*) P.A. Grieco, "Stereoselective Synthesis of Natural Products," ed. by W. Bartman and E. Winterfeldt, Excerpta Medica, Amsterdam and Oxford, 1979, pp. 121—129; *c*) P. Kok, P. De Clercq, M. Vandewalle, J.P. Declercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.,* **1979**, 2063.
9) Y. Ohfune, P.A. Grieco, C.-L.J. Wang, and G. Majetich, *J. Am. Chem. Soc.,* **100**, 5946 (1978); M.R. Roberts and R.H. Schlessinger, *ibid.,* **101**, 7626 (1979).
10) This assumption was verified by the isolation of the acetonide (**17**).
11) *a*) P.J. De Clercq, *J. Org. Chem.,* **46**, 667 (1981) and its supplementary material; *b*) E. Toromanoff, *Tetrahedron,* **36**, 2809 (1980).
12) S-W. Kim, K. Nagao, I. Yoshimura, and Y. Ozaki, *Chem. Pharm. Bull.,* **28**, 989 (1980).
13) A similar reaction was attempted by Grieco. See ref. 8*b*.
14) P.A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.,* **41**, 1485 (1976).
15) See, for example, O. Itoh, N. Iwakoshi, T. Saitoh, H. Katano, Y. Fujisawa, Y. Hasegawa, T. Sugita, and K. Ichikawa, *Bull. Chem. Soc. Jpn.,* **55**, 177 (1982).
16) E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.,* **94**, 6190 (1972).
17) The silyl group of **19** was deprotected without incident to give **18** under the same reaction conditions.
18) R.J. Batten, A.J. Dixon, R.J.K. Taylor, and R.F. Newton, *Synthesis,* **1980**, 234.
19) The PMR spectrum of the synthetic material was also superimposable on that of natural 6α-hydroxy-2,3-dihydroaromaticin.
20) The melting point of our sample was quite different from that [mp 145—148 °C (sublimes)] reported by Vandewalle.5) In a private communication he stated, "though the PMR spectra of the two samples are almost identical, the slight broadening of the signals of CHOH group in our sample is due to the inclusion of water of crystallization." However, such a protic contaminant, present in a minute amount relative to that in the solvent used, should facilitate proton exchange to result in sharpening of such signals. The difference in melting points may instead be due to polymorphism.
21) P.D. Bartlett and J.M. McBride, *J. Am. Chem. Soc.,* **87**, 1727 (1965).