[Chem. Pharm. Bull. 31(1) 114—121 (1983)]

Synthetic Studies on Pseudoguaianolides. I. Preparation of a Key Intermediate, 1β-*tert*-Butoxy-2,3,3aα,4,5,8a-hexahydro-4α, 8aβ-dimethyl-6(1*H*)-azulenone, for Helenanolides

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

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

(Received July 17, 1982)

The preparation of the title compound (**1**), a key intermediate for the synthesis of helenanolides (pseudoguaianolides with a C_{10} α-methyl group), is described starting from the readily available enone (**3**). The correct stereochemistry of the C_{10}-metyl group was obtained because of the severe 1,3-diaxial interaction in the perhydroindanone (**5**). The ring expansion of **5** by one carbon unit, the key step in our approach, was examined in three ways. Reaction of **5** with ethyl diazoacetate catalyzed by a Lewis acid was not highly regioselective, giving the perhydroazulenone (**8**) and (**9**) in a ratio of 1 to 4. Metal salt-catalyzed decomposition of the diazoester (**10**) produced only the β-ketoester (**11**). However, the desired ketone (**8**) was obtained by the rearrangement of the β-oxido carbenoid derivative from the dibromohydrin (**12**). Introduction of the Δ^6-double bond into **8** for the conversion to **1** was achieved regiospecifically *via* kinetic enolization.

Keywords——pseudoguaianolide; helenanolide; ring expansion reaction; α-diazo-β-hydroxy ester; β-oxido carbenoid; perhydroindanone; perhydroazulenone

The pseudoguaianolides constitute one of the largest groups of sesquiterpene lactones and are widely distributed in the plant kingdom, especially in the *Compositae* family.[1] They are subdivided into helenanolides (with a C_{10} α-methyl group) and ambrosanolides (with a C_{10} β-methyl group). The basic structural features and representative examples are shown in Chart 1.

Some of these compounds are associated with interesting biological activities (*e.g.*, antitumor activity) and their modes of action have been studied in detail.[2] These interesting physiological activities as well as the structural features are the major reasons for the recent surge of interest in the synthesis of these compounds, which has culminated in many reports of total syntheses.[3]

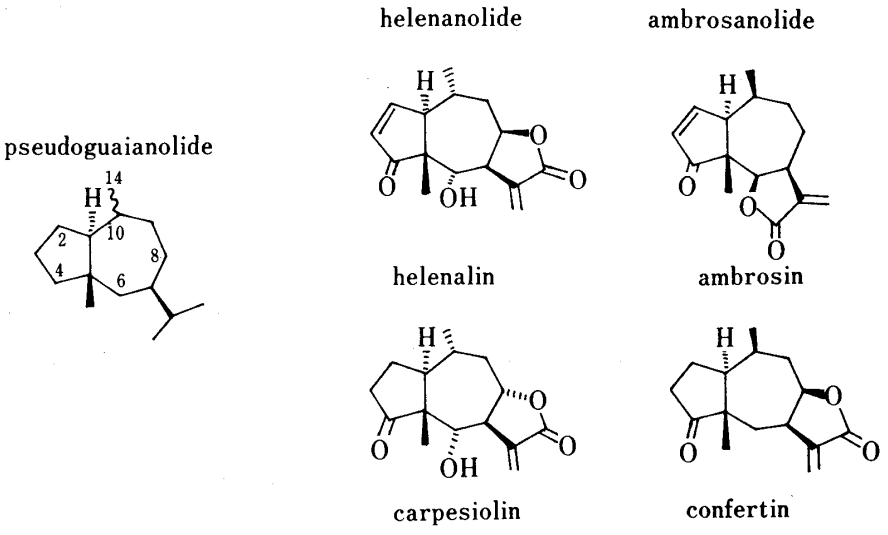

Chart 1

Recently we have devised a new and efficient route, potentially applicable to variously substituted pseudoguaianolides, and have accomplished a total synthesis of (±)-carpesiolin, one of the helenanolides, along these lines.[4] In this report, we describe the details of the preparation of hydroazulenone (**1**), a key intermediate for the synthesis of helenanolides, and in the subsequent paper we will present the total synthesis of (±)-carpesiolin starting from **1**.

Our initial efforts were directed to the syntheses of helenanolides, and the perhydroazulenone (**1**) was chosen as the most appropriate precursor. It incorporates the *trans* junction of two rings, the C_{10} α-methyl group,[5] the α,β-unsaturated carbonyl system suitable for the introduction of C_6 to C_8 functionalities, and the cyclopentanol equivalent for the eventual conversion to cyclopentanone or cyclopentenone. Our projected route for the preparation of **1** is shown in Chart 2 using as the key step the ring expansion reaction,[6] which is well known to play a crucial role in the synthesis of many compounds, especially those containing medium and large rings.

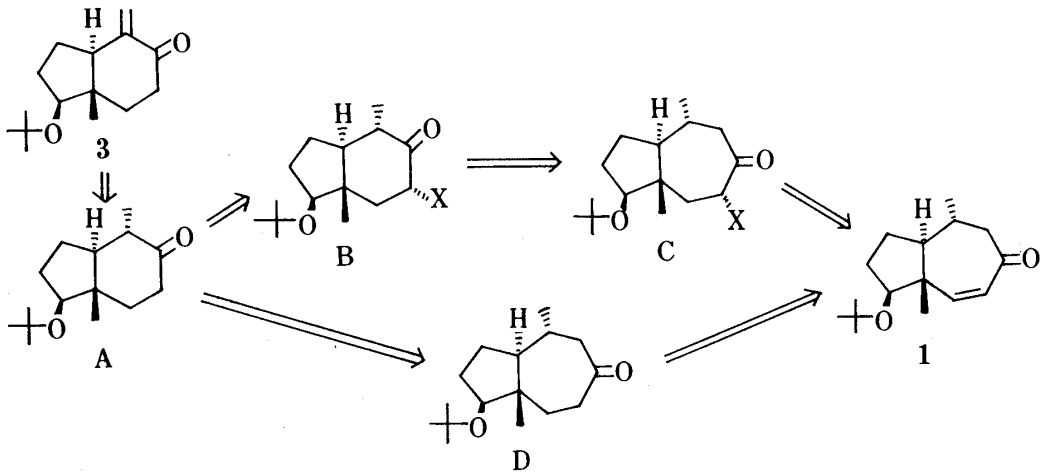

Chart 2

In our scheme, the α-orientation of the C_{10}-methyl group in **1** should be easily established as shown in the formula (A) by virtue of the severe 1,3-diaxial interaction with the angular methyl group. The *trans* junction of two rings would be pre-determined if we start from the known enone (**3**). The success of our route would depend on the regioselectivity in (i) the ring expansion of the unsymmetrical ketone (A) or (B), and (ii) the introduction of the Δ^6-double bond into the ketone (D). If these problems can be solved, extension of this route would enable the preparation of intermediates for the syntheses of other pseudoguaianolides (*e.g.* ambrosanolides, C_9-, and C_{14}-functionalized compounds).

The starting enone (**3**) was prepared from the carboxylic acid (**2**) according to the literature procedures[7] with slight modifications and was used without purification due to its thermal instability. Basic reaction conditions (*e.g.* sodium thiophenoxide or lithium in liquid ammonia) were found to be incompatible with **3**. However, catalytic hydrogenation in methanol over platinum oxide proved successful, giving a mixture of the axial (**4**) and the equatorial methyl ketone (**5**) in good yield. Subsequent equilibration of the mixture with sodium methoxide in refluxing methanol gave, as expected, the desired ketone (**5**=A), mp 74—75.5°C, stereospecifically in 72.5% overall yield from **2**. In the proton magnetic resonance (PMR) spectrum of **5**, the secondary methyl group is observed as a clear doublet (J=6 Hz) at δ 0.93.

The most promising candidates for the substituent X in the formula (C) might be halogen or a phenylthio group, on the basis of ease of introduction and suitability as a leaving group to form the double bond. Treatment of **5** with phenyltrimethylammonium perbromide gave the rather unstable bromide (**6**) quantitatively. The phenylthio ketone (**7**) was obtained in 78.7% yield by reaction of the enolate of **5**, generated by the action of lithium diisopropylamide

(LDA), with diphenyldisulfide.[8] The regio- and stereochemistry of **6** and **7** was ascertained from their PMR spectra: each of them shows a double doublet signal (J=6, 12 Hz) due to the newly formed methine proton at δ 4.90 and δ 4.12, respectively, besides the doublet signal due to the secondary methyl group (as in **5**). These results are in good accord with those in other similar systems.[9]

Among the ring expansion reactions by one-carbon unit of cyclic ketones[10] the ethyl diazoacetate–triethyloxonium fluoroborate method is probably the most popular. When this reaction was applied to **5**, followed by hydrolysis and decarboxylation, two perhydroazulenones (**8**=D) and (**9**) were obtained in 94% combined yield in a ratio of 1 to 4 as determined by gas chromatography (GC); they were difficult to separate. Their structure determination will be discussed later. On the other hand, application of this reaction to **6** and **7** proved fruitless: no reaction took place with **6** and no ring-expanded products were detected with **7**.

Our attention was then directed to the report by Pellicciari that β-ketoesters and β-diketones were obtainable in high yields from the α-diazo-β-hydroxy carbonyl compounds derived from aldehydes on treatment with rhodium (II) acetate.[11] The ketone (**5**) was readily converted to the diazoester (**10**) in 96.5% yield as a single isomer. The stereochemistry of **10** is assumed to be as shown on the basis of the well-precedented equatorial attack of bulky reagents in the Grignard and Reformatsky reactions.[12] Reaction of **10** with rhodium (II) acetate in pentane at room temperature proceeded smoothly to afford only the β-ketoester (**11**) in 90% yield. In its infrared (IR) spectrum the characteristic absorptions due to the β-ketoester group are observed at 1700 and 1735 cm^{-1}, and the regiospecificity of this rearrangement was attested by the GC examination of its hydrolyzate (no trace of **8** was detected). Examination of the catalytic efficiency of other metal salts in this reaction revealed that (i) Wilkinson's catalyst, palladium chloride, cobalt chloride, zinc bromide, and zinc iodide also gave **11** in good yields (62.5—100%) and (ii) the regioselectivity of this reaction could not be reversed by any salt tested.[13] These observations may be rationalized by considering the more stable conformer (E) rather than the diastereomeric conformer (F) as the preferential intermediate betaine, which would collapse by concerted antiperiplanar bond migration to give **11**.

Thus the regiospecific route to **9** *via* **11** was explored. However, as the desired ketone (**8**) was obtained by the following route, 1,2-transposition of the carbonyl group in **9** was not investigated in detail.

Another promising route for the preparation of **8** seemed to be *via* the β-oxido carbenoid intermediate developed by Nozaki and co-workers.[10d] This reaction was reported to give the product in which the more substituted carbon migrated, as in the transformation of **5** to **8**. Treatment of **5** with dibromomethyllithium, generated from dibromomethane and LDA *in situ*, gave the rather unstable dibromohydrin (**12**) as a single stereoisomer,[12] which on treatment with butyllithium in ether at −78°C gave the desired ketone (**8**), mp 68.5—71.5°C, regiospecifically in 59% yield from **5**.[14] Though no trace of **9** was detected in the crude product, thin-layer chromatographic (TLC) analysis showed the presence of several minor components, whose formation could not be prevented by changes of the reaction parameters.[15]

Definitive information on the location of the carbonyl group in **8** [IR: 1692 cm^{-1}; PMR δ: 0.95 (3H, d, J=6 Hz)] and **9** [IR: 1682 cm^{-1}; PMR δ: 1.05 (3H, d, J=6 Hz)] could not be obtained from the spectra. This problem was solved by the use of deuterium exchange reactions as follows. In order to eliminate disturbance from the intense signal of the *tert*-butyl group, **8** and **9** were converted to the alcohols (**13**) and (**14**), respectively, by heating with *p*-toluenesulfonic acid (TsOH) in toluene. After refluxing overnight with CD_3ONa in CD_3OD, **13** still exhibited a doublet signal due to the secondary methyl group in its PMR spectrum. In contrast, the corresponding signal in **14** changed to a singlet. These results unequivocally established the structures of **8** and **9** as shown.

Conversion of **8** to **1** critically depends on the regioselective introduction of a leaving

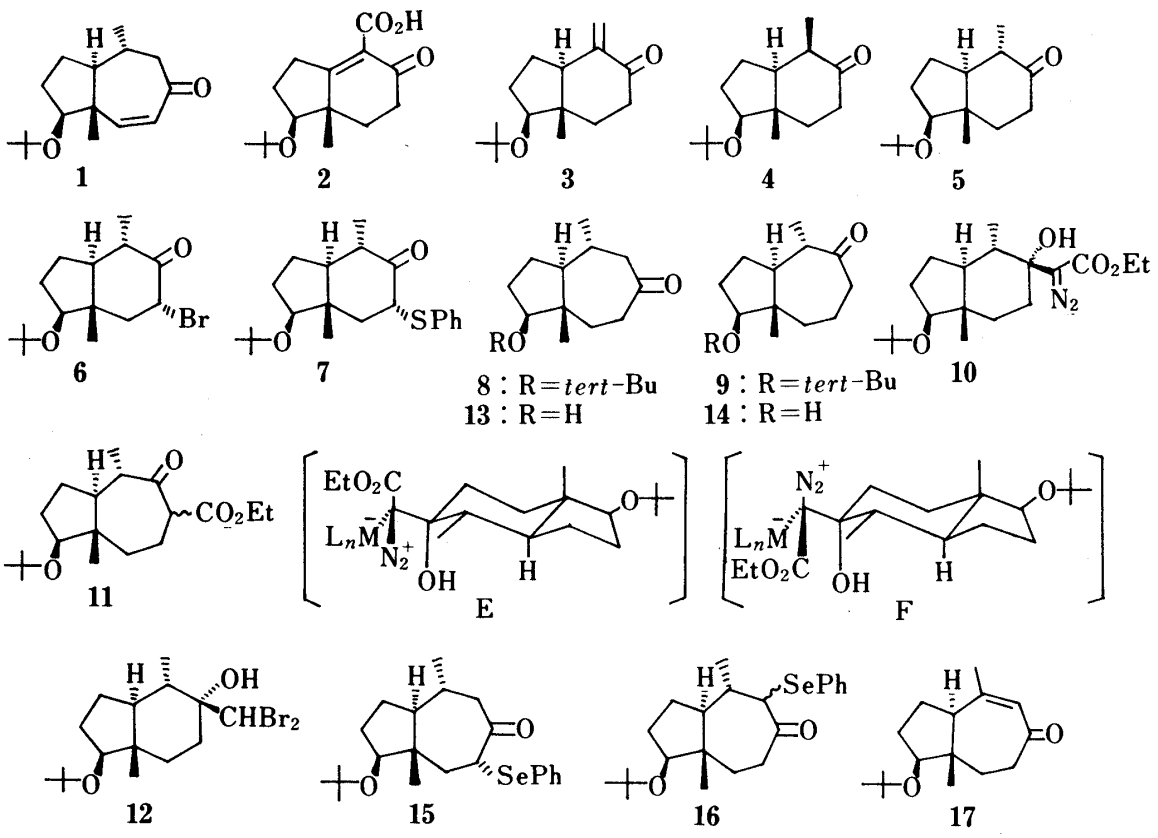

Chart 3

group at C_7. It seemed probable, *a priori*, that the Δ^7- and Δ^8-enolates of **8** would have comparable thermodynamic stability, which would result in decreased regioselectivity under thermodynamically controlled conditions. Consequently **8** was subjected to kinetic enolization. When **8** was treated with LDA in tetrahydrofuran at −78°C followed by addition of phenylselenenyl bromide, the desired selenide (**15**) was obtained in good yield. Hydrogen peroxide oxidation of **15** proceeded smoothly to give **1** in 81% yield. Though the spectral properties of **15** and **1** did not indicate the presence of their regioisomers, a more rigorous examination of the isomeric purities of these compounds was performed as follows. The regioisomeric selenide (**16**) was prepared by reaction of phenylselenenyl bromide with the Δ^8-enolate of **8**, the intermediate in the preparation of **8** from **12**. Oxidation of **16** as mentioned above gave, though in low yield, the regioisomeric enone (**17**). The enone (**1**) was easily distinguished from **17** on TLC and GC analyses as well as by the spectral data, thus confirming that **15** and **1** were obtained regiospecifically.

The reason for this specificity was inferred from inspection of the molecular model. In the lowest energy conformation of **8**, the bond between the C_7 and C_7 α-hydrogen would be most favorably oriented for overlap with the π bond of the carbonyl group, so that this proton would have the highest acidity.[3e]

Thus, a convenient stereo- and regiospecific route to **1** was developed. Its structural features should permit the syntheses of a variety of helenanolides, as exemplified by a total synthesis of (±)-carpesiolin presented in the subsequent paper.

Experimental

All melting points and boiling points are uncorrected. GC analyses were performed with 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 spectrometer using tetramethylsilane (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-OlSG spectrometer. All extracts were dried over anhydrous $MgSO_4$.

1β-*tert*-Butoxy-1,2,3,3aα,4,6,7,7a-octahydro-4α,7aβ-dimethyl-5*H*-inden-5-one (5)——A solution of the carboxylic acid (**2**) (17.0g, 63.9 mmol) in AcOEt (750 ml)–MeOH (80 ml) was hydrogenated over PtO_2 (1 g) under H_2 (3 kg/cm^2) at room temperature for 2 h. The catalyst was filtered off, washed well with AcOEt, and the solvent was removed *in vacuo* at 30—40°C. A cold mixture of dimethyl sulfoxide (DMSO) (280 ml)–formalin (210 ml)–piperidine (4.25 ml) was added to the above residue at 0°C, and the mixture was stirred at 0°C for 30 min and at room temperature for 1 h. The mixture was poured into cold 50% brine (500 ml), and the product was extracted with Et_2O. The extract was washed with sat. aq. $NaHCO_3$ and brine, then dried. Removal of Et_2O *in vacuo* at 30—40°C gave a yellow oil, which was hydrogenated in MeOH (250 ml) over PtO_2 (1 g) under an H_2 pressure of 3 kg/cm^2 at room temperature for 2 h. The catalyst was filtered off and washed well with MeOH. Removal of MeOH gave a mixture of **4** and **5**, which was distilled *in vacuo* to give pure **5** (9.73 g). The higher boiling fraction (3.2 g) was equilibrated with a catalytic amount of MeONa in absolute MeOH (70 ml) under reflux for 1 h. The solvent was removed *in vacuo* after addition of sat. aq. NH_4Cl, and the product was extracted with AcOEt. The extract was washed with brine, and dried. Evaporation of the solvent and distillation of the residue gave a further crop of **5** (1.30 g); total yield, 11.03 g (72.5% from **2**), bp 100°C (0.15 Torr), mp 74—75.5°C. IR ($CHCl_3$): 1700, 1080 cm^{-1}. PMR ($CDCl_3$) δ: 0.93 (3H, d, J=6 Hz), 1.03 (3H, s), 1.13 (9H, s), 3.35 (1H, dd, J=6, 9 Hz). MS m/e: 238 (M^+), 57. An analytical sample was obtained as the 2,4-dinitrophenylhydrazone, mp 206—207°C (from EtOH). *Anal.* Calcd for $C_{21}H_{30}N_4O_5$: C, 60.27; H, 7.23; N, 13.39. Found: C, 60.39; H, 7.15; N, 13.39.

6α-Bromo-1β-*tert*-Butoxy-1,2,3,3aα,4,6,7,7a-octahydro-4α,7aβ-dimethyl-5*H*-inden-5-one (6)——A mixture of **5** (1.0 g, 4.2 mmol) and phenyltrimethylammonium perbromide (2.0 g, 4.2 mmol) in tetrahydrofuran (THF) (30 ml) was stirred under N_2 at 0°C for 5 min and at room temperature for 1 h. The mixture was filtered and the filtrate was washed with brine containing aq. $Na_2S_2O_3$, then dried. Evaporation of the solvent *in vacuo* gave chromatographically pure **6** (1.97 g, quant.), mp 100—102°C (from hexane). IR ($CHCl_3$): 1722, 1075 cm^{-1}. PMR ($CDCl_3$) δ: 1.03 (3H, d, J=6 Hz), 1.15 (12H, s), 3.52 (1H, t, J=7 Hz), 4.90 (1H, dd, J=6, 12 Hz). MS m/e: 316, 318 (M^+). High-resolution MS m/e: 316.1037 and 318.0995 (M^+) Calcd for $C_{15}H_{25}BrO_2$ 316.1037 and 318.1017. Further attempts at purification by column chromatography on silica gel resulted in the decomposition of a substantial amount of **6**.

1β-*tert*-Butoxy-1,2,3,3aα,4,6,7,7a-octahydro-4α,7aβ-dimethyl-6α-phenylthio-5*H*-inden-5-one (7)——Butyllithium (20 ml of 1.5 M solution in hexane, 30 mmol) was added to a solution of diisopropylamine (6.0 ml, 42.9 mmol) in dry THF (30 ml) at −65°C under Ar, and the mixture was stirred at −65°C for 10 min and at −25°C for 30 min. A solution of **5** (3.0 g, 12.6 mmol) in dry THF (20 ml)–dry hexamethylphosphoric triamide (20 ml) was added to the resulting solution, and stirring was continued at −20°C for 30 min, at 0°C for 30 min, and finally at room temperature for 40 min. This solution was cooled to 0°C, and a solution of diphenyldisulfide (6.0 g, 27.5 mmol) in dry THF (30 ml) was added. The whole was stirred at room temperature for 2 h, then the reaction was quenched by addition of sat. aq. NH_4Cl. The product was extracted with Et_2O, and the extract was washed with 10% HCl, sat. aq. $NaHCO_3$, water, 50% brine and brine, then dried. The crude product, after evaporation of the solvent, was chromatographed on silica gel. Elution with CCl_4 gave the unreacted diphenyldisulfide (4.7 g) and further elution with CCl_4–CH_2Cl_2 gave crude **7** (5.75 g). Recrystallization from MeOH and chromatography of the mother liquor on silica gel was repeated several times to give pure **7** (3.43 g, 78.7%), mp 124—126°C (from MeOH). IR ($CHCl_3$): 1705, 1110 cm^{-1}. PMR ($CDCl_3$) δ: 0.96 (3H, d, J=5 Hz), 1.10 (12H, s), 3.20—3.60 (1H, m), 4.12 (1H, dd, J=6, 12Hz), 7.13—7.56 (5H, m). MS m/e: 346 (M^+). *Anal.* Calcd for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.73. Found: C, 72.78; H, 8.73.

1β-*tert*-Butoxy-2,3,3aα,4,6,7,8,8a-octahydro-4a,8aβ-dimethyl-5(1*H*)-azulenone (9) from the Reaction of 5 with Ethyl Diazoacetate——A solution of **5** (1.0 g, 4.2 mmol) and ethyl diazoacetate (0.78 ml, 7.4 mmol) in dry CH_2Cl_2 (70 ml) was added to a solution of triethyloxonium fluoroborate (0.78 g, 4.2 mmol) in dry CH_2Cl_2 (10 ml) under Ar with ice cooling. After being stirred at ambient temperature overnight, the mixture was washed with sat. aq. $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo* and 5% NaOH (30 ml) was added to a solution of the residue in MeOH (30 ml). The mixture was stirred at room temperature for 2.5 h and then acidified with 10% HCl. After saturation with NaCl, the product was extracted with AcOEt. The extract was washed with brine, and dried. The residue, after evaporation of the solvent, was dissolved in toluene (35 ml) and this solution was refluxed for 1.5 h. Toluene was then removed *in vacuo* and the residue was chromatographed on silica gel (elution with Et_2O–hexane) to give a mixture of **8** and **9** (1.0 g, 94%). GC analysis indicated that the ratio of **8** to **9** was 1:4. A pure sample of **9** was obtained by trituration of the crude β-keto acid with petroleum ether followed by decarboxylation of the crystalline acid, but a pure sample of **8** could not be obtained. The data for pure **9** are as follows. bp 110—115°C (0.12 Torr), mp 47—49°C (from hexane). IR ($CHCl_3$): 1682, 1110, 1087 cm^{-1}. PMR ($CDCl_3$): δ 0.64 (3H, s), 1.05 (3H, d, J=6Hz), 1.13 (9H, s), 3.28—3.70 (1H, m). MS m/e: 252 (M^+). The analytical sample was obtained as its 2,4-dinitrophenylhydrazone, mp 183—186°C (from EtOH). *Anal.* Calcd for $C_{22}H_{32}N_4O_5$: C, 61.09; H, 7.46; N, 12.96. Found: C, 61.00; H, 7.56; N, 12.88.

Reaction of the Bromide (6) with Ethyl Diazoacetate——The reaction was performed in the same manner

as above using a solution of **6** (0.394 g, 1.24 mmol) and ethyl diazoacetate (0.27ml, 2.56 mmol) in CH_2Cl_2 (15 ml) and a solution of triethyloxonium fluoroborate (0.467 g, 2.46 mmol) in CH_2Cl_2 (25 ml). GC–MS and TLC analyses showed that the residue (0.468 g) was mostly recovered **6**, and no ring-expanded product was observed.

Reaction of the Phenylthio Ketone (7) with Ethyl Diazoacetate———The reaction was performed analogously using a solution of **7** (0.2 g, 0.57 mmol) and ethyl diazoacetate (0.27 ml, 2.56 mmol) in CH_2Cl_2 (15 ml) and a solution of triethyloxonium fluoroborate (0.52 g, 2.74 mmol) in CH_2Cl_2 (25 ml). GC–MS and TLC analyses indicated that the residue (0.396 g) was a mixture of recovered **7**, its debutylated alcohol [MS *m/e*: 290 (M^+)], and the ethyl enol ether of **7** [MS *m/e*: 374 (M^+)], but no ring-expanded product was detected.

1β-*tert*-Butoxy-5β-ethoxycarbonyldiazomethyl-2,3,3aα,4,5,6,7,7a-octahydro-4α,7aβ-dimethyl-5α-indenol(10)———A solution of LDA [prepared from diisopropylamine (1.8 ml, 11.4 mmol) and butyllithium (7.12 ml of 1.5M solution in hexane, 10.7 mmol)] in dry THF (10 ml) was added to a solution of **5** (2.00 g, 8.4 mmol) and ethyl diazoacetate (1.136 g, 9.96 mmol) in dry THF (20 ml) at −78°C under Ar. The mixture was stirred at the same temperature for 0.5 h, then sat. aq. NH_4Cl was added rapidly. Extraction with Et_2O, followed by washing the extract briefly with 10% HCl, sat. aq. $NaHCO_3$, and brine, furnished the crude product, which was purified by column chromatography on silica gel (elution with Et_2O–hexane) to give pure **10** (2.856 g, 96.5%), mp 103.5—106.5°C (from hexane). IR ($CHCl_3$): 3510, 2080, 1670 cm. PMR ($CDCl_3$): 0.76 (3H, s), 0.90 (3H, d, J=6Hz), 1.10 (9H, s), 1.26 (3H, t, J=7Hz), 3.20—3.70 (1H, m), 3.43 (1H, br s, disappeared upon D_2O addition), 4.22 (2H, q, J=7Hz). MS *m/e:* 352 (M^+), 324. *Anal.* Calcd for $C_{19}H_{32}N_2O_4$: C, 64.74; H, 9.15; N. 7.95. Found: C, 64.85; H, 8.91; N, 8.00.

1β-*tert*-Butoxy-6-ethoxycarbonyl-2,3,3aα,4,6,7,8,8a-octahydro-4α,8aβ-dimethyl-5(1*H*)-azulenone (11)——i) Method A: $Rh_2(OAc)_4$ (20 mg) was added to a solution of **10** (370 mg, 1.05 mmol) in pentane (30 ml) and the mixture was stirred at room temperature for 0.5 h. The catalyst was filtered and washed well with pentane. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (elution with Et_2O–hexane) to give pure **11** (308 mg, 90%). IR ($CHCl_3$): 1735, 1700 cm^{-1} PMR ($CDCl_3$): 0.62 (3H, s), 1.13 (9H, s), 1.21 (3H, t, J=7Hz), 3.20—3.80 (2H, m), 4.11 (2H, q, J=7Hz). MS *m/e*: 324 (M^+). *Anal.* Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.15; H, 9.56.

ii) Method B: A mixture of **10** (400 mg, 1.14 mmol) and $RhCl(Ph_3P)_3$ (20 mg), $PdCl_2$ (25 mg), or anhydrous $CoCl_2$ (70 mg) in C_6H_6 (10 ml) was heated under reflux until **10** was completely consumed. The mixture was filtered through a short pad of silica gel, which was further eluted with Et_2O–hexane (1:4). The product was obtained by evaporation of the solvent and distillation of the residue, bp 135—140°C (0.1 Torr). The yields of **11** were as follows: with $RhCl(Ph_3P)_3$, 367 mg (100%); with $PdCl_2$, 284 mg (77%); and with $CoCl_2$, 293 mg (79.6%).

iii) Method C: $ZnBr_2$ (130 mg) or ZnI_2 (150 mg) was added to a solution of **10** (400 mg, 1.14 mmol) in C_6H_6 (10 ml) and stirring was continued at room temperature overnight. To this mixture was added brine (in the case of ZnI_2, a mixture of brine and aq. $Na_2S_2O_3$), and the product was extracted with C_6H_6. The extract was washed with brine, and dried. The solvent was removed *in vacuo* and the residue was passed through a short pad of silica gel with Et_2O–hexane (1:4). Evaporation of the solvent and distillation gave **11** in the following yields: with $ZnBr_2$, 247 mg, (67%); and with ZnI_2, 230 mg (62.5%) after further purification of the distillate by column chromatography on silica gel (elution with Et_2O–hexane). Samples (30 mg) from each run were hydrolyzed with 5% aq. KOH (10 ml) at room temperature overnight. The crude acids, obtained by acidification of the reaction mixtures with conc. HCl and extraction with Et_2O, were refluxed in C_6H_6 (10 ml) for 1 h. GC analyses showed that the product was entirely **9** and no trace of **8** could be detected.

1β-*tert*-Butoxy-2,3,3aα,4,5,7,8,8a-octahydro-4α,8aβ-dimethyl-6(1*H*)-azulenone (8) *via* the Dibromohydrin (12)———A solution of LDA [prepared from diisopropylamine (15.0 ml, 107.2 mmol) and butyllithium (66 ml of 1.5 M solution in hexane, 99.0 mmol)] in dry THF (50 ml) was added to a solution of **5** (10.014 g, 42.1 mmol) and CH_2Br_2 (6.7 ml, 95.4 mmol) in dry THF (100 ml) at −78°C under Ar, and the mixture was stirred for 1 h. The reaction mixture was poured into cold 10% HCl (150 ml) with vigorous stirring, and the product was extracted with Et_2O after saturation of the aq. phase with NaCl. The extract was washed with sat. aq. $NaHCO_3$ and brine, then dried. A half of the solvent was removed *in vacuo*, then about the same volume of hexane was added, followed by evaporation of all the volatiles *in vacuo* at 35—40°C. The crude dibromohydrin (**12**) thus obtained was usually subjected to the next step without further purification. A portion of the crude **12** was purified in one experiment by column chromatography on silica gel (elution with Et_2O–hexane) to give pure **12**, mp 98—102°C. IR ($CHCl_3$): 3450, 1090 cm^{-1}. PMR ($CDCl_3$): δ 0.73 (3H, s), 0.75 (3H, d, J=6Hz), 1.17 (9H, s), 3.30—3.70 (1H, m), 5.95 (1H, s). MS *m/e*: 410, 412, 414 (M^+). A solution of the crude **12** mentioned above in dry Et_2O (150 ml) was treated with butyllithium (68 ml of 1.5 M solution in hexane, 102 mmol) at −78°C under Ar, and the mixture was stirred at −78°C for 1 h. The mixture was poured into cold 10% HCl (100 ml) with vigorous stirring, and the product was extracted with Et_2O after saturation of the aq. phase with NaCl. The extract was washed with sat. aq. $NaHCO_3$, brine, and dried. Evaporation of Et_2O *in vacuo* and column chromatography of the residue on silica gel (elution with Et_2O–hexane and Et_2O–CH_2Cl_2) gave crude **8**. Distillation under reduced pressure gave pure **8** (4.454 g). Column chromatography of the residue (4.0 g) on silica gel (elution with Et_2O–hexane, Et_2O, and Et_2O–CH_2Cl_2) gave a further crop of **8** (1.830 g); total yield, 6.284 g (59%), bp 105—115°C (0.1 Torr), mp 68.5—71.5°C (from hexane) (lit[3e]; mp

66.5—68°C). IR ($CHCl_3$): 1692, 1105, 1085 cm^{-1}. PMR ($CDCl_3$) δ: 0.61 (3H, s), 0.95 (3H, d, J=6Hz), 1.15 (9H, s), 3.25—3.65 (1H, m). MS m/e: 252 (M^+). An analytical sample was obtained as the 2,4-dinitrophenylhydrazone, mp 167—169°C (from EtOH). *Anal.* Calcd for $C_{22}H_{32}N_4O_5$: C, 61.09; H, 7.46; N, 12.96. Found: C, 61.09, H, 7.44; N, 13.08.

Deuterium Exchange Reactions of 8 and 9——i) With **8**: solution of **8** (80 mg, 0.336 mmol) and a catalytic amount of TsOH in toluene (15 ml) was heated under reflux for 3 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$, and the product was extracted with C_6H_6. The extract was washed with brine and dried. The residue, after evaporation of the solvent, was chromatographed on silica gel (elution with $CHCl_3$–MeOH) to give **13** (50 mg, 80%). PMR (CD_3OD) δ: 0.96 (3H, d, J=6Hz). MS m/e: 196 (M^+). A solution of **13** (50 mg, 0.25 mmol) in CD_3OD (0.8 ml) containing a catalytic amount of CD_3ONa (prepared from oil-free NaH and CD_3OD) was heated under reflux overnight, but the doublet signal at δ 0.96 did not change in the PMR spectrum. Direct MS analysis of the reaction mixture showed that the content of the d_5 isomer [MS m/e: 201 (M^+)] was 31.9%.

ii) With **9**: The ketone (**9**) (110 mg, 0.436 mmol) was pyrolyzed and chromatographed in the same manner as above to give **14** (70 mg, 82%). PMR (CD_3OD) δ: 1.06 (3H, d, J=6Hz). MS m/e: 196 (M^+). A solution of **14** (70 mg, 0.36 mmol) in CD_3OD (0.8 ml) containing a catalytic amount of CD_3ONa was refluxed overnight. PMR measurement showed that the doublet signal at δ 1.06 changed to a singlet and direct MS analysis showed that the content of the d_4 isomer [MS m/e: 200 (M^+)] was 21.3%.

1β-*tert*-Butoxy-2,3,3aα,4,5,7,8,8a-octahydro-4α,8aβ-dimethyl-7α-phenylseleno-6(1*H*)-azulenone (15)——Butyllithium (19 ml of 1.5 M solution in hexane, 28.5 mmol) was added to a solution of diisopropylamine (4.9 ml, 35.0 mmol) in dry THF (54 ml) at −10——−20°C under Ar. After being stirred for 15 min, the solution was cooled to −78°C and a solution of **8** (4.866 g, 19.3 mmol) in dry THF (60 ml) was added. Stirring was continued at the same temperature for 30 min and at −50°C for 5 min, then a solution of phenylselenenyl bromide (5.5 g, 23.3 mmol) in dry THF (60 ml) was added at −78°C, and the mixture was stirred for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl, and the product was extracted with Et_2O. The extract was washed with brine, and dried. Evaporation of the solvent and column chromatography of the residue on silica gel (elution with CCl_4–CH_2Cl_2 and CH_2Cl_2–MeOH) gave pure **15** (6.893 g, 88%), mp 111—113°C (from hexane). IR ($CHCl_3$): 1680, 1085 cm^{-1}. PMR ($CDCl_3$) δ: 0.62 (3H, s), 0.95 (3H, d, J=6Hz), 1.17 (9H, s), 3.73 (1H, dd, J=6, 12 Hz), 7.20—7.65 (5H, m). MS m/e: 406, 408 (M^+). *Anal.* Calcd for $C_{22}H_{32}O_2Se$: C, 64.85; H, 7.91. Found: C, 64.79; H, 7.89.

1β-*tert*-Butoxy-2,3,3aα,4,5,8a-hexahydro-4α,8aβ-dimethyl-6(1*H*)-azulenone (1)——A solution of **15** (1.082 g, 2.65 mmol) in THF (10 ml) was treated with 30% aq. H_2O_2 (0.36 ml, 3.18 mmol) under Ar with ice cooling, and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of aq. $NaHSO_3$ and the organic solvent was removed *in vacuo*. The product was extracted with Et_2O after saturation of the aq. phase with NaCl, and the extract was washed with brine, and dried. Evaporation of the solvent and column chromatography of the residue on silica gel (elution with Et_2O–hexane) gave pure **1** (536 mg, 81%), bp 105—110°C (0.15 Torr). IR ($CHCl_3$): 1660, 1085 cm^{-1}. PMR ($CDCl_3$) δ: 1.02 (3H, s), 1.02 (3H, d, J=6 Hz), 1.17 (9H s), 5.87 (1H, dd, J=1, 12 Hz), 6.60 (1H, d, J=12 Hz). MS m/e: 250 (M^+). *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.78; H, 10.30.

1β-*tert*-Butoxy-2,3,3aα,4,5,7,8,8a-octahydro-4α,8aβ-dimethyl-5-phenylseleno-6(1*H*)-azulenone (16)——A solution of LDA [prepared from diisopropylamine (1.43 ml, 10.22 mmol) and butyllithium (6 ml of 1.5 M solution in hexane, 9 mmol)] in dry THF (5 ml) was added to a solution of **5** (1.005 g, 4.22 mmol) and CH_2Br_2 (0.7 ml, 10.05 mmol) in dry THF (10 ml) at −78°C under Ar. The mixture was stirred for 1 h, then a solution of AcOH (1 ml) in THF (1 ml) was added at the same temperature followed by addition of 10% HCl. The aq. phase was saturated with NaCl, and the product was extracted with Et_2O. The extract was washed with 10% HCl, sat. aq. $NaHCO_3$, brine, and dried. The solvent was evaporated off *in vacuo* at less than 40°C and the crude **12** was dissolved in dry Et_2O (30 ml). To this solution was added butyllithium (5.2 ml of 1.5 M solution in hexane, 7.8 mmol) at −78°C under Ar, and stirring was continued for 1 h. Then phenylselenenyl bromide [prepared from diphenyldiselenide (658 mg, 2.11 mmol) and Br_2 (0.1 ml, 1.93 mmol) in $CHCl_3$ (10 ml)] in dry Et_2O (15 ml) was added at −78°C, and the whole was stirred for 40 min. After addition of sat. aq. NH_4Cl, the product was extracted with Et_2O. The extract was washed with brine, and dried. Evaporation of the solvent and column chromatography of the residue on silica gel (elution with Et_2O–hxane and CH_2Cl_2–MeOH) gave pure **16** (776 mg, 45% from **5**). IR ($CHCl_3$): 1675, 1090 cm^{-1}. PMR ($CDCl_3$) δ: 0.78 (3H, s), 1.10 (9H, s), 1.20 (3H, d, J=6Hz), 3.28 (1H, d, J=9 Hz), 7.17—7.70 (5H, m). MS m/e: 406, 408 (M^+). High-resolution MS m/e: 406.1585 and 408.1551 (M^+) calcd for $C_{22}H_{32}O_2Se$ 406.1585 and 408.1566. The relatively small coupling constant (J=9 Hz) for the proton adjacent to the phenylseleno group in **16** indicates that this group is largely in the α orientation, but its non-crystallinity casts some doubt on its stereohomogenity.

1β-*tert*-Butoxy-2,3,3aα,7,8,8a-hexahydro-4,8aβ-dimethyl-6(1*H*)-azulenone (17)——A solution of **16** (658 mg, 1.62 mmol) in THF (6 ml) was treated with 30% aq. H_2O_2 (0.24 ml, 2.12 mmol), with ice cooling, and the solution was stirred for 1.5 h. The reaction was quenched with aq. $NaHSO_3$, and the volatiles were removed *in vacuo*. The product was extracted with Et_2O, and the extract was washed with brine, and dried. Evaporation of the solvent and chromatography of the residue on silica gel (elution with Et_2O–hexane and CH_2Cl_2–MeOH)

gave pure **17** (41 mg, 10%). IR ($CHCl_3$): 1640, 1090 cm^{-1}. PMR ($CDCl_3$) δ: 0.80 (3H, s), 1.15 (9H, s), 1.92 (3H, br s), 5.85—6.10 (1H, m). MS *m/e*: 250 (M^+). High-resolution MS *m/e*: 250.1922 (M^+) calcd for $C_{16}H_{26}O_2$ 250.1931.

References and Notes

1) N.H. Fischer, E.J. Oliver, and H.D. Fischer, "Progress in the Chemistry of Natural Products," Vol. 38, ed. by W. Herz, H. Grisebach, and G.W. Kirby, Springer-Verlag, Vienna and New York, 1979, pp. 47—390 and references cited therein.
2) E. Rodriguez, G.H.N. Towers, and J.C. Mitchell, *Phytochemistry*, **15**, 1573 (1976); K.H. Lee, T. Ibuka, R.Y. Wu, and T.A. Geissman, *ibid.*, **16**, 1177 (1977); S.M. Kupchan, M.A. Eakin, and A.M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); I.H. Hall, C.O. Starnes, Jr., K.H. Lee, and T.G. Waddell, *J. Pharm. Sci.*, **69**, 537 (1980); F.J. Evans and C.J. Soper, *Lloydia*, **41**, 193 (1978).
3) *a*) P.A. Grieco, Y. Ohfune, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 7393 (1977); *b*) P. De Clercq and M. Vandewalle, *J. Org. Chem.*, **42**, 3447 (1977); *c*) Y. Ohfune, P.A. Grieco, C.-L.J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **100**, 5946 (1978); *d*) P.A. Grieco, Y. Ohfune, and G. Majetich, *Tetrahedron Lett.*, **1979**, 3265; *e*) M.R. Roberts and R.H. Schlessinger, *J. Am. Chem. Soc.*, **101**, 7626 (1979); *f*) G.J. Quallich and R.H. Schlessiger, *ibid.*, **101**, 7627 (1979); *g*) P. Kok, P.J. De Clercq, and M.E. Vandewalle, *J. Org. Chem.*, **44**, 4553 (1979); *h*) M. Demuynck, P. De Clercq, and M. Vandewalle, *ibid.*, **44**, 4863 (1979); *i*) P.T. Lansbury, D.G. Hangauer, Jr., and J.P. Vacca, *J. Am. Chem. Soc.*, **102**, 3964 (1980); *j*) C.H. Heathcock, E.G. DelMar, and S.L. Graham, *ibid.*, **104**, 1907 (1982).
4) Preliminary communication: K. Nagao, M. Chiba, I. Yoshimura, and S-W. Kim, *Chem. Pharm. Bull.*, **29**, 2733 (1981).
5) In this text the numbering of the natural product is used.
6) Another example based on a similar strategy has been reported, but it is limited to the synthesis of ambrosanolides. See J.A. Marshall and R.H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976).
7) Z.G. Hajos, D.R. Parrish, and E.P. Oliveto, *Tetrahedron*, **24**, 2039 (1968); R.A. Micheli, Z.G. Hajos, N. Cohen, D.R. Parrish, L.A. Portland, W. Sciamanna, M.A. Scott, and P.A. Wehrli, *J. Org. Chem.*, **40**, 675 (1975).
8) B.M. Trost, T.N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
9) P.A. Grieco, N. Fukamiya, and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, **1976**, 573.
10) *a*) W.L. Mock and M.E. Hartman, *J. Org. Chem.*, **42**, 459, 466 (1977); *b*) N. Hashimoto, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 119 (1982); *c*) B. Tchoubar, *Bull. Soc. Chim. Fr.*, **1949**, 164; *d*) H. Taguchi, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 1588, 1592 (1977); *e*) T. Cohen, D. Kuhn, and J.R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975); *f*) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976); *g*) J-P. Deprés and A.E. Green, *ibid.*, **45**, 2036 (1980).
11) R. Pellicciari, R. Fringuelli, P. Ceccerelli, and E. Sisani, *J. Chem. Soc. Chem. Commun.*, **1979**, 959; R. Pellicciari, R. Fringuelli, E. Sisani, and M. Curini, *J. Chem. Soc., Perkin Trans., 1*, **1981**, 2566.
12) See, for example, F. Rocquet, J.P. Baltioni, M.L. Capmau, and W. Chodkiewicz, *C. R. Acad. Sci.*, **268**, 1449 (1969); T. Matsumoto and K. Fukui, *Bull. Chem. Soc. Jpn.*, **44**, 1090 (1971); J. Bertrand, L. Gorrichon-Guigon, Y. Koudsi, M. Perry, and Y. Maroni-Barnaud, *C. R. Acad. Sci.*, **277**, 723 (1973).
13) K. Nagao, M. Chiba, and S-W. Kim, *Synthesis*, in press.
14) During the course of this study, Schlessinger *et al.* also prepared **8** by another route, and transformed it into (±)-helenalin. See ref. 3*e*.
15) G. Köbrich and W. Werner, *Tetrahedron Lett.*, **1969**, 2181.