A New Stereoselective Approach for the Total Synthesis of (±)-Isotadeonal, (±)-Polygodial, (±)-Warburganal, and (±)-Muzigadial

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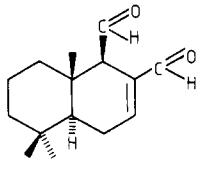
Stereoselective total syntheses of (±)-isotadeonal (**20**), (±)-polygodial (**1**), (±)-warburganal (**2**), and (±)-muzigadial (**4**) are described starting from 4a-methylperhydronaphthalen-2-ones. The functionalized carbon atoms at C-8 and C-9 were introduced via formylation and hydrocyanation, respectively. A key transformation in the approach involved the base catalyzed epimerization of the C-9 α-carboxaldehyde function to the 9β-position. The total synthesis of (±)-warburganal was achieved in ten steps in 38% overall yield from ketone **7a**. The conversion of (4aα,7α,8aβ)-(±)-octahydro-4a,7-dimethyl-8-methylene-2(1*H*)-naphthalenone (**8**) into (±)-muzigadial was achieved in 24% overall yield, following the procedure developed for (±)-warburganal.

Much effort has been devoted recently to the development of total syntheses for natural insect antifeedants. Especially the synthesis of the drimane sesquiterpenes (warburganal and congeners) was strongly stimulated by the discovery of the antifeedant activity of these compounds against the African army worms *Spodoptera littoralis* and *S. exempta*.[1]

A common structural feature in the drimanic sesquiterpenes polygodial (**1**), warburganal (**2**), and cinnamodial (**3**) is the presence of a 7,8-ene 11,12β-dialdehyde functionality and, except for polygodial, a 9α-hydroxyl group. An analogous set of functionalities is found in the rearranged drimane muzigadial (**4**), which also exhibits strong antifeedant properties.



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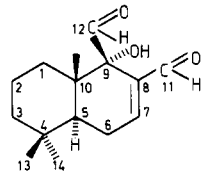

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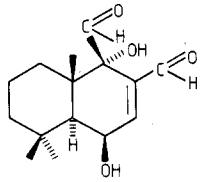

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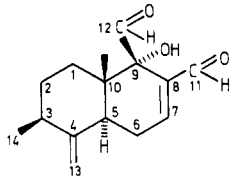

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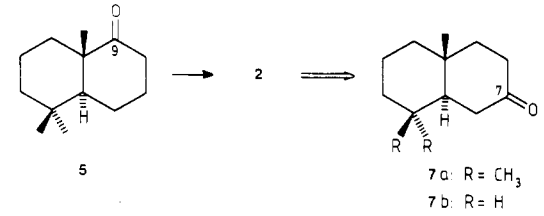
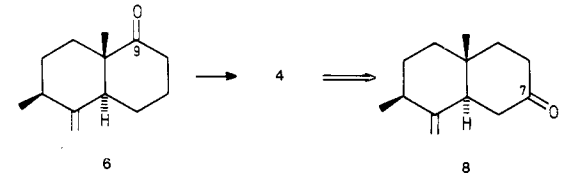
A variety of methods was used for the total syntheses of the drimanes **1**–**4**.[2-5] Among others, the decalones **5** and **6**, possessing a carbonyl group at C-9,[6] have turned out to be versatile intermediates in several syntheses of 2^{3h-k} and **4**.[5] In all these cases the 9α-hydroxyl group was



5 7a: R = CH_3 7b: R = H



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introduced via oxidation of an exocyclic double bond or an enol ether in one of the final steps of the synthesis using OsO_4[3i,h,5] or *m*-CPBA[3h] as the oxidizing reagent. A total synthesis of muzigadial, with its exocyclic double bond in ring A, along these lines is risky since it remains speculative until the final steps in such an approach whether the required selectivity in these oxidation reactions can be achieved. However, recently it was shown in the first synthesis of muzigadial that selective osmylation of an enol ether in the presence of the exocyclic 4,13-double bond can be accomplished under careful controlled conditions.[5] Although we also considered and investigated a total

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(6) To avoid confusion and to allow direct comparison between the various structures, the numbering system of warburganal (**2**) and muzigadial (**4**) has been used throughout the discussion.

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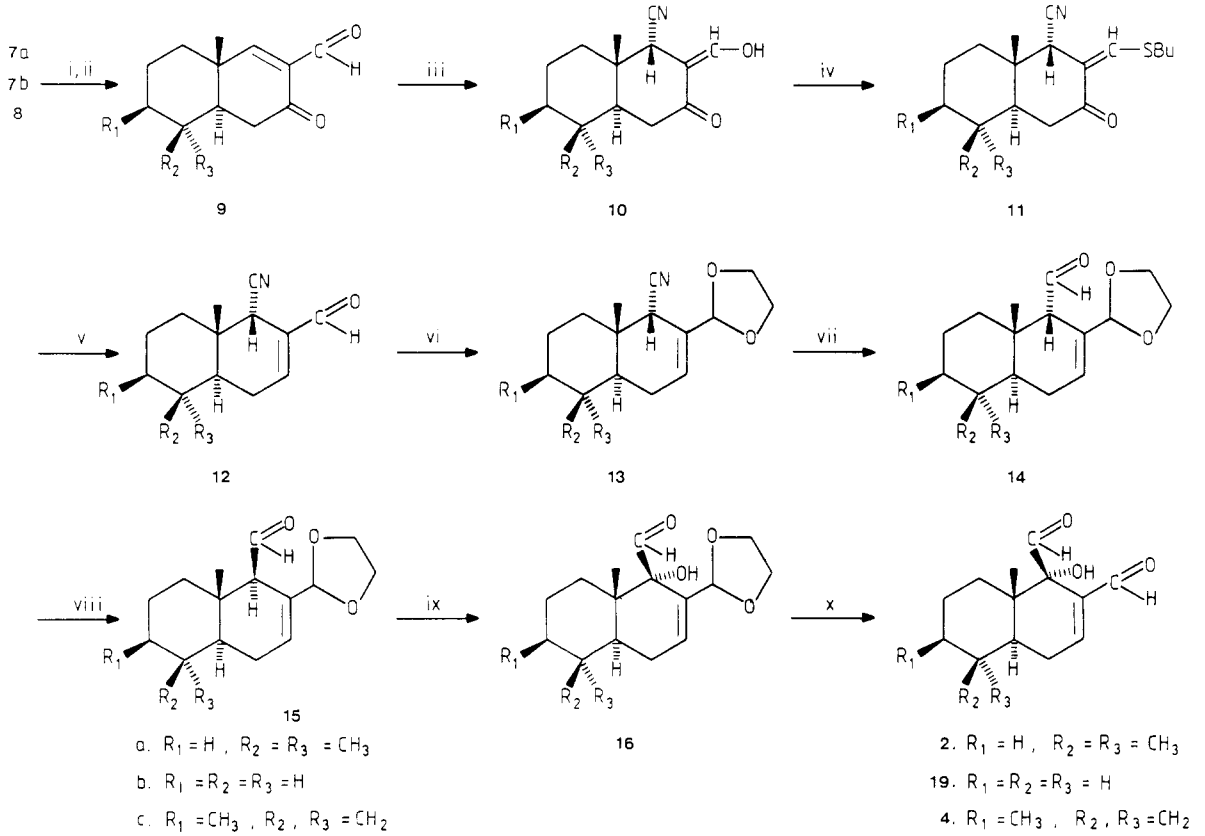
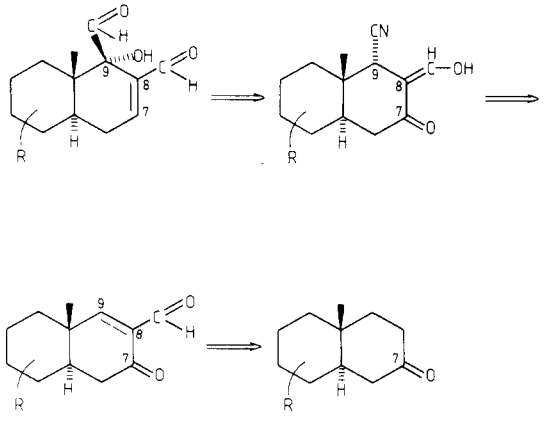
Scheme I[a]



[a] Reagents: (i) NaH, HCOOEt; (ii) PhSeCl, pyr, H_2O_2; (iii) KCN; (iv) *n*-BuSH, H^+; (v) $NaBH_4$, H_3O^+, $HgCl_2$; (vi) $CH_2(OH)_2$, H^+; (vii) DIBAH; (viii) KO-*t*-Bu, HO-*t*-Bu; (ix) LDA, MoO_5·HMPA·pyr; (x) H_3O^+.

synthesis of muzigadial starting from **6**,[7] we finally decided to develope a new and possibly general route for the synthesis of polygodial, warburganal, and especially muzigadial in which the necessity of highly selective oxidation reactions could be avoided. This new approach was found starting from the decalones **7a,b** and **8**. These decalones, with the carbonyl function at C-7 are easily accessible (vide infra), the carbonyl function is ideally located for the introduction of the necessary functionalized carbon atoms at C-8 (by formylation) and at C-9 (by hydrocyanation) and it can be used later on for the construction of the $\Delta^{7,8}$ double bond. The reaction sequence was first worked out for the synthesis of (±)-polygodial and (±)-warburganal and their dinor congeners and finally applied to the synthesis of (±)-muzigadial.



Results and Discussion

The required decalones **7a** and **7b** were easily accessible via the known literature procedures[8-10] starting from 4,4a,5,6,7,8-hexahydro-4a-methyl-naphthalene-2(3*H*)-one.[11] The synthesis of decalone **8**, necessary for the preparation of muzigadial, was achieved before in our laboratory[12] and proved to be suitable for production on a good scale.

The conversion of these decalones into the 7,8-ene 11,12β-dialdehyde functionalities was first investigated for the ketones **7a** and **7b**. Formylation of ketones **7a** and **7b** occurred at C-8 exclusively and the olefinic bond was introduced via a selenylation–deselenenylation procedure[13,3i] (Scheme I). The unsaturated keto aldehydes **9a**[14] and **9b**[15] smoothly underwent a conjugate addition to the 9α-nitriles **10a** and **10b**.[16] The conversion of the formyl ketone moiety in these molecules into the protected α,β-unsaturated aldehydes **13a** and **13b** was performed via reduction of the (*n*-butylthio)methylene derivatives **11a** and **11b**

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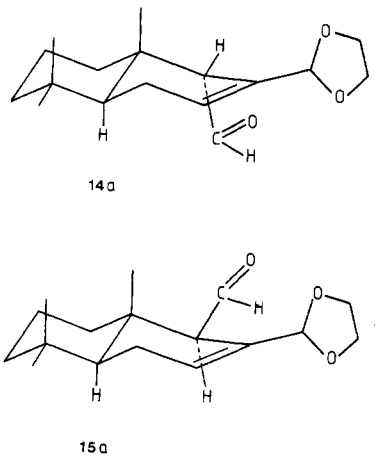
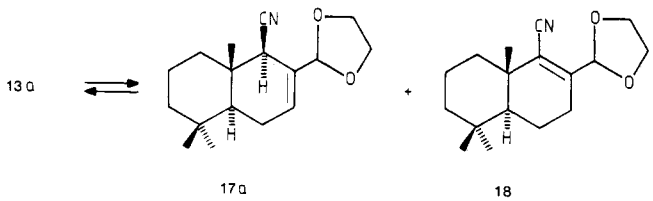


14a

15a

Figure 1.

Scheme II



13a 17a 18

followed by hydrolysis[17] and protection with glycol. The conversion of the ketones **7a** and **7b** into the protected nitriles **13a** and **13b** can be accomplished in 46% overall yield in six steps without extensive purification of the intermediates. The nitrile group in **13a** and **13b** was reduced with DIBAH to give the 9α-aldehydes **14a** and **14b** in 85% yield.

The α-hydroxylation of the 8-(1,3-dioxolan-2-yl) 9α-aldehyde **14a** to **16a** has been accomplished by Ohsuka et al.[3a] in a rather low 24% yield via oxidation of the corresponding enolate. In our hands this procedure either gave the desired product **16a** or **16b** in very low yield or failed completely. This may be due to the steric crowding around the 9β-proton so that nucleophilic attack on the carbonyl function of the relatively exposed 9α-aldehyde group is the preferred reaction (see Figure 1). The reduction product found by Ohsuka et al. as a byproduct in this reaction and some of our own observations are in agreement with this supposition. In contrast, the epimer **15a**, with an exposed α-proton and a relatively hindered aldehyde group (see Figure 1), is easily deprotonated and subsequently oxidized as was also demonstrated by Nakanishi et al.[2b] and by Ohno et al.[3b] in their syntheses of warburganal.

Faced with these difficulties it was decided to try to prepare the 9β-aldehyde **15a** via epimerization and reduction of the 9α-nitrile **13a**. This epimerization of **13a** could be accomplished partly to an equilibrium mixture which contained 25% of the 9β-nitrile **17a**, 70% of the 9α-nitrile **13a**, and a small amount of the α,β-unsaturated nitrile **18**. Prolonged treatment of **13a** with base gave the nitrile **18** as the sole product (Scheme II). Unfortunately the reduction of **17a** as well as **18** failed in our hands.

Therefore, the attention was focused again on the transformation of the 9α-aldehyde **14a** and finally it was discovered that nearly complete epimerization could be accomplished by a 10-min treatment of **14a** with a fivefold excess of KO-*t*-Bu in refluxing HO-*t*-Bu. The resulting 8-(1,3-dioxolan-2-yl) 9β-aldehyde **15a** was converted into (±)-warburganal (**2**) as described in the literature[2b,3b] in high yield. The same procedure could be applied to the dinor compound **14b** to give (±)-dinorwarburganal **19** in 63% yield. The intermediates **14a**, **15a**, **14b**, and **15b** were hydrolyzed to (±)-isotadeonal[18] (**20**) and (±)-polygodial (**1**) and their dinor congeners 13,14-dinorpolygodial (**21**) 13,14-dinorisotadeonal (**22**), respectively.

With this procedure firmly established our attention was turned toward the synthesis of (±)-muzigadial. Since all the reaction conditions and reagents used for the conversion of ketone **7a** into (±)-warburganal are compatible with the presence of an exocyclic double bond in the molecule, the transformation of ketone **8** into (±)-muzigadial was expected to be straightforward and indeed no serious problems were encountered. The hydrolysis of the reduced (*n*-butylthio)methylene compound (**11c** → **12c**) must be carried out at room temperature to prevent isomerization of the exocyclic olefinic bond. The key transformation in this sequence, e.g., the epimerization of the 9α-aldehyde **14c** to the 9β-aldehyde **15c** was performed in nearly quantitative yield although the monitoring of this reaction with TLC was deceiving since both epimers have the same R_f values. (±)-Muzigadial (**4**) was obtained via this 10-step procedure in an overall yield of 24% from **8**.

This novel approach is a valuable addition to the known methods for the synthesis of the insect-antifeedant drimanic sesquiterpenes. It enables the use of 2-decalones as starting compounds and the method is compatible with sensitive functional groups in the molecule. Especially the epimerization procedure for the 9α-aldehyde group can be considered as an increment of existing methods and may be useful for the synthesis of other terpenes with similar sets of functional groups like the spongiane-type diterpenes and the scarlarane-type sesterterpenes.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were determined on a Bruker CXP-300 or a Varian EM-390 spectrometer. Chemical shifts are reported in δ units with tetramethylsilane as the internal standard and in chloroform-*d* as the solvent, unless otherwise noted. Mass spectral data and HRMS measurements were obtained on a AEI MS 902 spectrometer, and GCMS analysis was performed on a VG Micro-mass 7070F spectrometer. Extracts were dried over anhydrous sodium sulfate prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. All reactions were routinely carried out under an inert atmosphere of nitrogen.

3,4,4aα,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethyl-3-oxonaphthalene-2-carboxaldehyde (9a). To an ice-cooled solution of 7.66 g (40 mmol) of benzene selenenyl chloride in 300 mL of dichloromethane were added 3.48 g (44 mmol) of pyridine and 8.88 g (40 mmol) of 3-(hydroxymethylene)-3,4,4a,5,6,7,8,8aα-octahydro-4aβ,8,8-trimethylnaphthalene-2(1*H*)-one[8-11] in 25 mL of dichloromethane. The reaction mixture was stirred for 1 h and washed with 25 mL of 4 N hydrochloric acid and with 50 mL of brine. The dichloromethane solution was cooled in ice, and 4.5 mL of 30% hydrogen peroxide was added in three portions with intervals of 15 min. The residue was purified by flash column chromatography on silica gel using 4:1 petroleum ether/ether as eluent to give 8.45 g (96%) of **9a** as a colorless oil.[14] ^{1}H NMR δ 0.97 (s, 3 H), 0.99 (s, 3 H), 1.20 (s, 3 H), 1.3–1.9 (m, 7 H), 2.50 (dd, J = 5.2, 1.5 Hz, 2 H), 7.34 (s, 1 H), 10.07 (s, 1 H).

6β,8aβ-Dimethyl-5-methylene-3,4,4aα,5,6,7,8,8a-octahydro-3-oxonaphthalene-2-carboxaldehyde (9c). Compound **9c** was prepared in 85% yield from ketone **8** in a two-step procedure. The formylation of **8** was performed by suspending 1.8 g (60 mmol) of sodium hydride in 150 mL of dry ether. To this suspension was added a mixture of 9.95 g (51.8 mmol) of **8** and 8.9 g (120 mmol) of ethyl formate in 150 mL of dry ether over

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30 min at room temperature. After being stirred for 16 h the resulting mixture was poured into water. The aqueous layer was separated, and the ethereal solution was extracted twice with 50 mL of 4 N aqueous potassium hydroxide. The combined alkaline solutions were acidified with concentrated hydrochloric acid and extracted with ether. The etheral solution was washed with brine and dried, and the ether was evaporated. The residue was crystallized from methanol to give 10.49 g (92%) of 4aβ,7β-dimethyl-3-(hydroxymethylene)-8-methylene-3,4,4a,5,6,7,8,8aα-octahydronaphthalene-2(1*H*)-one as a light yellow crystalline compound, mp 92–93 °C. ^{1}H NMR δ 0.67 (s, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.25–2.50 (m, 10 H), 4.63 (br s, 1 H), 4.83 (br s, 1 H), 8.60 (s, 1 H), 14.40 (br s, 1 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.91; H, 9.12. HRMS, calcd (M$^+$) m/e 220.1463, found m/e 220.1469.

The dehydrogenation of this compound was performed as described for **9a**. Compound **9c** was obtained in 93% yield as a yellow oil. ^{1}H NMR δ 1.00 (s, 3 H), 1.12 (d, J = 6 Hz, 3 H), 1.30–2.65 (m, 8 H), 4.66 (br s, 1 H), 4.97 (br s, 1 H), 7.60 (s, 1 H), 10.13 (s, 1 H). HRMS, calcd for $C_{14}H_{18}O_2$ (M$^+$) m/e 218.1307, found m/e 218.1310.

2-(Hydroxymethylene)-5,5,8aβ-trimethyl-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (10a). To a solution of 7.70 g (35 mmol) of compound **9a** in 100 mL of dioxane and 10 mL of water was added a solution of 2.47 g (38 mmol) of potassium cyanide in 10 mL of dioxane and 1 mL of water. The reaction mixture was stirred at room temperature for 30 min, and after that time the dioxane was evaporated. The residue was treated with 20 mL of 4 N aqueous potassium hydroxide and extracted with ether. The basic water solution was acidified with 5 mL of concentrated hydrochloric acid and extracted with ether. The ethereal solution was washed with brine and dried. The ether was evaporated and the residue was recrystallized from diisopropyl ether to give 7.90 g (91%) of **10a** as a white crystalline compound, mp 88–94 °C. ^{1}H NMR δ 0.94 (s, 3 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 1.3–1.9 (m, 9 H), 2.44 (dd, J = 6, 18 Hz, 2 H), 3.06 (s, 1 H), 8.77 (s, 1 H), 11.70 (br s, 1 H); HRMS, calcd for $C_{15}H_{21}NO_2$ (M$^+$) m/e 247.1572, found m/e 247.1572.

2-(Hydroxymethylene)-6β,8aβ-dimethyl-5-methylene-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (10c). Compound **10c** was prepared from **9c** as described for **10a**. Evaporation of the ether gave an oily residue, which was purified by column chromatography on silica gel using 60:40 petroleum ether/ether as eluent. Compound **10c** was obtained as a colorless oil in 76% yield. ^{1}H NMR δ 0.80 (s, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.30–2.65 (m, 8 H), 3.28 (s, 1 H), 4.72 (br s, 1 H), 4.94 (br s, 1 H), 8.87 (s, 1 H), 14.50 (br s, 1 H); HRMS, calcd for $C_{15}H_{21}NO_2$ (M$^+$) m/e 245.1416, found m/e 245.1419.

2(*E*)-[(Butylthio)methylene]-5,5,8aβ-trimethyl-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (11a). A solution of 7.41 g (30 mmol) of **10a**, 4 mL of 1-butanethiol and 25 mg of p-toluenesulfonic acid in 200 mL of dry benzene was refluxed for 3 h in a Dean–Stark apparatus. After cooling the reaction mixture was washed with 20 mL of saturated $NaHCO_3$ solution, with 20 mL of water, and with 20 mL of brine and dried. The benzene was evaporated, and the residue was crystallized from 3:7 diisopropyl ether/hexane to give 9.10 g (95%) of **11a** as a white crystalline compound, mp 75–76 °C. ^{1}H NMR δ 0.91 (s, 3 H), 0.93 (s, 3 H), 1.00 (s, 3 H), 0.9–2.1 (m, 14 H), 2.40 (dd, J = 6, 12 Hz, 2 H), 2.95 (t, J = 7 Hz, 2 H), 3.24 (s, 1 H), 7.96 (s, 1 H). Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.24; H, 9.15. Found: C, 71.13; H, 9.18. HRMS, calcd (M$^+$) m/e 319.1970, found m/e 319.1964.

2(*E*)-[(Butylthio)methylene]-6β,8aβ-dimethyl-5-methylene-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (11c). Compound **11c** was prepared from **10c** as described for **11a**. Crystallization from methanol gave **11c** in 79% yield as a white crystalline compound, mp 102–103 °C. ^{1}H NMR δ 0.83 (s, 3 H), 0.95 (t, J = 5 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H), 1.25–2.60 (m, 12 H), 2.97 (t, J = 6 Hz, 2 H), 3.47 (s, 1 H), 4.66 (br s, 1 H), 4.92 (br s, 1 H), 8.00 (s, 1 H). Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41. Found: C, 71.74; H, 8.67; N, 4.32. HRMS, calcd (M$^+$) m/e 317.1813, found m/e 317.1809.

2-Formyl-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1α-carbonitrile (12a). To a solution of 8.0 g (25 mmol) of **11a** in 50 mL of methanol was added 0.29 g (7.5 mmol) of sodium borohydride at 0 °C. The reaction mixture was stirred for 15 min, and the methanol was evaporated. Ether was added to the residue, and the solution was washed with water and with brine. The ether was evaporated and the reduction product was hydrolyzed without further purification.

The reduction product was dissolved in 75 mL of methanol and 25 mL of 4 N hydrochloric acid, and 8.13 g (30 mmol) of mercuric chloride was added. The reaction mixture was stirred at room temperature for 16 h and filtered. The methanol was evaporated, and 300 mL of ether was added. The ethereal solution was washed with saturated $NaHCO_3$ solution with brine and dried. The ether was evaporated and the residue was purified by column chromatography on silica gel using 75:25 petroleum ether/ether as eluent to give 5.1 g (88%) of **12a** as a white crystalline compound, mp 91–92 °C. ^{1}H NMR δ 0.90 (s, 3 H), 0.97 (s, 3 H), 1.00 (s, 3 H), 1.3–1.9 (m, 7 H), 2.2–2.6 (m, 2 H), 3.20 (s, 1 H), 7.03 (dd, J = 3, 4.5 Hz, 1 H), 9.47 (s, 1 H). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.11; H, 8.82. HRMS, calcd (M$^+$) m/e 231.1623, found m/e 231.1626.

6β,8aβ-Dimethyl-2-formyl-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (12c). Compound **12c** was prepared from **11c** as described for **12a**. After evaporation of the ether, the residue was crystallized from methanol to give a 94% yield of white crystalline **12c**, mp 120–121 °C. ^{1}H NMR δ 0.68 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.15–2.50 (m, 8 H), 3.42 (s, 1 H), 4.77 (br s, 1 H), 4.93 (br s, 1 H), 7.10 (dd, J = 1.5, 4.5 Hz, 1 H), 9.53 (s, 1 H). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.79; H, 8.51; N, 6.04. HRMS, calcd (M$^+$) m/e 229.1466, found m/e 229.1465.

2-(1,3-Dioxolan-2-yl)-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1α-carbonitrile (13a). A solution of 4.62 g (20 mmol) of **12a**, 5 mL of ethylene glycol, and 25 mg of p-toluenesulfonic acid in 50 mL of benzene was refluxed for 4 h in a Dean–Stark apparatus. The reaction mixture was cooled, 100 mL of ether was added, and the solution was washed with saturated $NaHCO_3$ solution and dried. The solvent was evaporated and the residue was purified by column chromatography on silica gel using 70:30 petroleum ether/ether as eluent. Compound **13a** was obtained in 90% yield as white crystals, mp 95–96 °C. ^{1}H NMR δ 0.97 (s, 9 H), 1.3–2.3 (m, 9 H), 2.81 (s, 1 H), 3.98 (m, 4 H), 5.27 (s, 1 H), 6.10 (dd, J = 3, 3.5 Hz, 1 H). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.43; H, 8.85. HRMS, calcd (M$^+$) m/e 275.1885, found m/e 275.1874.

6β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (13c). Compound **13c** was prepared from **12c** as described for **13a**. After evaporation of the ether the residue was crystallized from methanol to give a 91% yield of white crystalline **13c**, mp 108–110 °C. ^{1}H NMR δ 0.73 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 1.20–2.60 (m, 8 H), 3.00 (s, 1 H), 4.00 (m, 4 H), 4.70 (br s, 1 H), 4.87 (br s, 1 H), 5.28 (s, 1 H), 6.17 (dd, J = 3, 3.75 Hz, 1 H). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.46; H, 8.56; N, 4.94. HRMS, calcd (M$^+$) m/e 273.1729, found m/e 273.1726.

2-(1,3-Dioxolan-2-yl)-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1α-carboxaldehyde (14a). A solution of 2.75 g (10 mmol) of **13a** in 200 mL of dry toluene was cooled to −80 °C under nitrogen, and a solution of 15 mL of 1.5 M diisobutylaluminium hydride in toluene was added. The reaction mixture was stirred for 1 h at −80 °C and than poured into 250 mL of saturated NH_4Cl solution. The layers were separated, and the water solution was extracted 5 times with 100 mL of ether. The combined organic solutions were dried, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using 70:30 petroleum ether/ether as eluent to give 2.36 g (85%) of white crystalline **14a**, mp 65–66 °C.[17] ^{1}H NMR δ 0.95 (br s, 6 H), 0.97 (s, 3 H), 1.1–2.6 (m, 10 H), 3.7–4.0 (m, 4 H), 5.13 (s, 1 H), 6.20 (dd, J = 3, 4.8 Hz, 1 H), 9.53 (d, J = 5 Hz, 1 H). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.09; H, 9.42.

6β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carboxaldehyde (14c). Compound **14c** was prepared from **13c** via a modification of the procedure used for **14a**. After the reduction the temperature was raised to 0 °C, and 1 mL of water was added. The mixture was stirred for 15 min and 3 mL of a 4 N aqueous sodium hydroxide was added which gave a precipitate. This precipitate was

not filtered, but sodium sulfate was added to dry the mixture. After filtration the solvent was evaporated. The residue was purified by crystallization from methanol. Compound **14c** was obtained in 93% yield as a white crystalline compound, mp 80–81 °C. ^{1}H NMR δ 0.73 (s, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.25–2.50 (m, 8 H), 2.80 (d, J = 5 Hz, 1 H), 3.70–4.10 (m, 4 H), 4.72 (br s, 1 H), 4.85 (br s, 1 H), 5.17 (s, 1 H), 6.27 (dd, J = 4, 3 Hz, 1 H), 9.62 (d, J = 5 Hz, 1 H). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.92; H, 8.91. HRMS, calcd (M^+) m/e 276.1725, found m/e 276.1728.

2-(1,3-Dioxolan-2-yl)-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1β-carboxaldehyde (15a). To a solution of 2.08 g (18.6 mmol) of potassium *tert*-butoxide in 25 mL of *tert*-butyl alcohol under nitrogen was added 1.11 g (4 mmol) of the 1α-carboxaldehyde **14a**, and the reaction mixture was refluxed for 10 min. The solution was cooled, and water and ether were added. The water solution was extracted with ether, and the combined ethereal solutions were washed with brine and dried. The solvent was evaporated, and the residue was chromatographed on silica gel by using 8:2 petroleum ether/ether as eluent to give 1.03 g (93%) of **15a** as white crystals, mp 62–62.5 °C. ^{1}H NMR δ 0.87 (s, 3 H), 0.94 (s, 3 H), 1.10 (s, 3 H), 1.20–1.80 (m, 7 H), 2.15 (m, 2 H), 2.70 (m, 1 H), 3.80 (m, 4 H), 5.17 (s, 1 H), 6.20 (m, 1 H), 9.57 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.51; H, 9.43. HRMS, calcd (M^+) m/e 278.1882, found m/e 278.1882.

6β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1β-carboxaldehyde (15c). Compound **15c** was prepared from **14c** as described for **15a**. The residue was chromatographed on silica gel using 3:1 petroleum ether/ether as eluent and subsequently recrystallized from methanol to give a 90% yield of white crystalline **15c**, mp 59–60 °C. ^{1}H NMR δ 0.90 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 1.20–2.20 (m, 8 H), 2.88 (m, 1 H), 3.87 (m, 4 H), 4.70 (br s, 1 H), 4.88 (br s, 1 H), 5.22 (s, 1 H), 6.23 (m, 1 H), 9.53 (d, J = 5 Hz, 1 H). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.71; H, 8.68. HRMS, calcd (M^+) m/e 276.1725, found m/e 276.1728.

2-(1,3-Dioxolan-2-yl)-1α-hydroxy-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1β-carboxaldehyde (16a). A solution of 1.2 mmol of lithium diisopropylamide in 25 mL of THF under nitrogen was cooled to −80 °C, and a solution of 278 mg (1.0 mmol) of **15a** in 10 mL of THF was added. The reaction mixture was stirred for 30 min at −80 °C, and 650 mg (1.5 mmol) of MoO_5·HMPA·pyr complex was added. The solution was stirred for 1 h and then quenched with 100 mL of saturated Na_2SO_3 solution at −80 °C. The mixture was extracted with ether, and the ethereal solution was washed with brine and dried. The solvents were evaporated, and the residue was chromatographed on silica gel by using 4:1 petroleum ether/ether as eluent. Compound **16a** was obtained in 91% yield as a white solid, mp 96–97 °C. ^{1}H NMR δ 0.90 (s, 3 H), 0.97 (s, 3 H), 1.20 (s, 3 H), 1.30–2.30 (m, 9 H), 3.80 (m, 4 H), 5.17 (s, 1 H), 6.33 (dd, J = 2.2, 3.7 Hz, 1 H), 9.83 (s, 1 H); HRMS, calcd (M^+) m/e 294.1831, found m/e 294.1837.

6β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-1α-hydroxy-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1β-carboxaldehyde (16c). Compound **16c** was prepared from **15c** as described for **16a**. A 77% yield of white crystalline **16c** was obtained after crystallization from methanol, mp 106–107 °C. ^{1}H NMR δ 0.97 (s, 3 H), 1.04 (d, J = 6 Hz, 3 H), 1.30–2.30 (m, 7 H), 2.57 (m, 1 H), 3.85 (m, 5 H), 4.70 (br s, 1 H), 4.87 (br s, 1 H), 5.20 (s, 1 H), 6.35 (dd, J = 4, 4.3 Hz, 1 H), 9.73 (s, 1 H). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.05; H, 8.50. HRMS, calcd (M^+) m/e 292.1674, found m/e 292.1682.

1α-Hydroxy-1,4,4aα,5,6,7,8,8a-octahydro-5,5,8aβ-trimethylnaphthalene-1β,2-dicarboxaldehyde (Warburganal) (2). A solution of 149 mg (0.5 mmol) of **16a** in 10 mL of acetone and 3 mL of 1 N hydrochloric acid was stirred for 30 min at room temperature. The reaction mixture was poured into 100 mL of water and extracted 4 times with 50 mL of ether. The ethereal solution was washed with saturated $NaHCO_3$ solution and with brine and dried. The solvent was evaporated and the residue was chromatographed on silica gel by using 7:3 petroleum ether/ether as eluent to give 102 mg (81%) of warburganal (**2**) as white crystals, which were recrystallized from hexane, mp 96–97 °C (lit. 96–98 °C).[3e] ^{1}H NMR δ 0.93 (s, 3 H), 0.99 (s, 3 H), 1.08 (s, 3 H), 7.27 (dd, J = 2.5, 6 Hz, 1 H), 9.40 (s, 1 H), 9.73 (s, 1 H); HRMS, calcd (M^+) m/e 250.1569, found m/e 250.1572.

6β,8aβ-Dimethyl-1α-hydroxy-5-methylene-1,4,4aα,5,6,7,-8,8a-octahydronaphthalene-1β,2-dicarboxaldehyde (Muzigadial) (4). Muzigadial (**4**) was prepared from **16c** as described for **2**. Muzigadial (**4**) was obtained in 87% yield after crystallization from hexane, mp 105–106 °C (lit. 115–118 °C).[5] ^{1}H NMR δ 0.87 (s, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.30–2.30 (m, 6 H), 2.53 (m, 2 H), 4.05 (s, 1 H), 4.75 (br s, 1 H), 4.93 (br s, 1 H), 7.23 (dd, J = 3.2, 2.5 Hz, 1 H), 9.43 (s, 1 H), 9.65 (s, 1 H). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.15. HRMS, calcd (M^+) m/e 248.1412, found m/e 248.1413. A pronounced NOE effect of approximately 15% (lit. 14%)[5] was observed between the angular methyl and the 1β-carboxaldehyde group.

1,4,4aα,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethylnaphthalene-1β,2-dicarboxaldehyde (Polygodial) (1). A solution of 60 mg (0.2 mmol) of **15a** in acetone was treated with 1 mL of 1 N hydrochloric acid. After being stirred for 30 min the reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with brine and dried. The solvent was evaporated and the residue was chromatographed on silica gel by using 4:1 petroleum ether/ether as eluent. A yield of 42 mg (84%) of polygodial (**1**) was obtained, mp 92–93 °C (lit. 93–94 °C).[2b] ^{1}H NMR δ 0.93 (s, 3 H), 0.96 (s, 3 H), 0.97 (s, 3 H), 1.10–1.60 (m, 6 H), 1.85 (m, 1 H), 2.43 (m, 2 H), 2.83 (m, 1 H), 7.13 (m, 1 H), 9.47 (s, 1 H), 9.54 (d, J = 6 Hz, 1 H); HRMS, calcd (M^+) m/e 234.1620, found m/e 234.1622.

1,4,4aα,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethylnaphthalene-1α,2-dicarboxaldehyde (Isotadeonal) (20). A solution of 280 mg (1 mmol) of **14a** and 25 mg of *p*-toluenesulfonic acid in 20 mL of acetone and 5 mL of water was stirred for 2 h at room temperature. The acetone was evaporated, and water and ether were added. The water solution was extracted with ether, and the combined ethereal solutions were washed with saturated $NaHCO_3$ solution, with water, and with brine and dried. The ether was evaporated and the residue was chromatographed on silica gel by using 7:3 petroleum ether/ether as eluent to give 210 mg (90%) of **20** as white crystals, mp 66–67 °C (lit. 60–61.5 °C).[3a] ^{1}H NMR δ 0.91 (s, 3 H), 0.93 (s, 3 H), 0.96 (s, 3 H), 1.05–2.45 (m, 9 H), 3.23 (br s, 1 H), 7.10 (dd, J = 3, 5 Hz, 1 H), 9.37 (s, 1 H), 9.82 (d, J = 3 Hz, 1 H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.29; H, 9.61. HRMS, calcd (M^+) m/e 234.1620, found m/e 234.1622.

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Registry No. (±)-**1**, 33118-34-2; (±)-**2**, 71537-00-3; (±)-**4**, 100484-67-1; (±)-**8**, 96617-08-2; (±)-**9a**, 56666-27-4; (±)-**9b**, 92121-91-0; (±)-**9c**, 112320-74-8; (±)-**10a**, 112320-75-9; (±)-**10b**, 112320-84-0; (±)-**10c**, 112320-76-0; (±)-**11a**, 112320-77-1; (±)-**11b**, 112320-85-1; (±)-**11c**, 112372-85-7; (±)-**12a**, 112320-78-2; (±)-**12b**, 112320-86-2; (±)-**12c**, 112347-63-4; (±)-**13a**, 112320-79-3; (±)-**13b**, 112320-87-3; (±)-**13c**, 112320-80-6; (±)-**14a**, 71493-15-7; (±)-**14b**, 112320-88-4; (±)-**14c**, 112320-81-7; (±)-**15a**, 79801-45-9; (±)-**15b**, 112320-89-5; (±)-**15c**, 112320-82-8; (±)-**16a**, 71493-16-8; (±)-**16b**, 112347-64-5; (±)-**16c**, 112320-83-9; (±)-**17a**, 112347-65-6; (±)-**18**, 112320-90-8; (±)-**19**, 112320-91-9; (±)-**20**, 71536-99-7; (±)-**21**, 112320-92-0; (±)-**22**, 112320-93-1; (±)-3-(hydroxymethylene)-3,4,4a,5,6,7,8,8aα-octahydro-4aβ,8,8-trimethylnaphthalen-2-(1*H*)-one, 56666-26-3; (±)-4aβ,7β-dimethyl-3-(hydroxymethylene)-8-methylene-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one, 112347-33-8; (±)-3-(hydroxymethylene)-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one, 102728-11-0.

Supplementary Material Available: Experimental details and analytical data for compounds **9b–16b**, **17a**, **18**, **19**, **21**, and **22** (4 pages). Ordering information is given on any current masthead page.