Synthetic Studies on Terpenoid Compounds. XXXIII.[1] A Total Synthesis of (±)-15,16-Epoxy-*cis*-cleroda-3,13(16),14-triene

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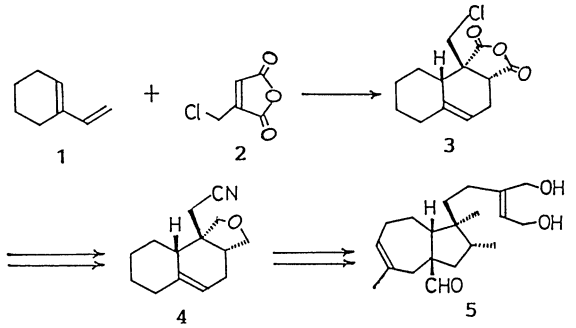
A total synthesis of title *cis*-clerodane diterpene **9** has been achieved starting from a bicyclic intermediate **4**, which was developed previously by us. Firstly the compound **4** was converted by five steps to octalone derivative **6**, of which angular methylation, with the protection of 3-methylene group, afforded *cis*-decalone **7**. Appendage of 3-furyl group and deoxygenation at C-20 carbon atom transformed the compound **7** to furanoid ketone **8**. Methylenation of **8** followed by the double bond isomerization led to the completion of the synthesis.

Previously we reported that the Diels-Alder reaction of 1-vinylcyclohexene (**1**) with (chloromethyl)maleic anhydride (**2**) afforded stereoselectively an adduct **3**, which has appropriate stereochemistry and functionality for the synthesis of clerodane diterpenoids.[2,3] Starting from this intermediate **3** a total synthesis of portulal (**5**), a diterpene with the clerodane substitution, has been accomplished[5] (Scheme 1). This paper deals with the synthesis of a more typical clerodane diterpenoid from the adduct **3**.[6]



Scheme 1.

The selected natural product as the target is 15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**9**), which was isolated from *Solidago arguta* Ait.[7] Its structure has been confirmed by a single crystal X-ray analysis of the related compounds.[8] The compound **9** was chemically correlated with both *cis*[9] and *trans*[10,11] clerodane diterpenoids, representing a pivotal role in this class of natural products. We achieved already the total synthses of the compound **9** using two methods (the second[4] and the third generation approaches[12] for the stereoselective construction of clerodane skeleton).

This work represents the demonstration of the first generation approach to be feasible for synthesis of a

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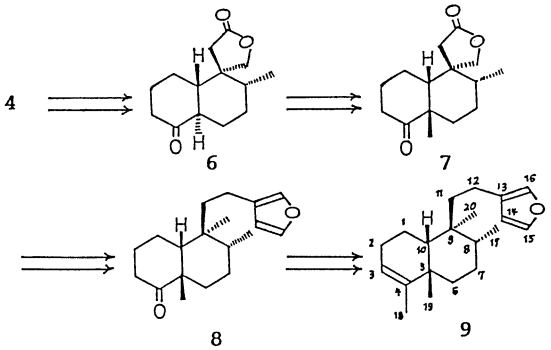
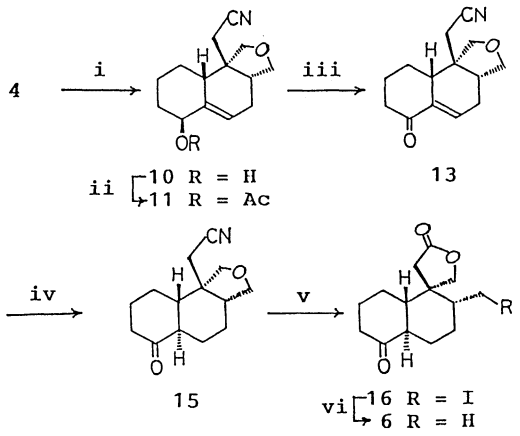


Scheme 2.

cis-clerodane diterpene. The Diels-Alder adduct **3** has been converted to an intermediate **4** by an efficient three steps process (86% overall yield) in the synthesis of portulal (**5**) and our synthesis started from **4**.

Synthetic operations necessary for the synthesis of the target compound **9** from **4** are: (1) construction of the side chain by the appendage of 3-furyl ring and deoxygenation of C-17 and C-20 carbon atoms[13] to form methyl groups, (2) introduction of a *cis* angular methyl group and (3) elaboration of a vinyl methyl grouping in A ring from C-4 carbonyl. With reference to the experience obtained in the synthesis of **5**, a synthetic sequence shown in Scheme 2 was designed. Since $\Delta^{5,6}$ double bond has propensity to move into the tetrasubstituted angular position specially in acidic conditions, it is to be reduced after the allylic oxygenation at C-4 and, subsequent reactions involving acid treatment and reduction will lead to the formation of a keto γ-lactone **6** (phase 1). Then the angular methyl group is introduced by a appropriate means in cis manner (phase 2). The 3-furyl group is appended to C-12 and the attendantly formed C-20 hydroxymethyl group is converted to a methyl group (phase 3). Finally the attachment of the methyl group at C-4, accompanied by the double-bond formation between C-3 and C-4, will give the target compound **9** (phase 4).

Thus our study initiated from the allylic oxidation



Scheme 3. Reagents: i, SeO_2, C_5H_5N-H_2O or EtOH-H_2O (9:1), ii, Ac_2O, C_5H_5N; iii, MnO_2, $CHCl_3$; iv, H_2, Pd-C, EtOH; v, 57% HI-H_2O, P, AcOH; vi, Zn,AcOH.

of the starting material **4**. Treatment of **4** with selenium dioxide in ethanol or pyridine containing 5—10% water under reflux gave an allylic alcohol **10** in modest yields (50—30%) with variable amount of the recovered starting material (35—20%). The oxidation under Sharpless modification[14] afforded the product **10** in comparable yields with less recovery of **4**. In order to confirm the site of the hydroxylation (at C-4 rather than at C-6) the derived acetate **11** was oxidized with Collins' procedure. The obtained conjugated ketone **12** exhibited in the ^{1}H NMR spectrum the signals due to C-17 methylene protons at deshielded positions (δ 4.31 and 3.91) than the corresponding signals (δ 3.94 and 3.53) of **11**, which indicated the introduction of the carbonyl group in the adjacent C-7 position in the former. Configuration of the hydroxyl group in the allylic alcohol **10** is assigned to be β by assumption of the reagent attack from less hindered convex side and this was corroborated by the ^{1}H NMR evidence that the half length-width of the resonance due to the proton of the hydroxyl-bearing methine group was 6 Hz. Thus the oxidizing agent would attack the C-5, C-6 double bond from β-side of **4** to form $\Delta^{4,5}$-6-seleninic acid which afford the allylic alcohol **10** by [2,3]sigmatropy and subsequent hydrolysis of a resulting selenium (II) ester.[15]

The oxidation of **10** to the conjugated ketone **13** was performed by the agency of manganese dioxide in chloroform in 68% yield. The use of chromium trioxide (Jones, Collins or Sarett reagents) gave erratic results, being accompanied by the migration of the

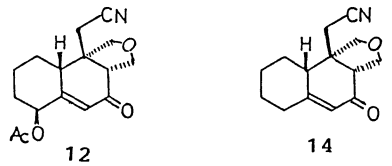


Fig. 1.

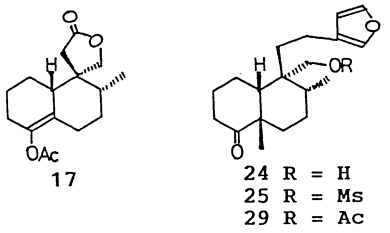
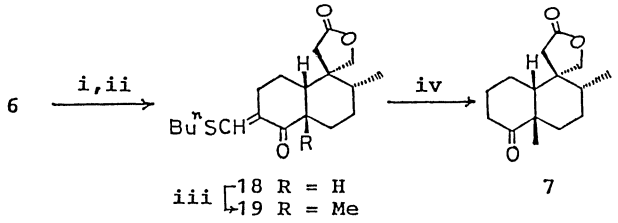


Fig. 2.

double bond to the site of ring fusion or allylic rearrangement. As expected the product **13** (λ_{max} 250 nm) was different from the $\Delta^{5,6}$-7-ketone **14** (λ_{max} 246 nm) obtained by the oxidation of **4** with Sarett reagent.[16] The saturated ketone **15** obtained from **13** by catalytic hydrogenation was treated with hydroiodic acid in acetic acid under reflux to furnish iodide **16** smoothly via regioselective cleavage of the tetrahydrofuran ring and concomitant hydrolysis of the cyano group. The reduction of the iodide **16** produced the first subgoal compound **6** in an overall yield of 82% from **13**.

Next phase of the synthesis was the introduction of a methyl group at the angular position. Our initial tactics for this object was the carbene addition to the enol acetate **17** derived from **6** and subsequent cleavage of the cyclopropane ring,[17] which was frustrated since **17** was unreactive to the Simmon-Smith and related reagents in various conditions.[18] The reason for such resistancy would be ascribed to the presence of steric hindrance even for the attack from the convex β-side by the carbonyl methylene group of the lactone ring. Then the enolate alkylation after blocking of C-3 methylene group by Ireland's procedure[19] was investigated. The derived butylthiomethylene ketone **18** was much harder to alkylate as anticipated. However, we found that the methylation could be achieved by the use of a large excess of base. Thus the reaction of **18** with methyl iodide in the presence of potassium *t*-butoxide (13 equivalents) resulted in 29% conversion to the methylated product **19** as revealed by the ^{1}H NMR inspection of crude product. Eventually by the use of potassium *t*-pentyloxide[20] (25—30 equivalents) the methylated product **19** was obtained in a yield up to 74%.

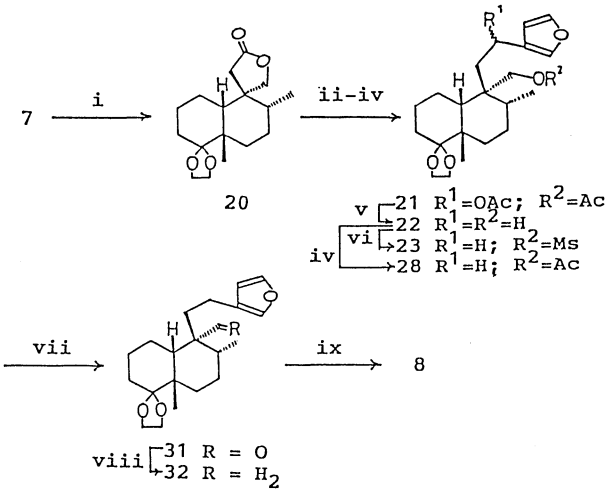
Deprotection of **19** by alkaline hydrolysis afforded the methylated keto lactone **7**. The obtained product



Scheme 4. Reagents: i, HCO_2Et, NaH, C_6H_6; ii, *n*-BuSH, TsOH, C_6H_6, Δ; iii, MeI, *t*-$C_5H_{11}OK$, *t*-$C_5H_{11}OH$; iv, H_2O, KOH, $HOCH_2CH_2OH$, Δ.

represents single stereoisomer and its configuration is presumed to be *cis* since the alkylation of **18** would occur from less hindered β-side. The methylation of 2-(butylthiomethylene)-1-decalone is reported to give *cis* and *trans* products in comparable ratio,[21] whereas in the reaction of 2-benzylidene derivative they are produced in yields of 68 and 23%. In our case the β-attack would become exclusive due to reinforcement of the steric hindrance in α-side by the hydroxymethylene group of the spiro-γ-lactone ring. The confirmative evidence for the configuration of ring junction was obtained in the reactions at later stage (vide infra).

With the keto lactone **7** in hand we set forth the third phase of the synthesis, namely the construction of the side chain and the amendment of C-20 to a methyl group. The former operation was performed in the same way as established in the synthesis of portulal.[5] After the protection of the C-4 keto group as a ethylene acetal the compound **7** was allowed to react with 3-furyllithium and the produced furoyl derivative was reduced with sodium bis(2-methoxyethoxy)aluminum hydride to corresponding alcohol to avoid the easy dehydration via a five-membered hemiacetal.[5] Then the reduction product was acetylated to give a diacetate **21**. Removal of the allylic acetoxyl group in **21** by Birch reduction completed the construction of the side chain to give furanoid compound **22**. For the deoxygenation of C-20 carbon atom in **22** it was converted to mesylate **23** and then treated with zinc and sodium iodide in hot hexamethylphosphoric triamide (HMPA),[22] but only a complex mixture of products was obtained. When the same reduction procedure was carried out on the corresponding free ketone **25** to avoid the conceived steric intervention caused by the ethylene acetal



Scheme 5. Reagents: i, $HOCH_2CH_2OH$, TsOH, C_6H_6; ii, 3-furyllithium, Et_2O; iii, $NaAl(OCH_2CH_2OMe)_2H_2$, C_6H_6; iv, Ac_2O, C_5H_5N; v, Li, liq.NH_3, THF; vi, MsCl, C_5H_5N; vii, $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2; viii, $NH_2NH_2 \cdot H_2O$, KOH, $HOCH_2CH_2OH$; ix, 1M HCl.

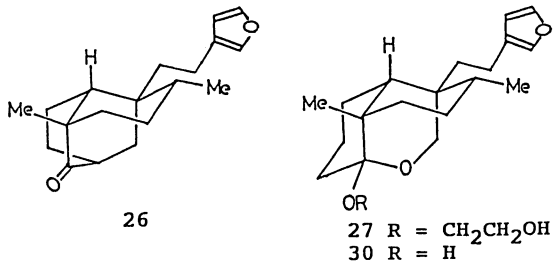
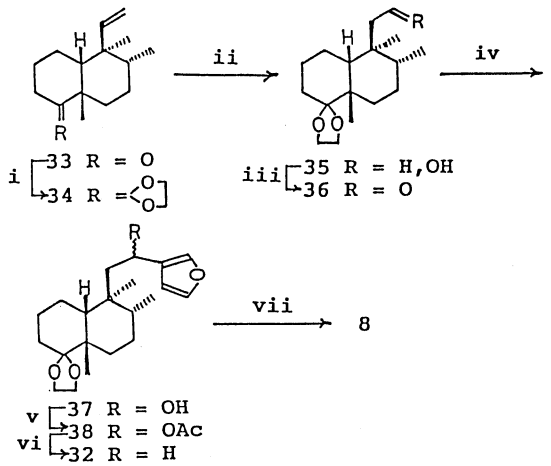


Fig. 3.

group, a demesylated product, $C_{19}H_{26}O_2$, $\nu_{C=O}$ 1725 cm^{-1} was obtained in 68% yield. Its molecular composition contained the hydrogen atoms less by two than expected for the desired reduction. The absence of double bond additional to those in the furan ring suggested a tricyclic structure **26**, which would form via intramolecular displacement of the mesylate group by enolate anion rather than by iodide anion (neopentyl-type mesylate !). This result provides a conclusive support for the *cis*-ring junction of **25**, since the cyclization reaction is possible only in such structure. The steric congestion inherent in *cis*-decalin structure was manifested also in the other type of intramolecular interactions. On acidic treatment the compound **22** furnished a product **27** formed by intramolecular transacetalization. Although the removal of the acetal group in the acetate **28** corresponding to **22** afforded the ketone **29** smoothly, treatment of the latter with methyllithium produced a hemiacetal **30** instead of alcohol formation. The conversion of the C-20 hydroxymethyl in **22** to a methyl group was effected by the transformation of **22** to an aldehyde **31** followed by reduction according to the Huang-Minlon procedure. Deprotection of the product gave the crucial subgoal compound **8**.

Later this compound was found to be obtainable



Scheme 6. Reagents: i, $HOCH_2CH_2OH$, CSA, C_6H_6; ii, $CH_3CH(CH_3)C(CH_3)_2BH_2$, THF then H_2O_2, NaOH; iii, PCC, CH_2Cl_2; iv, 3-furyllithium, Et_2O; v, Ac_2O, C_5H_5N; vi, Li, liq.NH_3, THF; vii, 1 M HCl, Me_2CO.

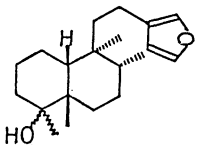


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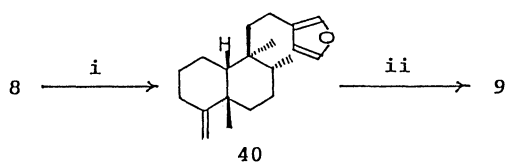
Fig. 4.

more conveniently from the decalone derivative **33** which was effectively synthesized by our third generation approach[12] as shown in Scheme 6. After protection of the ketonic group the vinyl side chain was transformed to a 2-hydroxyethyl group by hydroboration and oxidation to afford alcohol **35**, which was oxidized to aldehyde **36**. The appendage of 3-furyl group to **36** in the same way as before and subsequent deprotection led to the formation of the furanoid ketone **8**.

Having explored the synthetic path to the compound **8** we proceeded to the last phase of our synthesis—namely the introduction of a methyl group at C-4 and the associated formation of a double bond between C-3 and C-4. An obvious tactics to this task, the methylation with a suitable organometallic reagent followed by dehydration of the resulting tertiary hydroxyl group, was ineffective, since the reaction of the ketone **8** with methylmagnesium iodide or methyllithium afforded only a trace of the corresponding tertiary alcohol **39**. The result indicates that a profound enolization instead of the methylation by the organometallic reagents occurs due to the highly hindered nature of the carbonyl group in the compound **8**. This discouraging situation was circumvented by the use of Nozaki's reagent,[23] which was recognized recently to be nicely effective for the methylenation of easily enolizable carbonyl group.[24] Its reaction with the ketone **8** proceeded also smoothly to give the methylene compound **40** in 62% yield. The isomerization of the double bond[25] in **40** to *endo* position was effected by the application of the Brown's procedure.[26] The product obtained after purification by silica-gel chromatography was identical with the natural *cis*-clerodane diterpene **9** in spectral comparison.

In conclusion a total synthesis of (±)-15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**9**) has been accomplished starting from the intermediate **4** previously developed for the stereoselective construction of clerodane skeleton. The fourth stereogenic center at angular position was introduced with complete stereoselectivity by enolate alkylation of a derived C-4 bicyclic ketone **18** in which C-3 methylene group was protected. A problem associated with introduction of C-18 methyl group in A ring due to an extensive enolization of the C-4 ketone group was overcomed by the use of Nozaki's methylenation procedure. Thus the utility of our first generation intermediate for the synthesis of clerodane diterpenoids has been demonstrated.



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Scheme 7. Reagents: i, Zn-CH_2Br_2-$TiCl_4$, CH_2Cl_2; ii, $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$.

Experimental

All melting points were measured on a Yanagimoto micro hot-stage appratus MP-S2 and are uncorrected. IR spectra were recorded on a JASCO IRA-1 and an A-100 spectrometers. ^{1}H NMR spectra were taken, on a JEOL PS-100, a Hitachi R-90H, and a JEOL FX-100 spectrometers. ^{13}C NMR spectra were measured on GX-400 (100 MHz) spectrometer. High-resolution mass spectra were measured on a JEOL D-300 spectrometer. Microanalyses were carried out at the Microanalytical Laboratory, Faculty of Science, Osaka City University. Merck Kieselgel (70—230 mesh) or Fuji-Davison BW-820MH silica gel were used for column chromatography.

(3a*R,6*S**,9a*R**,9b*S**)-1,3,3a,4,6,7,8,9,9a,9b-Decahydro-9b-(cyanomethyl)naphtho[1,2-*c*]furan-6-ol (10).** To a solution of the nitrile **4** (2.0 g, 9.22 mmol) in pyridine (25 ml) and water (8 ml) was added selenium dioxide (1.3 g, 11.7 mmol) and the mixture was heated in an oil bath kept at 80 °C for 3 h. After dilution with water the product was extracted with ether and the organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was separated by silica-gel chromatography. Following to fractions of the recovered starting material (9 : 1 benzene-ethyl acetate), the title alcohol **10** was eluted by 2 : 1 benzene-ethyl acetate and obtained as a light yellow oil (1.05 g, 49%). The product was still contaminated with small amount of impurities containing selenium. Ultimate purification could be performed by conversion to the acetate **11**, recrystallization and subsequent alkaline hydrolysis (NaOH, MeOH, H_2O): IR (CCl_4) 3450, 2260, and 1065 cm^{-1}; ^{1}H NMR (CCl_4) δ=2.50 (2H, s, CH_2CN), 3.34, 3.60 (2H, ABq, J=9 Hz, CH_2O), 3.52 (1H, d, J=8 Hz, $CHCH_\alpha H_\beta O$), 3.93 (1H, dd, J=4.5, 8 Hz, $CHCH_\alpha H_\beta O$), and 4.12 (1H, m, $W_{\frac{1}{2}}$=6 Hz, $CHOH$), 5.49 (1H, m, CH_2CH=).

(3a*R,6*S**,9a*R**,9b*S**)-1,3,3a,4,6,7,8,9,9a,9b-Decahydro-6-acetoxy-9b-(cyanomethyl)naphtho[1,2-*c*]furan (11).** The above allylic alcohol **10** (1.05 g, 4.51 mmol) was acetylated with acetic anhydride (3 ml) and pyridine (3 ml) at room temperature for 20 h. The product obtained by usual working-up was recrystallized from hexane-benzene to give the acetate **11** as plates, mp 120—123 °C: IR (CCl_4) 2250, 1740, 1240, and 1065 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.98 (3H, s, AcO), 2.46 (2H, s, CH_2CN), 3.34, 3.62 (2H, ABq, J=9 Hz, CH_2O), 3.53 (1H, d, J=8 Hz, $CHCH_\alpha H_\beta O$), 3.94 (1H, dd, J=4,8 Hz, $CHCH_\alpha H_\beta O$), 5.22 (1H, m, $W_{\frac{1}{2}}$=6 Hz, $CHOAc$), and 5.66 (1H, m, CH_2CH=C). Found: C, 69.80; H, 7.67; N, 4.94%. Calcd for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09%.

(3a*R,6*S**,9a*R**,9b*S**)-1,3,6,7,8,9,9a,9b-Octahydro-6-acetoxy-9b-(cyanomethyl)naphtho[1,2-*c*]furan-4(3a*H*)-one (12).** To a stirred mixture of chromium trioxide (600 mg, 6

mmol), pyridine (1.2 ml) and dichloromethane (10 ml) was added a solution of the acetate **11** (47 mg, 0.17 mmol) in dichloromethane, and total mixture was allowed to react at room temperature for 2 days. Supernatant solution was decanted and the precipitate was triturated throughly with chloroform. The combined solution and extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$. The residue left after the evaporation of the solvent was purified by chromatography (5:1 benzene-ethyl acetate) to give the title ketone **12** as a colorless oil (9 mg, 18%), IR (CCl_4) 1750, 1685, 1230, and 1065 cm^{-1}; ^1H NMR (CCl_4) δ=2.06 (3H, s, Me), 2.54 (2H, s, CH_2CN), 3.40, 3.53 (2H, ABq, J=9 Hz, CH_2-O), 3.94 (1H, dd, J=7.5, 9.5 Hz, $CHCH_\alpha H_\beta$), 4.31 (1H, dd, J=3, 9.5 Hz, $CHCH_\alpha H_\beta$-O), 5.36 (1H, m, $W_{\frac{1}{2}}$=6 Hz, CHOAc), and 5.98 (1H, d, J=2 Hz, CHC=CH).

(3a*R,9a*R**,9b*S**)-1,3,3a,4,8,9,9a,9b-Octahydro-9b-(cyanomethyl)naphtho[1,2-*c*]furan-6(7*H*)-one (13).** A solution of the allylic alcohol **10** (3.0 g, 12.8 mmol) in chloroform (20 ml) was stirred with active manganese dioxide[27] (33 g) at room temperature overnight. The solid material was filtered with aid of Celite and washed throughly with ethyl acetate. The combined filtrate and washings were concentrated in vacuo and the residue was separated by silica-gel chromatography (5:1 benzene-ethyl acetate). With recovery of the starting material **10** (599 mg, 20%) the title ketone **13** was obtained as an oil (1.622 g, 54%), UV(EtOH) 250 nm (ε 5750); IR (CCl_4) 2250, 1075, 950, and 900 cm^{-1}; ^1H NMR. (CCl_4) δ=2.59 (2H, s, CH_2CN), 3.22 (1H, dd, J=7.9 Hz, $CH_2CH_\alpha H_\beta O$), 3.39 (2H, s, CH_2-O), 4.08 (1H, dd, J=7.9 Hz, $CH_2CH_\alpha H_\beta O$), and 7.01 (1H, m, CH_2CH=).

(3a*R,9a*R**,9b*S**)-1,3,6,7,8,9,9a,9b-Octahydro-9b-(cyanomethyl)naphtho[1,2-*c*]furan-4(3a*H*)-one (14).** To the Sarett reagent, prepared from CrO_3 (500 mg, 5 mmol) and anhydrous pyridine (5 ml) was added a solution of the nitrile **4** (90 mg, 0.41 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with ether and the precipitate was filtered off. The filtrate was washed with brine and dried over $MgSO_4$. The residue left after evaporation of the solvent was chromatographed on a column of silica-gel. After recovery of the starting material (82 mg) eluted with 20:1 benzene-ethyl acetate, elution with 5:1 benzene-ethyl acetate yielded the title ketone **14** as a colorless oil (8 mg), UV(EtOH) 246 nm (ε 7900); IR (CCl_4) 2250, 1680, and 1065 cm^{-1}; ^1H NMR (CCl_4) δ=2.55 (2H, s, CH_2CN), 3.36, 3.47 (2H, ABq, J=8.5, CH_2-O), 3.92 (1H, dd, J=7,9 Hz, $CHCH_\alpha H_\beta$-O), 4.33 (1H, dd, J=2,9 Hz, $CHCH_\alpha H_\beta$-O), and 5.78 (1H, m, $W_{\frac{1}{2}}$=4 Hz, COCH=C).

(3a*R,5a*R**,9a*R**,9b*S**)-1,3,3a,4,5,5a,8,9,9a,9b-Decahydro-9b-(cyanomethyl)naphtho[1,2-*c*]furan-6(7*H*)-one (15).** A solution of the conjugated ketone (306 mg, 1.31 mmol) in ethanol (50 ml) was stirred in the presence of 10% palladium-on-charcoal under hydrogen atmosphere for 21 h. After removal of the catalyst by filtration the solvent was evaporated and the oily residue (285 mg, 93%) was crystallized from benzene-petroleum ether to give the saturated ketone **15** as colorless prisms, mp 155—157 °C: IR (CCl_4) 2240, 1715, and 1070 cm^{-1}, ^1H NMR (CCl_4) δ=3.52 (2H, s, CH_2CN), 3.39, 3.62 (2H, ABq, J=9 Hz, CH_2-O), 3.57 (1H, dd, J=4.9 Hz, $CH_2CH_\alpha H_\beta$-O), and 3.97 (1H, dd, J=7,9 Hz, $CH_2CH_\alpha H_\beta O$). Found: C, 72.13; H, 8.25; N, 5.99%. Calcd for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00%.

(1'*R,2'*R**,4'a*R**,8'a*R**)-2',3',4',4'a,6',7',8',8'a-Octahydro-2'-methylspiro[furan-3(2*H*),1'(5'*H*)-naphthalene]-5(4*H*),5'-dione (6).** A solution of the decalone **15** (526 mg, 2.26 mmol) in acetic acid (4 ml) was mixed with 57% aqueous hydroiodic acid (4 ml) and red phosphorus (1 g), and the mixture was heated at 120—130 °C for 4 h. After dilution with water the reaction mixture was filtered and the filtrate was extracted with benzene. The combined extracts were washed successively with water, saturated aqueous $NaHCO_3$, aqueous Na_2SO_3 and brine, and dried ($MgSO_4$). Evaporation of the solvent afforded (1'*S**,2'*R**,4'a*R**,8'a*R**)-2',3',4',4'a,6',7',8',8'a-octahydro-2'-iodomethylspiro-[furan-3(2*H*),1'(5'*H*)-naphthalene]-5(4*H*),5'-dione (**16**) as a colorless oil (665 mg, 81%), IR ($CHCl_3$) 1770, 1710, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.48, 2.67 (2H, ABq, J=18.5 Hz, CH_2CO_2), 2.82 (1H, d, J=10 Hz, $CHCH_\alpha H_\beta I$), 3.47 (1H, dd, J=2.5, 10 Hz, $CHCH_\alpha H_\beta I$), and 4.07, 4.28 (2H, ABq, J=10 Hz, CH_2OCO). The iodide **16** (665 mg) dissolved in acetic acid (13 ml) was stirred with zinc dust (3 g) at room temperature for 16 h. The inorganic material was filtered off and the filtrate diluted with benzene was washed successively with water, aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography (10:1 benzen-ethyl acetate) afforded the title lactone **6** as crystals (416 mg, 79% from **15**). Recrystallization from benzene-hexane gave pure **6**, mp 108—110 °C: IR ($CHCl_3$) 1770, 1710, 1180, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.99 (3H, d, J=6.5 Hz, CHMe), 2.38, 2.58 (2H, ABq, J=18 Hz, CH_2CO_2), and 4.15, 4.25 (2H, ABq, J=11.5, CH_2COO). Found: C, 71.21; H, 8.56%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.

(1'*R,2'*R**,4'a*R**,8'a*R**)-2',3',4',4'a,6',7',8',8'a-Octahydro-2'-methyl-6'-(butylthiomethylene)spiro[furan-3(2*H*),1'(5'*H*)-naphthalene]-5(4*H*),5'-dione (18).** To a solution of the keto lactone **6** (565 mg, 2.39 mmol) in benzene (1 ml) was stirred with sodium hydride (50% oil dispersion 226 mg, 4.7 mmol) and ethyl formate (0.34 ml, 4.2 mmol) at room temperature for 3 h. The reaction mixture was diluted with benzene and shaked three times with water. The combined aqueous layers were separated and acidified with 1M HCl. The product was extracted with benzene and the extract solution was washed with brine, and dried ($MgSO_4$). Evaporation of the solvent left a light yellow oil (553 mg), IR ($CHCl_3$) 3500—2300, 1770, 1630, 1580, and 1180 cm^{-1}, which was dissolved in benzene (50 ml) and treated with 1-butanethiol (2.0 ml, 18.6 mmol) in the presence of a catalytic amount of *p*-toluenesulfonic acid under reflux and with removal of water formed (Dean-Stark apparatus) for 3 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude product, obtained by evaporation of the solvent, was chromatographed on a column of silica gel (23 g) and eluted with 19:1 benzene-ethyl acetate to give the butylthiomethylene derivative **18** as crystals (664 mg, 82%). Recrystallization from ether-petroleum ether afforded pure **18** as colorless needles, mp 101—103 °C: IR ($CHCl_3$) 1770, 1650, 1530, 1180, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.94 (3H, t, J=7 Hz, CH_2Me), 1.00 (3H, d, J=7 Hz, CHMe), 2.56 (2H, s, CH_2CO_2), 2.89 (2H, t, J=7 Hz, CH_2CH_2S), 4.19 (2H, s, CH_2OCO), and 7.67 (1H, m, CH_2C=CHS). Found: C, 67.81; H, 8.37%. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.37%.

(1'*R,2'*R**,4'a*S**,8'a*R**)-2',3',4',4'a,6',7',8',8'a-Octahydro-2',4'a-dimethylspiro[furan-3(2*H*),1'(5'*H*)-naphthalene]-5(4*H*),5'-dione (7).** Potassium metal (420 mg, 10.7 mmol)

was dissolved in anhydrous *t*-pentyl alcohol (40 ml) under argon atmosphere and to this solution was added the butylthiomethylene derivative **18** (150 mg, 0.44 mmol). After 10 min methyl iodide (2.2 ml, 35.5 mmol) was added and the mixture was stirred at room temperature for 15.5 h. The reaction mixture was quenched by the addition of ice-water and acidified with 1 M HCl. The product, obtained by extraction with benzene, was chromatographed on a column of silica gel and elution with 20:1 benzene-ethyl acetate furnished (1′*R**,2′*R**,4′a*S**,8′a*R**)-2′,3′,4′,4′a,6′,7′,8′,8′a-octahydro-2′,4′a-dimethyl-6′-(butylthiomethylene)-spiro[furan-3(2*H*),1′(5′*H*)-naphthalene]-5(4*H*),5′-dione (**19**) as an oil (117 mg, 74%), IR ($CHCl_3$) 1770, 1655, 1530, and 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (3 H, t, J=7 Hz, $CH_2\underline{Me}$), 0.96 (3H, d, J=7 Hz, $CH\underline{Me}$), 1.20 (3H, s, Me), 2.51 (2H, s, CH_2CO_2), 2.89 (2H, t, J=7 Hz, $CH_2\underline{CH_2}S$), 3.93, 4.01 (2H, ABq, J=10.5 Hz, CO_2CH_2), and 7.66 (1H, m, CH_2=C$\underline{CH}$S). The butylthiomethylene compound **19** (64 mg, 0.18 mmol) was heated with KOH (1.0 g), water (9 ml) and ethylene glycol (9 ml) under reflux for 16 h. The reaction mixture was diluted with water and the product was extracted with benzene. The extract solution was washed with brine and dried over $MgSO_4$. The residue (50 mg) left after evaporation of the solvent was purified by chromatography (20:1 benzene-ethyl acetate) to give the title ketone **7** as crystals (31 mg, 68%). Recrystallization from ether-hexane afforded pure **7** as a colorless needles, mp 117—119 °C: IR ($CHCl_3$) 1770, 1705, 1185, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.01 (3H, d, J=7 Hz, $CH\underline{Me}$), 1.32 (3H, s, Me), 2.26, 2.67 (2H, ABq, J=18 Hz, CH_2CO_2), and 4.00, 4.09 (2H, ABq, J=12 Hz, CH_2OCO). Found: C, 71.96; H, 8.88%. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.88%.

(1′*R,2′*R**,4′a*S**,8′a*R**)-2′,3′,4′,4′a,6′,7′,8′,8′a-Octahydro-5′,5′-ethylenedioxy-2′,4′a-dimethylspiro[furan-3(2*H*),1′(5′*H*)-naphthalene]-5(4*H*)-one (20).** A solution of the keto lactone **7** (202 mg, 0.69 mmol) in benzene (40 ml) was heated with ethylene glycol (0.2 ml) in the presence of *p*-toluenesulfonic acid under removal of water for 3 h. Working-up gave title acetal **20** (236 mg, 100%) as plates (from ether-petroleum ether), mp 150—151 °C: IR ($CHCl_3$) 1775, 1190, 1095, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.08 (3H, s, Me), 1.12 (3H, d, J=6 Hz, $CH\underline{Me}$), 2.53 (2H, s, CH_2CO_2), 4.00 (4H, s, OCH_2CH_2O), 4.24 (1H, brd, J=10 Hz, $C\underline{H}_\alpha H_\beta OCO$), and 4.44 (1H, d, J=10 Hz, $C\underline{H}_\alpha H_\beta OCO$). Found: *m/z* 294.1816. Calcd for $C_{17}H_{26}O_4$: M, 294.1829.

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5-ethylenedioxy-1-[2-(3-furyl)ethyl]-1-hydroxymethyl-2,4a-dimethylnaphthalene (22).** To a stirred solution of the lactone **20** (42 mg, 0.14 mmol) in anhydrous ether (6 ml) was added dropwise a portion of 3-furyllithium solution, prepared from 3-bromofuran (140 mg, 1.0 mmol), butyllithium solution (2.3 M in hexane, 0.5 ml, 1.15 mmol) and ether (1 ml), at −10 °C until the solution became yellow in color. Having been stirred for 40 min, the reaction mixture was allowed to react for 1 h with the addition of sodium bis(2-methoxyethoxy)aluminum hydride solution (RDB, 70% in benzene, 0.3 ml). Ice-water was added and the product was extracted with benzene. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo to give an oil (58 mg) which was acetylated with acetic anhydride (2 ml) and pyridine (3 ml) at room temperature overnight. Crude product obtained by working-up was purified by chromatography (20:1 benzene-ethyl acetate) to furnish the diacetate **21** as colorless oil (53 mg, 87%), IR (CCl_4) 3040, 1745, 1235, 1025, and 875 cm^{-1}. This product dissolved in tetrahydrofuran (THF) (2 ml) was added to a solution of lithium (40 mg, 5.7 mmol) in liquid ammonia (10 ml) at −78 °C. Since blue coloration of the solution disappeared after 5 min, an additional amount of metallic lithium (10 mg, 1.5 mmol) was added. After 1 h the reaction mixture was quenched by the addition of solid NH_4Cl and the ammonia was allowed to evaporate. Ice-water was added and the mixture was extracted with benzene. The combined extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent afforded crude **22** (43 mg, 94%). Purification was performed by chromatography (20:1 benzene-ethyl acetate) to afford the title compound **22** as an oil, IR (CCl_4) 3470, 1090, and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.07 (3H, d, J=7 Hz, $CH\underline{Me}$), 1.18 (3H, s, Me), 3.04 (1H, brs, OH), 3.40, 3.62 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 3.94 (4H, m, OCH_2CH_2O), 6.14 (1H, m, furan), 7.13 (1H, m, furan), and 7.24 (1H, m, furan).

Formation of Tricyclic Ketone (26). The furanoid alcohol **22** (43 mg, 0.12 mmol) was mesylated with methanesulfonyl chloride (0.015 ml, 0.2 mmol) and pyridine at room temperature overnight. The crude product (47 mg) was chromatographed with 30:1 benzene-ethyl acetate as eluant. The earlier fractions (18 mg) represent the mesylated product **23**, IR (CCl_4) 1180, 940, and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (3H, d, J=6 Hz, $CH\underline{Me}$), 1.15 (3H, s, Me), 2.91 (3H, s, mesyl Me), 3.96 (4H, m, OCH_2CH_2O), 4.38, 4.58 (2H, ABq, J=10 Hz, $C\underline{H}_2OMs$), 6.22 (1H, m, furan), 7.18 (1H, m, furan), and 7.27 (1H, m, furan), the later fractions being the recovery of the alcohol **22** (10 mg). The mesylate **23** (18 mg) was hydrolyzed by treatment with 1 M HCl (3 drops) and acetone (0.5 ml) at room temperature for 2 h. Working-up gave the keto mesylate **25** (14 mg), IR (CCl_4) 1715, 1340, 1178, 938, and 875 cm^{-1}. This product (0.036 mmol) dissolved in HMPA (0.5 ml) was stirred with sodium iodide (30 mg, 0.2 mmol) at 80—100 °C for 4 h. Zinc dust (80 mg, 1.2 mmol) was added and the mixture was stirred at 100 °C for 17 h. Benzene was added and insoluble inorganic material was removed by filtration. The filtrate was washed with water and brine, and dried (Na_2SO_4). The residue left after evaporation of the solvent was purified by chromatography. Eluant with 10:1 benzene-ethyl acetate was collected to give (1*R**,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5-ethylenedioxy-1-[2-(3-furyl)ethyl]-2,4a-dimethyl-1,6-methanonaphthalene (**26**) as colorless oil (7 mg, 68%), IR (CCl_4) 1725, 1025, and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82 (3H, d, J=6 Hz, $CH\underline{Me}$), 1.04 (3H, s, Me), 2.22 (2H, m, $C\underline{H}_2$-furyl), 2.40 (1H, dd, J=4,6 Hz, $CH_2C\underline{H}CO$), 6.20 (1H, m, furan), 7.18 (1H, m, furan), and 7.32 (1H, m, furan). Found: *m/z* 286.1930. Calcd for $C_{19}H_{26}O_2$: M, 286.1931.

Formation of the Acetal 27. A solution of the furanoid alcohol **22** (15 mg, 0.043 mmol) in acetone (0.5 ml) was stood with the addition of a few drops of 1 M HCl at room temperature for 7 h. The reaction mixture was diluted with benzene and washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave (2*S**,5*R**,6*R**,7*R**)-6-[2-(3-furyl)ethyl]-1-(2-hydroxyethoxy)-2,5-dimethyl-11-oxatricyclo[4.4.2.$0^{2,7}$]-dodecane (**27**) as colorless oil (15 mg, 100%), IR ($CHCl_3$) 3400, 1070, and 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.92 (3H, d, J=6 Hz, $CH\underline{Me}$), 1.00 (3H, s, Me), 3.54 (4H, m, OCH_2CH_2O), 3.77 (2H, m, CH_2-O), 6.16 (1H, m, furan),

7.10 (1H, m, furan), and 7.22 (1H, m, furan). Found: *m/z* 348.2312. Calcd for $C_{21}H_{32}O_4$: 348.2312.

Formation of the Cyclic Hemiacetal 30. The alcohol **22** (10 mg) was acetylated by standing with acetic anhydride (0.7 ml) and pyridine (1.5 ml) at room temperature overnight. Working-up gave (1*R**,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-acetoxymethyl-5,5-ethylenedioxy-1-[2-(3-furyl)ethyl]-2,4a-dimethylnaphthalene (**28**) as an oil (12 mg), IR (CCl_4) 1737, 1240 and 875 cm^{-1}. The product was dissolved in acetone (0.5 ml) and treated with 1 M HCl (3 drops) at room temperature for 1.25 h. Working-up yielded (1*R**,2*R**,4a*R**,8a*R**)-1,2,3,4,4a,7,8,8a-octahydro-1-[2-(3-furyl)ethyl]-1-hydroxymethyl-2,4a-dimethyl-5(6*H*)-naphthalenone (**29**) as an oil (12 mg), IR (CCl_4) 1737, 1707, 1230, and 877 cm^{-1}. A solution of the keto acetate **29** (10 mg, 0.029 mmol) in ether was added to a methyllithium solution in ether (1.25 M, 0.24 ml, 0.029 mmol) at 0 °C. After 2 h, ice-water was added and the mixture was extracted with benzene, washed with brine and dried (Na_2SO_4). The solvent was removed to afford (2*S**,5*R**,6*R**,7*R**)-6-[2-(3-furyl)ethyl]-1-hydroxy-2,5-dimethyl-11-oxatricyclo[4.4.2.0^{2,7}]-dodecane (**30**) as an oil (10 mg), IR (CCl_4) 3400, 1080, 1025, and 870 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.91 (3H, d, *J*=6 Hz, CHMe), 1.00 (3H, s, Me), 3.75 (2H, s, CH_2-O), 6.17 (1H, m, furan), 7.15 (1H, m, furan), and 7.29 (1H, m, furan).

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5-ethylenedioxy-1-formyl-1-[2-(3-furyl)ethyl]-2,4a-dimethylnaphthalene (31).** A solution of the alcohol **22** (121 mg, 0.35 mmol) in dry dichloromethane (2 ml) was added all at once to a stirred suspension of chromium trioxide-pyridine complex (900 mg, 35 mmol) in dichloromethane (4 ml) and the mixture was stirred for 6 h. The precipitate was filtered through a pad of Celite and washed throughly with ethyl acetate. The removal of the solvent from the filtrate left brownish black residue which was purified by chromatography (9:1 benzene-ethyl acetate) to furnish the title aldehyde **31** as a colorless oil (111 mg, 92%), IR (CCl_4) 1710, 1255, 1090, 1025, and 872 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.92 (3H, d, *J*=6 Hz, CHMe), 1.11 (3H, s), 3.94 (4H, m, OCH_2CH_2O), 6.18 (1H, m, furan), 7.16 (1H, m, furan), 7.24 (1H, m, furan), and 10.07 (1H, s, CHO).

(1*S,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5-ethylenedioxy-1,2,4a-trimethyl-1-vinylnaphthalene (34).** A mixture of (1*S**,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,7,8,8a-Octahydro-1,2,4a-trimethyl-1-vinyl-5(6H)-naphthalenone (**33**) (42 mg, 0.19 mmol), ethylene glycol (62 mg, 1 mmol) and 10-camphorsulfonic acid (catalytic amount) was heated under reflux in a flask equipped with a Dean-Stark apparatus for 24 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The obtained product was purified with chromatography (20:1 hexane-ether) to afford the acetal **34** as an oil (45 mg, 89%), IR (film) 3090, 1635, 1140, 1095, 1050, and 914 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.74 (3H, d, *J*=6 Hz, CHMe), 1.07 (3H, s, Me), 1.13 (3H, s, Me), 3.90 (4H, s, OCH_2CH_2O), 4.83 (1H, dd, *J*=3,12 Hz, CH=CH_2), 4.99 (1H, dd, *J*=3,17 Hz, CH=CH_2), and 5.43 (1H, dd, *J*=12,17 Hz, CH=CH_2). Found: *m/z* 264.2089. Calcd for $C_{17}H_{28}O_2$: M, 264.2089.

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5-ethylenedioxy-1-(2-hydroxyethyl)-1,2,4a-trimethylnaphthalene (35).** 1,1,2-Trimethylpropylborane solution in THF[28] (1.34 M, 0.61 ml, 0.81 mmol) was added to a solution of the acetal **34** (435 mg, 0.165 mmol) at 0 °C and the mixture was allowed to react at room temperature for 24 h. The reaction mixture was quenched by careful addition of water. After addition of 10% aqueous NaOH and 30% H_2O_2 (1 ml), the mixture was stirred for further 33 h. The product was extracted with ethyl acetate, the combined extracts was washed with brine, and dried. Evaporation of the solvent left an oily residue, which was purified by chromatography (3:1 hexane-ether) to afford the title alcohol **35** as crystals, IR ($CHCl_3$) 3350, 1140, 1095, and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.84 (3H, d, *J*=6 Hz, CHMe), 0.96 (3H, s, Me), 1.11 (3H, s, Me), 3.59 (2H, t, *J*=7 Hz, CH_2OH), and 3.87 (4H, s). Found: *m/z* 282.2202. Calcd for $C_{17}H_{30}O_3$: M, 282.2195.

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5-ethylenedioxy-1,2,4a-trimethyl-1-(2-oxoethyl)naphthalene (36).** A solution of the alcohol **35** (190 mg, 0.674 mmol) in dichloromethane (6 ml) was stirred with pyridinium chlorochromate (PCC, 726 mg, 7 equiv.) at 0 °C for 30 min and at room temperature for 2 h. The reaction mixture was diluted with ether and filtered through a pad of Celite. The filtrate was chromatographed (5:1 hexane-ether) to afford the title aldehyde **36** as an oil (126 mg, 67%), IR (film) 2750, 1715, 1140, 1095, and 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, d, *J*=6 Hz, CHMe), 1.05 (3H, s, Me), 1.09 (3H, s, Me), 2.36 (2H, d, *J*=3 Hz, CH_2CHO), 3.86 (4H, s, OCH_2CH_2O), and 9.83 (1H, t, *J*=3 Hz, CH_2CHO). Found: *m/z* 280.2048. Calcd for $C_{17}H_{28}O_3$: M, 280.2038.

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-1-[2-acetoxy-2-(3-furyl)ethyl]-5,5-ethylenedioxy-1,2,4a-trimethylnaphthalene (38).** To a stirred solution of 3-furyllithium, prepared from 3-bromofuran (0.23 ml, 2.49 mmol) in anhydrous ether (4 ml) and butyllithium (1.45 M in hexane, 1.48 ml, 2.14 mmol), was added dropwise a solution of the aldehyde **36** (100 mg, 0.357 mmol) in ether (45 ml) at −17 °C. The reaction mixture was allowed to warm gradually up to 0 °C and stirred at this temperature for 2 h, then quenched by the addition of solid NH_4Cl. The mixture was washed successively with H_2O, saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was evaporated to give (1*R**,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5-ethylenedioxy-1-[2-(3-furyl-2-hydroxy)ethyl]-1,2,4a-trimethylnaphthalene (**37**) as a mixture of diastereomers, IR (film) 3450, 1135, 1090, 1050, 1020, and 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75, 0.91 (3H in total, d, *J*=6 Hz, CHMe), 0.98 (3H, s, Me), 1.06, 1.15 (3N in total, s, Me), 3.88 (4H, s, OCH_2CH_2O), 4.77 (1H, m, CHOH), 6.36 (1H, m, furan), and 7.33 (2H, m, furan). The product was acetylated by standing with acetic anhydride (4.5 ml), anhydrous pyridine (5 ml) and dichloromethane (10 ml) overnight. The reaction mixture was washed successively with H_2O, 2 M HCl, saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvent gave the title acetate **38** as an oil (140 mg), IR (film) 1760, 1235, and 875 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75, 0.85 (3H in total, s, Me), 0.97 (3H, s, Me), 1.06, 1.11 (3H in total, s, Me), 1.97 (3H, s, OAc), 3.88 (4H, s, OCH_2CH_2O),5.87 (1H, m, CHOAc), 6.35 (1H, m, furan), and 7.33 (2H, m, furan).

(1*R,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,7,8,8a-Octahydro-1-[2-(3-furyl)ethyl]-1,2,4a-trimethyl-5(6*H*)-naphthalenone (8).**

(a) From the aldehyde **31**. A mixture of the aldehyde **31** (111 mg, 0.32 mmol), hydrazine hydrate (85%, 0.1 ml, 2.7 mmol), KOH (87 mg, 1.6 mmol) and diethylene glycol (4 ml) was heated gradually until a complete solution resulted.

The bath temperature was then raised and maintained at 210—220 °C for 4 h with removal of excess hydrazine and water. After cooling the reaction mixture was diluted with water and extracted with benzene. The organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent and purification of the residue by chromatography (benzene) gave (1*R**,2*R**,4a*S**,8a*R**)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5-ethylenedioxy-1-[2-(3-furyl)ethyl]-1,2,4a-trimethylnaphthalene (**32**) as an oil (57 mg, 54%), IR (CCl_4) 1135, 1090, 1025, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82 (3H, d, *J*=6Hz, CHMe), 0.96 (3H, s, Me), 1.14 (3H, s, Me), 3.88 (4H, s, OCH_2CH_2O), 6.21 (1H, br s, furan), 7.16 (1H, br s, furan), and 7.29 (1H, m, furan). Found: *m/z* 332.2340. Calcd for $C_{21}H_{32}O_3$: M, 332.2350. The acetal **32** (20 mg, 0.06 mmol) was treated with 1 M HCl (1 drop) in acetone (1 ml). The reaction mixture was diluted with water, extracted with benzene, washed with saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvent yielded the title ketone **8** as colorless oil (17 mg), IR (CCl_4) 1710, 1160, 1025, and 872 cm^{-1}; ^1H NMR (CCl_4) δ=0.72 (3H, s, Me), 0.81 (3N, d, *J*=6 Hz, CHMe), 1.26 (3H, s, Me), 6.16 (1H, m, furan), 7.14 (1H, m, furan), and 7.29 (1H, m,furan). Found: *m/z* 288.2102. Calcd for $C_{19}H_{28}O_2$: M, 288.2098.

(b) From the acetate **38**. To a blue solution of lithium (450 mg, 64 mmol) in liquid ammonia (ca. 50 ml) was added a solution of the acetate **38** (140 mg, 0.35 mmol) in anhydrous THF (10 ml) at −78 °C and the mixture was stirred at this temperature for 2 h. The reaction was quenched by the addition of solid NH_4Cl and the ammonia was allowed to evaporate. Water was added and the product was extracted with ether. The extract solution was washed with brine, dried and evaporated to give the acetal **32**, which was found to be identical with the product obtained in (a) in spectral comparison (IR and ^1H NMR). The hydrolysis in the same way above and purification by chromatography (10 : 1 hexane–ether) gave the ketone **8** as crystals (55 mg, 55% from **36**), which was identified by high resolution MS, IR, and ^1H NMR.

15,16-epoxy-*cis*-cleroda-4(18),13(16),14-triene (40). To the CH_2Br_2-Zn-$TiCl_4$ reagent mixture, prepared[24] from activated zinc dust (0.6 g, 9.2 mmol), THF (7 ml), dibromomethane (0.22 ml, 3.1 mmol) and $TiCl_4$ (0.24 ml, 2.2 mmol), was added a solution of the ketone **8** (13 mg, 0.04 mmol) in dichloromethane (2 ml) and the mixture was stirred at room temperature for 24 h. Ether and saturated aqueous $NaHCO_3$ was added and the mixture was stirred for 20 min before extraction with ether. The extract solution was washed with 2 M HCl and brine, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (hexane) to give the title compound **40** as an oil (8.2 mg, 62%), IR ($CHCl_3$) 3080, 1640, 1025, 890, and 872 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.79 (3H, d, *J*=6 Hz, CHMe), 0.83 (3H, s, Me), 1.14 (3H, s, Me), 4.68 (2H, br s, $=CH_2$), 6.20 (2H, m, furan), 7.14 (1H, m, furan), and 7.28 (1H, br s, furan). Found: *m/z* 286.2307. Calcd for $C_{20}H_{30}O$: 286.2297.

15,16-Epoxy-*cis*-cleroda-3,13(16),14-triene (9). A solution of potassium 3-aminopropylamide (KAPA) solution, prepared from potassium hydride (35% oil dispersion, 280 mg, 2.45 mmol) and 1,3-propanediamine (2.5 ml), was added to methylene compound **40** (32 mg, 0.11 mmol) and the mixture was stirred at room temperature overnight. Solid NH_4Cl was added to quench the reaction and the mixture, after addition of water, extracted with ether. Ether extract was washed with water, diluted HCl and brine, dried and evaporated. The residue was purified by chromatography (hexane) to give the title compound as an oil (29.2 mg, 91%), IR ($CHCl_3$) 1160, 1025, and 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=0.79 (3H, d, *J*=6.7 Hz, CHMe), 0.83 (3H, s, Me), 1.06 (3H, s, Me), 1.69 (3H, d, *J*=1.6 Hz, =CMe), 5.28 (1H, m, CH=C), 6.27 (1H, m, furan), 7.21 (1H, m, furan), and 7.34 (1H, t, *J*=1.7 Hz, furan); ^{13}C NMR ($CDCl_3$) δ=16.04(C-17), 17.20(C-20), 17.85(C-1), 18.09(C-12), 19.79(C-18), 24.11(C-2), 28.82(C-7), 33.13(C-19), 36.94(C-9), 37.46(C-8), 37.84(C-6), 38.46(C-11), 40.25(C-5), 44.72(C-10), 111.07(C-14), 123.24(C-3), 125.98(C-13), 138.45(C-16), 139.89(C-4), and 142.66(C-15). The spectral data (IR and ^1H NMR) were identical with those of the natural product.

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