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THE SYNTHESIS OF A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF INSECT ANTIFEEDANT CLERODANES

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Abstract. The synthesis of a key intermediate, 1,2,3,4,4a,5,6,7,8,8aβ-perhydro-4α-isopropyldimethylsilyloxy-4aα-isopropyldimethylsilyloxy-methyl-1α,2α-dimethyl-5-methylene-naphthalene-1β-carbaldehyde **31**, in the total synthesis of insect antifeedant clerodanes is described. The stereochemistry of this intermediate is proven by an X-ray analysis of one of its precursors e.g. 10α-acetoxy-7β-(1,3-dioxolan-2-yl)-3,3aβ,4,5,6,6aβ,7,8,9,10-octahydro-7α,8α-dimethyl-1H-naphtho[1,8aα-c] furan **25**. Crystal data: $C_{19}H_{30}O_5$; monoclinic, $P2_1/n$, cell dimensions: a=7.9714(4), b=11.1722(4), c=19.7783(5) Å, β=92.595(5) °, Z=4; conventional R-factor=0.053.

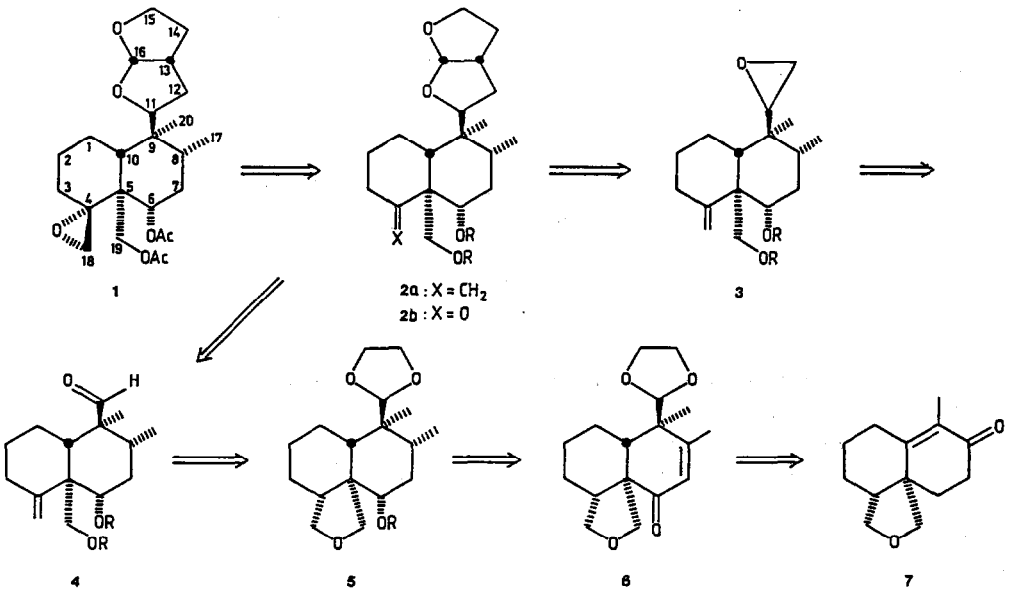
Clerodane diterpenes are known to exhibit a wide variety of physiological activities, such as antimicrobial[1], piscicidal[2], anti-peptic-ulcer[3], psychotropic[4] and cytotoxic[5] activity. The best known bioactivity, however, is their insect antifeedant activity[6]. The interesting bioactivities have stimulated many efforts towards the synthesis of clerodanes. A number of studies concerning *i* the synthesis of useful synthons[7], *ii* synthetic studies on modelcompounds[8], *iii* the total synthesis of low oxygenated clerodanes[9] and *iiii* the total synthesis of highly oxygenated insect antifeedant clerodanes[10] have been published.

In our laboratory dihydroclerodin **1** was chosen as the principal targetmolecule. Retrosynthetic studies led to the approach outlined in scheme 1.

The correct stereochemistry of the spiro epoxide may be expected via Sharpless oxidation ($VO(acac)_2$/tBuOOH) of the alkene **2a**[8d,e] (R=H) or via ozonolysis of the alkene **2a** (R≠H) and subsequent reaction with a sulfur ylide. An oxirane function as in **3** or an aldehyde function as in **4** seemed promising precursors for **2a**, especially since mild and stereoselective methods for the syntheses of furo[2.3b]furans from carbonyl compounds[11] and/or oxiranes[12] have been developed. Therefore the aldehyde **4** can be considered as a key intermediate in the total synthesis of dihydroclerodin **1** and its synthesis is described here.

Former work in our laboratory had shown that a regiospecific ringopening of a cyclic ether could be achieved[8d,10a] and some model work had confirmed this possibility[13]. The stereoselective reductions, necessary for the conversion of the enone **6** into the cyclic ether **5**, also had some presedence in the literature[8d,9b,10a]. This made the conversion of the known enone **7**[8d] into the dioxolan containing enone **6** to the first subject of our investigations.

Scheme 1

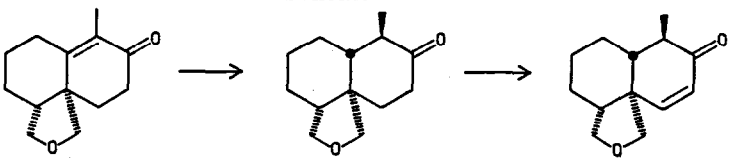


RESULTS AND DISCUSSION

The conversion of **7** into **6** required a stereospecific reduction of the α,β-double bond, the stereospecific introduction of the dioxolan group, the displacement of the carbonyl group by a methyl group and the oxidation of the β'-carbon atom. Three methods for these conversions were investigated and in all cases the enone **7** was first transformed into the enone **9**. Birch reduction of the enone **7** with lithium in ammonia afforded the **trans** ketone **8** in a quantitative yield. Bromination of **8** with bromine in acetic acid followed by dehydrobromination with lithium

bromide/lithium carbonate in hot dimethylformamide gave yields varying from 30-70%, moreover the resulting mixtures were separated only with difficulty. Modifications of this method suffered from the same drawbacks. Better and reproducable results were obtained when the ketone **8** was deprotonated under kinetic control and treated with phenylselenyl chloride. Oxidation of the α-phenylseleno ketone with either hydrogen peroxide or sodium *meta*-periodate and spontaneous selenoxide syn elimination[14] gave the enone **9** in 71% overall yield.

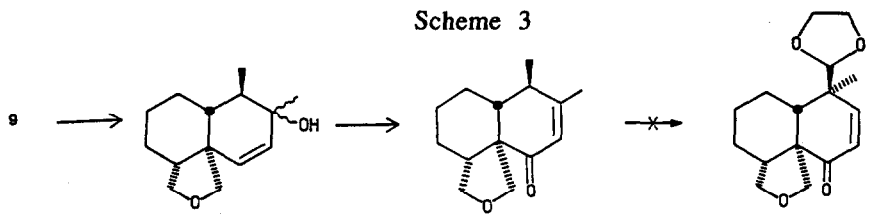
Scheme 2



7 **8** **9**

The first route for the conversion of **9** into **6** (see scheme 3) was based on the γ-alkylation of silyldienolethers[15]. The required enone **11** was synthesized via methyl lithium addition to the enone **9** and subsequent oxidation of the tertiary allylic alcohol **10**[16]. However attempts to alkylate the thermodynamic silyldienolether[17] of **11** with 2-methoxy-1,3-dioxolan[18] failed in our hands.

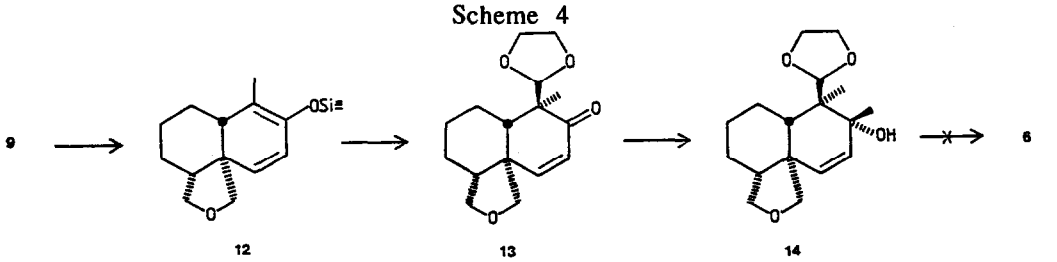
Scheme 3



10 **11** **6**

In a second attempt (see scheme 4) to synthesize the enone **6**, the enone **9** was converted into its cross silyldienolether **12** and alkylated with 2-methoxy-1,3-dioxolan in refluxing ethyl acetate to give the enone **13**. The β-orientation of the dioxolan group was proven by an X-ray structure determination[19]. Methyl lithium addition to **13** gave the desired tertiary allylic alcohol **14** but all attempts to oxidize this alcohol to the enone **6** were unsuccessful[9b].

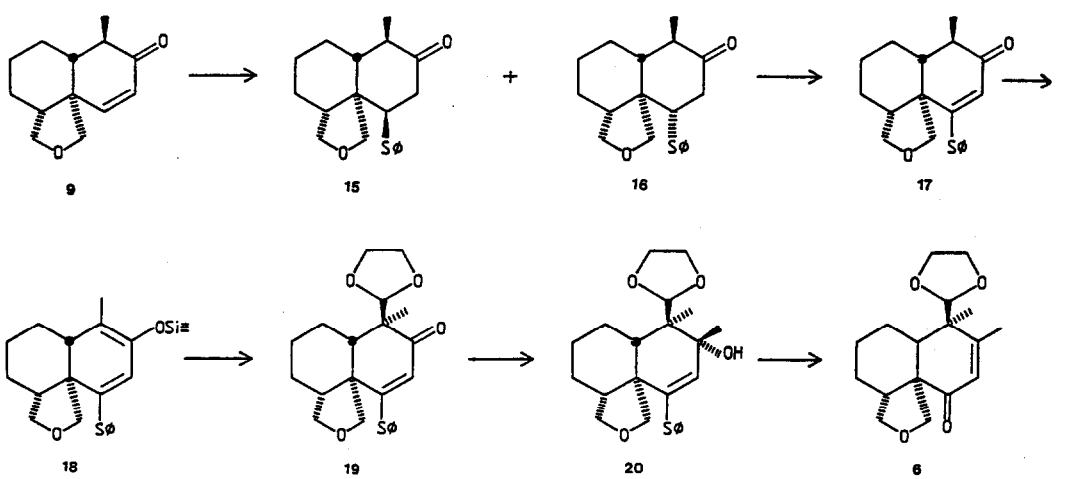
Scheme 4



12 **13** **14**

The third approach started with a reaction of the enone **9** with one equivalent of thiophenol and one equivalent of sodium thiophenolate. In this way the **axial** sulfide **15** was obtained with only minimal epimerization at C_6 to the **equatorial** sulfide **16**[20]. The oxidation of **15** with N-chlorosuccinimide gave the desired β-phenylthio-α,β-unsaturated ketone **17** in 50% yield. This reaction could be accomplished in 83% yield using trichloroisocyanuric acid[21] as the chlorinating agent[20]. At this stage the important alkylation reaction with 2-methoxy-1,3-dioxolan was studied. The alkylation was expected to result in a β-dioxolan substituent[19]. Furthermore it was anticipated that the silyldienolether **18** would have an enhanced reactivity with electrophiles, compared to the silyldienolether **12**, as a result of the mesomeric donating effect of the sulfide substituent. Indeed the dioxolanisation reaction could be accomplished in dichloromethane without external heating. The reaction depended very strongly on the concentrations of the reactants and after numerous experiments the reaction could be performed in 60% yield. Subsequent addition of methyl lithium to **19** gave the tertiary allylic alcohol **20** in a quantitative yield. In contrast to the usual rapid and clean hydrolysis of such γ-hydroxy-α,β-unsaturated thioethers[22] with mercury(II)chloride in aqueous acetone, the tertiary alcohol **20** gave rise to several unidentified products together with a small amount of the desired enone **6** in a slow reaction. Treatment of the alcohol **20** with a catalytic amount of p-toluenesulfonic acid monohydrate in chloroform gave the enone **6** in 63% yield, together with some dehydratated and deformylated products.

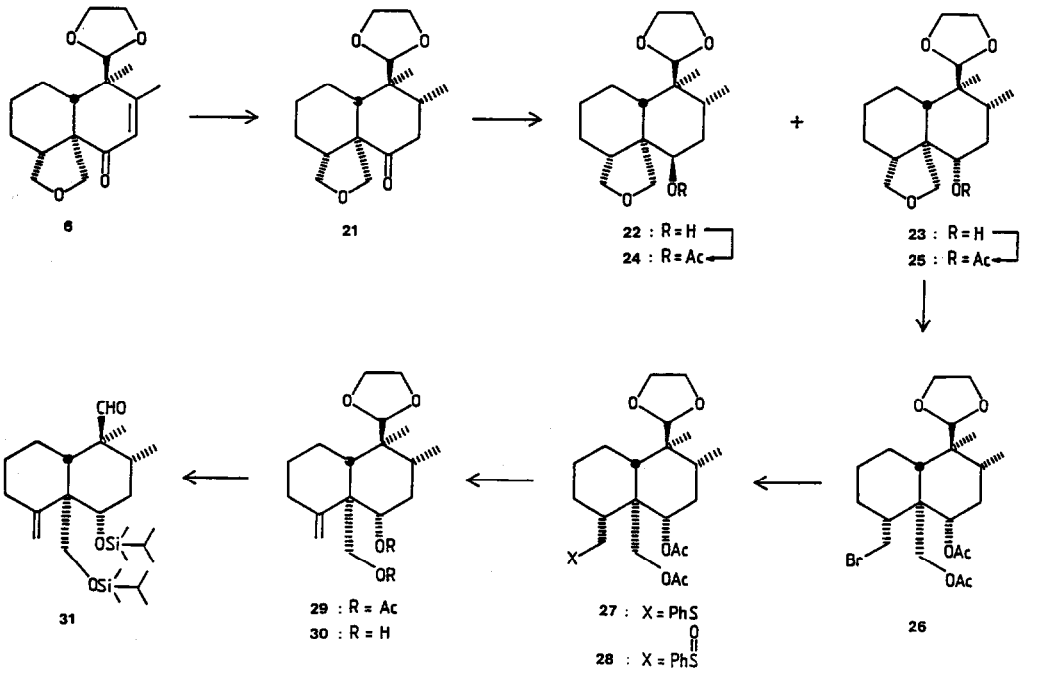
Scheme 5



The enone **6** was hydrogenated using palladium on charcoal as the catalyst to give the ketone **21** in 85% yield. No trace of the epimeric axial methyl compound was detected.

The reduction of the ketone **21** with lithium aluminum hydride gave the epimeric alcohols **22** and **23** in the ratio 45:55. This ratio was improved to 10:90 using L-selectride® as the reducing agent. The alcohol mixture was converted into the acetates **24** and **25**, which were easily separated by means of flash chromatography. In this way the desired equatorial acetate **24** was obtained in 87% yield. The structure of this acetate was additionally proved by an X-ray analysis (*vide infra*).

Scheme 6



At this stage the cyclic ether, which had acted as a methylene protecting group, had to be cleaved and converted into a methylene and an acetate group[10a]. Therefore the cyclic ether **25** was treated with pyridine/acetyl bromide in acetic anhydride at 70°C for 16 h[13] to give the bromide diacetate **26** in almost quantitative yield, with the dioxolan group left intact! Attempted dehydrobromination of **26** in hot dimethylformamide and lithium carbonate as proton scavenger did not give the desired alkene, but resulted in back formation of the cyclic ether **25**. In order to circumvent this problem the bromide **26** was treated with sodium thiophenolate in dimethylformamide to give the sulfide **27** in almost quantitative yield. Attempted pyrolysis of the corresponding sulfoxide **28** did not result in formation of the desired methylene compound **29**. This may be explained by the crowded surrounding of this sulfoxide which prevented adoption of the correct configuration necessary for the syn elimination. Therefore the acetate groups in **28** were saponified prior to the

pyrolysis. Using this reaction sequence, the sulfide **27** was transformed into a mixture of the cyclic ether **23** (20%) and the desired methylene diol **30** (40%). Hydrolysis of the acetal function and protection of the alcohol groups as isopropyldimethylsilyl ethers gave the aldehyde **31** in 94%.

THE CRYSTALSTRUCTURE OF THE ACETATE 25

Standard experimental details were as described by Smits *et al.*[23]. The crystal (0.27x0.35x0.45 mm) was obtained by recrystallization from *tert.*-butyl methyl ether. Unit cell dimensions are from reflections with $52^{o}<\theta<66^{o}$. Intensity data were collected for 11102 reflections (almost three quarters of the sphere up to $\theta=70^{o}$); the data for 15 extremely strong reflections could not be collected adequately because of counter buffer overflow: they were left out of the structure determination. Analysis of the standard reflections showed a considerable decrease in their net-intensities due to deterioration of the crystal. The data collection was stopped at the point where the correction curve lost its monotonous increasing character, resulting in correction factors of up to 1.12. Symmetry-equivalent reflections were averaged, resulting in 3320 unique reflections, of which 3060 were observed ($R_{merge}=0.025$). The structure was solved by direct methods. Least-square refinements: weight factor=0.00004, shift/error less than 0.04. Final difference Fourier peaks were less than 0.30 e $Å^{-3}$. R=0.053, $R_w=0.070$ for 2992 observed reflections and 307 variables. *Crystal data* : $C_{19}H_{30}O_5$, $M_r=338.443$, 290 K, monoclinic, space group $P2_1/n$, a=7.9714(4), b=11.1722(4), c=19.7783(5) Å, $\beta=92.595(5)^{o}$, V=1759.6(2) $Å^3$, Z=4, $D_x=1.278$ g cm^{-3}, CuKα radiation, $\mu=7.01$ cm^{-1}. Final structural parameters are given in Table 1. Programs used were EMPABS, MULTAN (Main *et al.*), DIFABS (Walker and Stuart), SHELX (Sheldrick), PLUTO (Motherwell), PARST (Nardelli); for program references see ref. 23. The structure is illustrated in Figures 1 and 2.

Figure 1

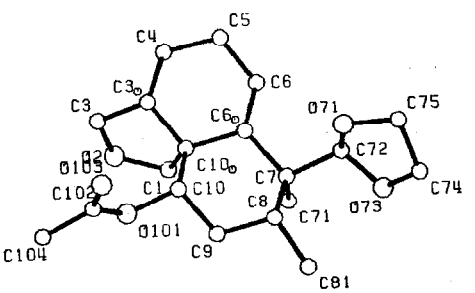


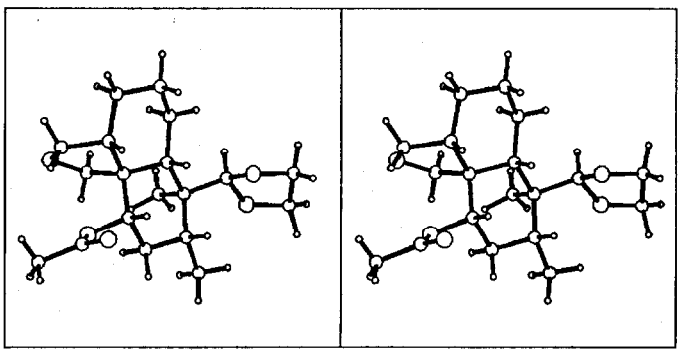
Table 1 (Atomic positional and vibrational parameters (with esd's) of **25**)

Atom	x	y	z	Ueq (Å^2)
C(1)	0.4965(3)	0.3278(2)	0.33995(9)	4.62(6)
O(2)	0.4974(2)	0.3336(1)	0.41226(7)	6.12(5)
C(3)	0.6038(3)	0.2438(2)	0.4415(1)	5.86(7)
C(3a)	0.7080(2)	0.1972(2)	0.38457(9)	4.77(6)
C(4)	0.8677(3)	0.2743(3)	0.3841(1)	6.43(8)
C(5)	0.9563(3)	0.2675(3)	0.3193(1)	6.39(8)
C(6)	0.8396(3)	0.3009(2)	0.2602(1)	5.20(6)
C(6a)	0.6878(2)	0.2158(2)	0.25416(8)	3.68(5)
C(7)	0.5764(2)	0.2290(2)	0.18714(8)	4.11(5)
C(71)	0.4876(3)	0.3498(2)	0.1812(1)	5.62(7)
O(71)	0.7933(2)	0.1188(1)	0.13034(6)	5.59(4)
C(72)	0.6971(2)	0.2235(2)	0.12812(9)	4.67(6)
O(73)	0.6135(2)	0.2269(2)	0.06316(6)	6.24(5)
C(74)	0.7003(3)	0.1471(3)	0.0205(1)	6.73(8)
C(75)	0.8512(3)	0.1088(3)	0.0631(1)	6.14(7)
C(8)	0.4499(2)	0.1230(2)	0.18325(9)	4.50(5)
C(81)	0.3199(3)	0.1233(3)	0.1242(1)	6.80(9)
C(9)	0.3564(2)	0.1126(2)	0.24850(9)	4.78(6)
C(10)	0.4686(2)	0.1063(2)	0.31244(8)	4.04(5)
O(101)	0.3537(2)	0.1016(1)	0.36797(6)	4.68(4)
C(102)	0.3543(2)	0.0051(2)	0.40789(9)	4.67(5)
O(103)	0.4454(2)	-0.0784(2)	0.40207(9)	7.65(6)
C(104)	0.2267(3)	0.0160(3)	0.4607(1)	5.88(7)
C(10a)	0.5888(2)	0.2132(2)	0.32074(8)	3.73(5)
H(011)	0.380(3)	0.330(2)	0.322(1)	0.050
H(012)	0.541(3)	0.400(2)	0.323(1)	0.050
H(03a)	0.726(3)	0.115(2)	0.387(1)	0.050
H(031)	0.538(3)	0.177(2)	0.465(1)	0.050
H(032)	0.672(3)	0.275(2)	0.482(1)	0.050
H(041)	0.936(3)	0.254(2)	0.425(1)	0.050
H(042)	0.836(3)	0.362(2)	0.391(1)	0.050
H(051)	0.989(3)	0.184(2)	0.317(1)	0.050
H(052)	1.065(3)	0.324(2)	0.324(1)	0.050
H(06a)	0.736(3)	0.136(2)	0.2504(9)	0.050
H(061)	0.897(3)	0.302(2)	0.219(1)	0.050
H(062)	0.803(3)	0.385(2)	0.267(1)	0.050
H(711)	0.443(3)	0.361(2)	0.139(1)	0.050
H(712)	0.388(3)	0.358(2)	0.213(1)	0.050
H(713)	0.552(3)	0.409(2)	0.186(1)	0.050
H(72)	0.772(3)	0.294(2)	0.1298(9)	0.050
H(741)	0.714(3)	0.180(2)	-0.024(1)	0.050
H(742)	0.624(3)	0.074(2)	0.008(1)	0.050
H(751)	0.889(3)	0.030(2)	0.059(1)	0.050
H(752)	0.949(3)	0.167(2)	0.059(1)	0.050

Table 1 (continued)

H(08)	0.515(3)	0.052(2)	0.178(1)	0.050
H(811)	0.243(3)	0.050(2)	0.128(1)	0.050
H(812)	0.376(3)	0.125(2)	0.076(1)	0.050
H(813)	0.259(3)	0.182(2)	0.131(1)	0.050
H(091)	0.286(3)	0.039(2)	0.2469(9)	0.050
H(092)	0.285(3)	0.176(2)	0.257(1)	0.050
H(10)	0.531(3)	0.033(2)	0.3132(9)	0.050
H(991)	0.196(3)	-0.060(2)	0.472(1)	0.050
H(992)	0.279(3)	0.054(2)	0.495(1)	0.050
H(993)	0.139(3)	0.057(2)	0.444(1)	0.050

Figure 2



EXPERIMENTAL

Boiling points and melting points are uncorrected. NMR spectra were recorded on Varian EM-390 and Bruker CXP-300 spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale), exept for the silyl-compounds in which case the methyl groups attached to the silyl atom were used as intramolecular internal standard. $CDCl_3$ was used as a solvent unless stated otherwise. Mass spectral data and accurate mass measurements were obtained using AEI-MS-902 and VG Micromass 7070F spectrometers. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Flash chromatography was preformed on silica gel 230-400 mesh. Other silica gel used was 70-230 mesh. Light petroleum refers to petroleum ether b.p. 40-60°C.

Aqueous solutions were usually extracted three times with ether. Combined organic extracts were washed with brine and dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure.

3aβ,4,5,6,6aβ,7,9,10-Octahydro-7β-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (8)

Lithium (1.4 g, 200 mmol) was added in small pieces to ammonia (600 mL, distilled from sodium) at -78°C under nitrogen. The mixture was stirred for 30 min and a solution of the enone 7 (10.30 g, 50 mmol) and water (0.90 mL, 50 mmol) in dry tetrahydrofuran (100 mL) was added dropwise. The reaction mixture was refluxed

for 30 min. Ammonium chloride was added and the ammonia was allowed to evaporate. Water and ether were added. The ether layer was separated and the water layer was extracted two more times with ether. Further work up as usual afforded a residue, which was taken up in acetone (40 mL). To this solution at 0°C was added Jones reagent untill the oxidation was complete. Work up as usual afforded the ketone **8** (10.34 g, 99%); mp 68-69°C. An analytic sample was prepared by recrystallisation from light petroleum; mp 70-71°C. Elemental analysis: calc. for $C_{13}H_{20}O_2$: 74.96% C, 9.68% H; found: 74.68% C, 9.69% H.
^{1}H-NMR: 0.97 (d, J=6 Hz, 3H), 1.1-2.7 (m, 13H), 3.58 (d, J=8 Hz, 1H), 3.8-4.2 (m, 3H). MS: m/e (%): 208 (100), 180 (5), 163 (17), 151 (23), 136 (23), 124 (34), 107 (25). Calc. for $C_{13}H_{20}O_2$: 208.1463; found 208.1472.

3aβ,4,5,6,6aβ,7-Hexahydro-7β-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (**9**)
Diisopropylamine (12.5 mL, 89 mmol) was added dropwise to a solution of n-butyl lithium (60 mL of a 15% solution in hexane) in dry tetrahydrofuran (250 mL) at -78°C under nitrogen. The solution was stirred for 10 min and a solution of the ketone **8** (17.3 g, 83 mmol) in tetrahydrofuran (50 mL) was added dropwise in 30 min. The mixture was stirred for 10 more min and a solution of phenylselenyl chloride (18.0 g, 94 mmol) in tetrahydrofuran (50 mL) was dropped to the reaction mixture in 10 min. Stirring was continued for 10 min and the mixture was worked up as usual. The resulting residue was dissolved in acetone (700 mL) and water (100 mL). Sodium bicarbonate (10.8 g) and sodium *meta*-periodate (36 g) were added succesively. The reaction mixture was stirred for 2 h, filtered and concentrated. Addition of water and extraction with ether, followed by the usual work up afforded a residue, which was chromatographed on silica gel with light petroleum/ether (2/1) as the eluant, to afford the enone **9** (13.25 g, 77%). Recrystallization from light petroleum afforded the pure enone **9** (12.2 g, 71%): mp 67-69°C. Elemental analysis: calc. for $C_{13}H_{18}O_2$: 75.69% C, 8.80% H; found: 75.36% C, 8.71% H.
^{1}H-NMR: 1.09 (d, J=6 Hz, 3H), 1.1-2.3 (m, 9H), 3.6-3.8 (m, 2H), 4.0-4.3 (m, 2H), 5.92 (d, J=10 Hz, 1H), 7.05 (d, J =10 Hz, 1H). MS: m/e (%): 206 (100), 178 (49), 176 (49), 161 (46), 157 (52), 143 (52), 130 (45), 105 (45), 91 (49). Calc. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1312.

3,3aβ,4,5,6,6aβ,7,8-Octahydro-7β,8α-dimethyl-1H-naphtho[1,8aα-c]furan-8β-ol (**10a**) and 3,3aβ,4,5,6,6aβ,7,8-octahydro-7β,8β-dimethyl-1H-naphtho[1,8aα-c]furan-8α-ol (**10b**)
The enone **9** (0.52 g, 2.5 mmol) was dissolved in dry ether (20mL) at -78°C under nitrogen. Methyl lithium (2 mL of a 1.5 N solution in ether) was added and the reaction mixture was stirred for 4 h. Aqueous ammonium chloride was added and the reaction was worked up as usual to give the allylic alcohols **10a** and **10b** (0.56 g) in the ratio 1/1. Separation of the isomeric alcohols could be effected by chromatography on silica gel and elution with light petroleum/ether (2/1). The axial alcohol **10a** was obtained as a colourless oil.
^{1}H-NMR: 0.97 (d, J=7 Hz, 3H), 1.12 (s, 3H), 1.0-1.9 (m, 10H), 3.4-3.7(m, 2H), 3.9-4.1 (m, 2H), 5.56 (d, J=10 Hz, 1H), 5.92 (d, J=10 Hz, 1H). MS: m/e (%): 222 (8), 207 (27), 205 (17), 204 (100), 159 (53), 149 (34). Calc. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1623.
The equatorial alcohol **10b** was obtained as a white solid (mp 67-68°C)

^{1}H-NMR: 0.91 (d, J=6 Hz, 3H), 1.13 (s, 3H), 1.0-1.9 (m, 10H), 3.4-3.6 (m, 2H), 3.9-4.1 (m, 2H), 5.45 (d, J=10 Hz, 1H), 5.78 (d, J=10 Hz, 1H). MS: m/e (%): 222 (15), 207 (61), 205 (18), 204 (97), 159 (100), 149 (55). Calc. for $C_{14}H_{22}O_2$: 222.1620; found 222.1619.

3aβ,4,5,6,6aβ,7-Hexahydro-7β,8-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**11**).

The alcohol mixture **10a** and **10b** (0.56 g, 2.5 mmol) was dissolved in dry dichloromethane (10 ml) and pyridinium chlorochromate (1.05 g, 4.9 mmol) was added. The reaction mixture was stirred for 6 h at roomtemperature, diluted with ether and decanted. Further work up as usual, filtration over a short silica gel column and recrystallization from light petroleum afforded the enone **11** (0.50 g, 90%) as a white solid (m.p. 58-60°C).

^{1}H-NMR: 1.11 (s, 3H), 1.91 (br s, 3H), 1.0-2.6 (m, 9H), 3.4-4.2 (m, 4H), 5.76 (br s, 1H). MS: m/e (%): 220 (95), 205 (6), 191 (29), 135 (25), 123 (12), 97 (50), 96 (100). Calc. for $C_{14}H_{20}O_2$: 220.1463; found: 220.1466.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6aβ,7-hexahydro-7α-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (**13**).

Diisopropylamine (0.37 mL, 2.7 mmol) was added dropwise to a solution of n-butyl lithium (1.7 mL of a 15% solution in hexane) in dry tetrahydrofuran (5 mL) at 0°C inder nitrogen. A solution of the enone **9** (0.412 g, 2.0 mmol) in tetrahydrofuran was added dropwise in 20 min. Stirring was continued for 20 min and trimethylchlorosilane (0.40 mL, 3.2 mmol) and triethylamine (0.25 mL) were added successively. The reaction mixture was poured into diluted aqueous sodium bicarbonate and worked up as usual. A mixture of the crude silyldienolether **12**, 2-methoxy-1,3-dioxolan (0.24 mL, 2.5 mmol), zinc chloride (0.30 g, 2.2 mmol) and dry ethyl acetate (3 mL) was refluxed for 6 h. The reaction mixture was cooled, poured into diluted aqueous sodium bicarbonate and worked up as usual. Chromatography on silica gel with light petroleum/ether (2/1) as the eluant afforded starting material (70 mg, 17%) and the enone **148** (150 mg, 27%) as a white solid, mp: 133-135°C (from diisopropylether).

^{1}H-NMR: 1.11 (s, 3H), 1.2-2.1 (m, 7H), 2.6-2.9 (m, 1H), 3.5-4.3 (m, 8H), 5.10 (s, 1H), 5.97 (d, J=10 Hz, 1H), 6.97 (d, J=10 Hz, 1H). MS: m/e(%): 278 (7), 263 (1), 233 (3), 206 (3), 205 (2), 175 (5), 161 (9), 73 (100). Calc for $C_{16}H_{22}O_4$: 278.1518; found: 278.1523.

7β-(1,3-Dioxolan-2-yl)-3,3aβ,4,5,6,6aβ,7,8-octahydro-7α,8β-dimethyl-naphtho[1,8aα-c]furan-8α-ol (**14**)

Methyl lithium addition to enone **13**, in the same way as described for **10**, afforded the alcohol **14** in a quantitative yield as a white solid (mp: 133-135°C from diisopropyl-ether).

^{1}H-NMR: 0.82 (s, 3H), 1.43 (s,3H), 1.1-2.2 (m, 8H), 3.25 (br s, 1H), 3.4-4.1 (m, 8H), 4.82 (s, 1H), 5.33 (d, J=10Hz, 1H), 5.68 (d, J=10Hz, 1H). MS: m/e (%): 294 (1), 279 (9), 276 (2), 204 (32), 167 (22), 159 (35), 73 (100). Calc. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1837.

3aβ,4,5,6,6aβ,7,9,10-Octahydro-7β-methyl-10β-phenylthio-1H-naphtho[1,8aα-c]furan-8(3H)-one (**15**).

Thiophenol (12.3 mL, 120 mmol) was dropped to a suspension of sodium hydride (1.8 g of a 80% dispersion in mineral oil, 60 mmol) in dry tetrahydrofuran (200 ml) under nitrogen. The mixture was stirred additionally for 20 min and the enone **9** (11.62 g, 56 mmol) in tetrahydrofuran (100 mL) was added dropwise. The reaction mixture was stirred overnight, diluted with ether and washed with aqueous 0.1 N sodium hydroxide. Further work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (3/1) afforded the **axial** sulfide **15** (15.29 g, 86%) as a white solid (mp 136-138°C from light petroleum/ether).
^{1}H-NMR (300 MHz): 1.05 (d, J=6 Hz, 3H), 1.2-1.6 (m, 3H), 1.8-1.9 (m, 3H), 2.0-2.1 (m, 2H), 2.68 (dd, J_1=15 Hz, J_2=2.5 Hz, 1H), 2.88 (m+dd, J_1=15 Hz, J_2=5.5 Hz, 2H), 3.67 (d, J=8 Hz, 1H), 3.76 (dd, J_1=5.5 Hz, J_2=2.5 Hz, 1H), 4.0-4.2 (m, 3H), 7.2-7.5 (m, 5H). MS: m/e (%): 316 (96), 207 (91), 206 (93), 110 (100). Calc for $C_{19}H_{24}O_2S$: 316.1497; found: 316.1496
Further elution with light petroleum/ether (2/1) afforded the **equatorial** sulfide **16** (0.86 g, 5%) as a white solid.
^{1}H-NMR (300 MHz): 1.02 (d, J=7 Hz, 3H), 1.4-2.0 (m, 7H), 2.13 (dq, J_1=7 Hz, J_2=12 Hz, 1H), 2.6-2.8 (m, 3H), 3.29 (dd, J_1=4 Hz, J_2=13 Hz, 1H), 3.74 (dd, J_1=4 Hz, J_2=9 Hz, 1H), 4.02 (d, J=10 Hz, 1H), 4.10 (d, J=10 Hz, 1H), 4.35 (t, J=8 Hz, 1H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 2H). MS: m/e (%): 316 (100), 207 (75), 206 (30), 110 (17). Calc for $C_{19}H_{24}O_2S$: 316.1497; found: 316.1495.

3aβ,4,5,6,6aβ,7-Hexahydro-7β-methyl-10-phenylthio-1H,naphtho[1,8aα-c]furan-8(3H)-one (**17**)
The saturated sulfide **15** (6.6 g, 20.9 mmol) was dissolved in benzene (200 mL) and ether (100 mL) at 0°C under nitrogen. Chloreal (1.78 g, 7.7 mmol) was added and the reaction mixture was stirred for 30 min. Evaporation of the solvents and flash chromatography on silica gel eluting with light petroleum/ether (3/1) afforded the unsaturated sulfide **17** (5.4 g, 83%) as a white solid (mp 149-150°C from *tert*-butyl methyl ether).
^{1}H-NMR: 1.10 (d, J=6 Hz, 3H), 1.2-2,2 (m, 8H), 2.8-3.1 (m, 1H), 3.7-4.0 (m, 2H), 4.2-4.6 (m, 2H), 5.3 (s, 1H), 7.4-7.5 (m, 5H). MS: m/e (%): 314 (100), 289 (25), 205 (33). Calc. for $C_{19}H_{22}O_2S$: 314.1341; found: 314.1340.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7-hexahydro-7α-methyl-10-phenylthio-1H-naphtho[1,8aα-c]furan-8(3H)-one (**19**)
A solution of the enone **17** (8.34 g, 26.6 mmol) was added dropwise at 0°C under nitrogen to a solution of lithium diisopropylamide (28.6 mmol). After stirring for 30 min. chlorotrimethylsilane (3.8 mL, 30.0 mmol) and triethylamine (2 mL) were added successively. Work up as usual afforded the crude silyldienolether **18**. Successive addition of 2-methoxy-1,3-dioxolan (5 mL, 52.5 mmol), dry dichloromethane (15 mL, distilled from calcium hydride) and dry zinc chloride (5.0 g), stirring for 2 h and direct flash chromatography on silica gel eluting with light petroleum/ether (2/1) afforded starting material (0.92 g, 11%) and the acetal **19** (6.14 g, 60%) as a white solid (mp 167-169 °C, from *tert*-butyl methyl ether). Elemental analysis: calc. for $C_{22}H_{26}O_4S$: 68.36% C, 6.78% H; found: 68.24% C, 6.81% H.
^{1}H-NMR: 1.11 (s, 3H), 1.2-2.2 (m, 6H), 2.7-3.1 (m, 2H), 3.5-4.0 (m, 6H), 4.1-4.6 (m, 2H), 4.99 (s, 1H), 5.32 (s, 1H), 7.3-7.6 (m, 5H). MS: m/e (%): 386 (33), 314 (85), 175 (61), 73 (100). Calc for $C_{22}H_{26}O_4S$: 386.1552; found: 386.1540.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7-hexahydro-7α,8-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**6**)

The enone **19** (1.21 g, 3.1 mmol) was dissolved in dry tetrahydrofuran at -78°C and methyl lithium (5 mL of a 1.6 N solution in ether) was added dropwise. The reaction mixture was stirred for 1 h, while the temperature was allowed to adopt roomtemperature. Saturated aqueous ammonium chloride was added and the mixture was worked up as usual to afford the rather unstable tertiary alcohol **20** in a quantitative yield.

^{1}H-NMR (CCl_4): 0.89 (s, 3H), 1.37 (s, 3H), 1.1-2.8 (m, 8H), 3.20 (br s, 1H), 3.4-4.5 (m, 8H), 4.81 (s, 1H), 5.14 (s, 1H), 7.3-7.6 (m, 5H).

The crude alcohol was dissolved in chloroform (30 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added. The reaction mixture was stirred for 2 h, neutralized and worked up. Flash chromatography on silica gel with light petroleum/ether (2/1) as the eluant afforded the enone **6** (0.58 g, 63%) as a white solid (mp 87-88°C, from light petroleum/ether). Elemental analysis: calc. for $C_{17}H_{24}O_4$: 69.83% C, 8.27% H; found 70.26% C, 8.66% H.

^{1}H-NMR: 1.05 (s, 3H), 1.87 (br s, 3H), 1.1-2.5 (m, 8H), 3.3-4.2 (m, 8H), 4.84 (s, 1H), 5.82 (br s, 1H). MS: m/e (%): 292 (23), 219 (67), 172 (29), 73 (100). Calc. for $C_{17}H_{24}O_4$: 292.1674; found: 292.1673.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7,8,9-octahydro-7α,8α-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**21**)

The enone **6** (2.212 g, 7.5 mmol) was dissolved in ethanol (30 mL) and triethylamine (1 mL). A catalytic amount of 10 % palladium on charcoal was added and the mixture was hydrogenated at 4.10^5 Pa in a Parr-apparatus overnight. The catalyst was removed by filtration and the solvents were evaporated. Flash chromatography on silicagel using light petroleum/ether (2/1) afforded the ketone **21** (1.966 g, 89%) as a colourless oil which solidified upon standing. Recrystallization in *tert*-butyl methyl ether afforded the pure keton **21** (1.862 g, 85 %) as a white solid (mp 90-91°C). Elemental analysis: calc. for $C_{17}H_{26}O_4$: 69.35% C, 8.90% H; found: 69.54% C, 9.02% H.

^{1}H-NMR: 0.96 (s, 3H), 1.00 (d, J=6 Hz, 3H), 1.2-1.4 (m, 3H), 1.6-1.8 (m, 2H), 1.8-1.9 (m, 1H), 2.0-2.3 (m,3H), 2.53 (dd, J_1=12 Hz, J_2=5 Hz, 1H), 2.63 (dd, J_1=13 Hz, J_2=12 Hz, 1H), 3.35 (d, J=7 Hz, 1H), 3.7-4.0 (m, 5H), 4.00 (d, J=9 Hz, 1H), 4.09 (d, J=9 Hz, 1H), 4.78 (s, 1H). MS: m/e (%): 294 (2), 276 (1), 204 (3), 127 (2), 73 (100). Calc. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1830.

10α-Acetoxy-7β-(1,3-dioxolan-2-yl)-3,3aβ,4,5,6,6aβ,7,8,9,10-octahydro-7α,8α-dimethyl-1H-naphtho[1,8aα-c]furan (**25**)

The ketone **21** (1.502 g, 5.2 mmol) was dissolved in dry tetrahydrofuran (20 mL) at -20°C and L-selectride® (7 mL of a 1 N solution in tetrahydrofuran) was added dropwise. The mixture was stirred for 4 h, poured out into water and worked up as usual. Flash chromatography on silica gel eluting with light petroleum/ether (1/2) afforded an alcohol mixture **22/23** (1.55 g), which was acetylated by treatment with acetic anhydride (4 mL), pyridine (4 mL) and dimethylaminopyridine (100 mg) overnight. The volatiles were evaporated at reduced pressure (50°C, 2 mm Hg) and the residue was chromatographed on silica gel with light petroleum/ether (2/1) as the eluant to afford the axial acetate **24** (167 mg, 10%).

The **axial** acetate **24** was obtained as a white solid, mp 151-152°C (from *tert*-butyl methyl ether), elemental analysis: calc. for $C_{19}H_{30}O_5$: 67.42% C, 8.93% H; found: 67.34% C, 8.99% H.
^{1}H-NMR: 0.73 (s, 3H), 0.87 (d, J=7 Hz, 3H), 1.2-2.3 (m, 11H), 2.12 (s, 3H), 3.35 (d, J=8 Hz, 1H), 3.76 (d, J=8 Hz, 1H), 3.8-4.0 (m, 6H), 4.81 (s, 1H), 4.9 (br s, 1H). MS: m/e (%): 338 (0.2), 279 (0.4), 204 (5), 159 (3), 73 (100). Calc for $C_{19}H_{30}O_5$: 338.2093; found: 338.2091.
Further elution with light petroleum/ether (2/1) gave the **equatorial** acetate **25** (1494 mg, 87%) as a white solid, mp 131-132°C (from *tert*-butyl methyl ether), elemental analysis: calc. for $C_{19}H_{30}O_5$: 67.42% C, 8.93% H; found: 67.68% C, 9.20% H.
^{1}H-NMR: 0.75 (s, 3H), 0.92 (d, J=7 Hz, 3H), 1.1-2.1 (m, 11H), 2.06 (s, 3H), 3.36 (dd, J_1=8 Hz, J_2=2 Hz, 1H), 3.7-4.1 (m, 7H), 4.77 (1, 1H), 4.83 (dd, J_1=11 Hz, J_2=5 Hz, 1H). MS: m/e (%): 338 (0.3), 279 (0.6), 204 (5), 159 (2), 73 (100). Calc for $C_{19}H_{30}O_5$: 338.2093; found: 338.2085.

1α-Acetoxy-8aα-acetoxymethyl-8α-bromomethyl-4β-(1,3-dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-3α,4α-dimethyl-naphthalene (**26**)
A mixture of the equatorial acetate **25** (952 mg, 2.8 mmol), pyridine (1.2 mL, 15 mmol), acetyl bromide (1.1 mL, 15 mmol) and acetic anhydride (4 mL) was stirred overnight at 70°C. The suspension was cooled, poured out into saturated aqueous sodium bicarbonate and extracted three times with ether. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated under reduced pressure (2 mm Hg). Flash chromatography on silica gel eluting with light petroleum/ether (5/2) afforded the bromide **26** (1.229 g, 95%) as a colourless oil which solidified upon standing.
^{1}H-NMR: 0.90 (s, 3H), 0.93 (d, J=5 Hz, 3H), 1.0-2.1 (m, 11H), 2.04 (s ,3H), 2.07 (s, 3H), 3.32 (t, J=10 Hz, 1H), 3.8-4.1 (m, 5H), 4.30 (d, J=12 Hz, 1H), 4.75 (s, 1H), 4.81 (d, J=12 Hz, 1Hz), 4.7-4.9 (m, 1H). MS: m/e (%): 462 (0.1), 460 (0.1), 389 (0.2), 387 (0.2), 151 (4), 73 (100). Calc. for $C_{21}H_{32}O_6Br$ (M-H): 459.1383; found: 459.1384.

1α-Acetoxy-8aα-acetoxymethyl-4β-(1,3-dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-3α,4α-dimethyl-8α-phenylthiomethyl-naphthalene (**27**)
The bromide **26** (1.229 g, 2.7 mmol) was dissolved in dimethylformamide (5 mL) and a solution of sodium thiophenolate (4 mmol) in dimethylformamide (3 mL) was added. The mixture was stirred overnight, poured out into aqueous ammonium chloride and worked up as usual. Flash chromatography on silica gel with light petroleum/ether (5/1→3/1) as the eluants gave the sulfide **27** (1.262 g, 97%) as a white solid; mp: 93-94°C (from light petroleum/ether 4/1). Elemental analysis: calc. for $C_{27}H_{38}O_6S$: 66.09% C, 7.80% H; found: 66.00% C, 7.94% H.
^{1}H-NMR: 0.90 (d, J=7 Hz, 3H), 0.91 (s, 3H), 1.0-2.1 (m, 17H), 2.79 (dd, J_1=13 Hz, J_2=9 Hz, 1H), 3.57 (dd, J_1=13 Hz, J_2=2 Hz, 1H), 3.7-4.0 (m, 4H), 4.37 (d, J=13 Hz, 1H), 4.6-4.9 (m, 1H), 4.74 (s, 1H), 4.79 (d, J=13 Hz, 1H), 7.2-7.3 (br s, 5H). MS: m/e (%): 490 (17), 446 (1.3), 417 (5), 381 (1), 380 (1), 356 (2), 182 (10), 173 (7), 123 (7), 73 (100). Calc. for $C_{27}H_{38}O_6S$: 490.2389; found: 490.2395.

4β-(1,3-Dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-8aα-hydroxymethyl-3α,4α-dimethyl-8-methylene-naphthalen-1α-ol (**30**)

Sodium *meta*-periodate (400 mg) in water (4 mL) was added dropwise to a solution of the sulfide **27** (740 mg, 1.5 mmol) in methanol/dichloromethane (10 mL/1 mL) and the mixture was stirred overnight at roomtemperature. The reaction mixture was filtered, concentrated and worked up as usual. The crude sulfoxide diacetate **28** was dissolved in methanol (5 mL), potassium hydroxide (1 pellet) was added, the mixture was stirred overnight, poured out into aqueous ammonium chloride and worked up as usual. The formed sulfoxide diol was taken up in toluene, refluxed for 6 h, cooled and worked up as usual. Flash chromatography on silica gel eluting with light petroleum/ether (3/1→3/2) gave the cyclic ether **23** (92 mg, 20%) and the alkene diol **30** (167 mg, 40%).

^{1}H-NMR: 0.83 (s, 3H), 0.94 (d, J=6 Hz, 3H), 1.1-2.0 (m, 8H), 2.1-2.3 (m, 2H), 2.93 (dd, J_1=7 Hz, J_2=4 Hz, 1H), 3.16 (d, J=4 Hz, 1H), 3.7-4.1 (m, 7H), 4.72 (s, 1H), 4.97 (br s, 1H), 5.11 (br s, 1H). MS: m/e (%): 296 (0.1), 295 (0.2), 278 (0.5), 248 (3), 223 (0.5), 206 (5), 188 (5), 173 (6), 73 (100). Calc. for $C_{17}H_{26}O_3$ (M-H_2O): 278.1882; found: 278.1880. Calc. for $C_{14}H_{23}O_2$ (M-$C_3H_5O_2$): 223.1698; found: 223.1698.

1,2,3,4,4a,5,6,7,8,8aβ-Perhydro-4α-isopropyldimethylsilyloxy-4aα-isopropyldimethylsilyloxymethyl-1α,2α-dimethyl-5-methylene-naphthalene-1β-carbaldehyde (**31**)

The acetal **30** (167 mg, 0.60 mmol) was dissolved in actone (4 mL) and 1 N hydrochloric acid (1 mL). The reaction mixture was stirred overnight, neutrlized concentrated and worked up as usual. The crude aldehyde diol was dissolved in dimethylformamide (5 mL) and imidazole (340 mg, 5.0 mmol) and isopropyldimethylsilyl chloride (300 μL, 1.9 mmol) were added and the reaction mixture was stirred overnight. The mixture was poured out into diluted aqueous sodium bicarbonate, extracted with light petroleum, further worked up as usual and chromatographed on silica gel. Elution with light petroleum/ether (30/1) gave the aldehyde **31** (256 mg, 94%) as a colourless oil.

^{1}H-NMR: 0.0-0.1 (m, 12H), 0.69 (d, J=6 Hz, 3H), 0.7-0.9 (m, 2H), 0.9-1.0 (m, 15H), 1.2-2.3 (m,10H), 3.92 (d, J=11 Hz, 1H), 3.85 (d, J=11 Hz, 1H), 4.04 (dd, J_1=11 Hz, J_2=6 Hz, 1H), 4.75 (br s, 1H), 4.85 (br s, 1H), 9.09 (s, 1H). MS: m/e (%): 452 (0.1), 409 (0.3), 247 (6), 219 (100), 185 (34), 147 (37), 133 (39), 75 (48), 73 (34). Calc. for $C_{25}H_{48}O_3Si_2$: 452.3141; found: 452.3140.

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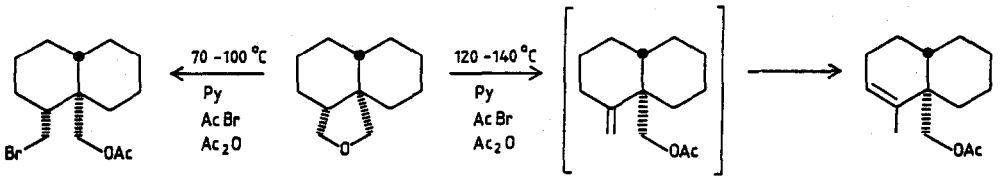

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