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Total Synthesis of Drimane Sesquiterpenes from S-(+)-Carvone (Part 5)[1]

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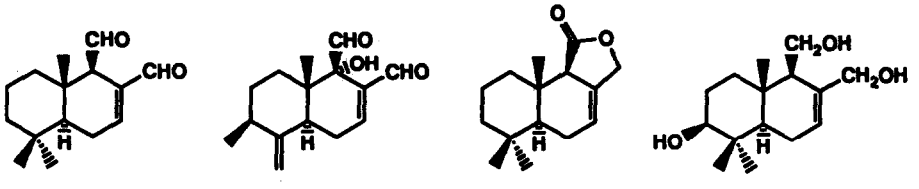
Abstract: Conjugate addition of potassium cyanide to S-(+)-carvone followed by annulation with methyl vinyl ketone gave keto nitrile **4** in high yield. Methylation of **4**, removal of the isopropenyl group and the introduction of C-12 via formylation then gave the unsaturated keto lactone **21** which is an excellent intermediate in the total synthesis of drimane sesquiterpenes. This was demonstrated with the total synthesis of 3β-acetoxydrimenin **24**.

The insect antifeedant properties of drimane sesquiterpenes, *e.g.*, polygodial and the related coloratanes, *e.g.*, muzigadial (figure 1) are well known[2]. This interesting biological activity has greatly stimulated the development of new and general synthetic routes to this class of compounds. Besides the ene-dialdehyde functionality, other oxidized functionalities in the B-ring, like annulated lactones and furans are common in drimanes (figure 1). Also ring A-oxidized drimanes are common in nature[3]. Numerous syntheses of drimanes have appeared in the last two decades[4]. In our laboratory several new methods for the regioselective introduction of the required functionalities were explored[5] and a new approach to drimanes was developed[5e] starting from *trans*-decalones, with the carbonyl group at C-7[6]. The total synthesis of enantiomerically pure drimanes and the coloratane muzigadial was performed starting from S-(+)- and R-(-)-carvone respectively[1a].

Figure 1

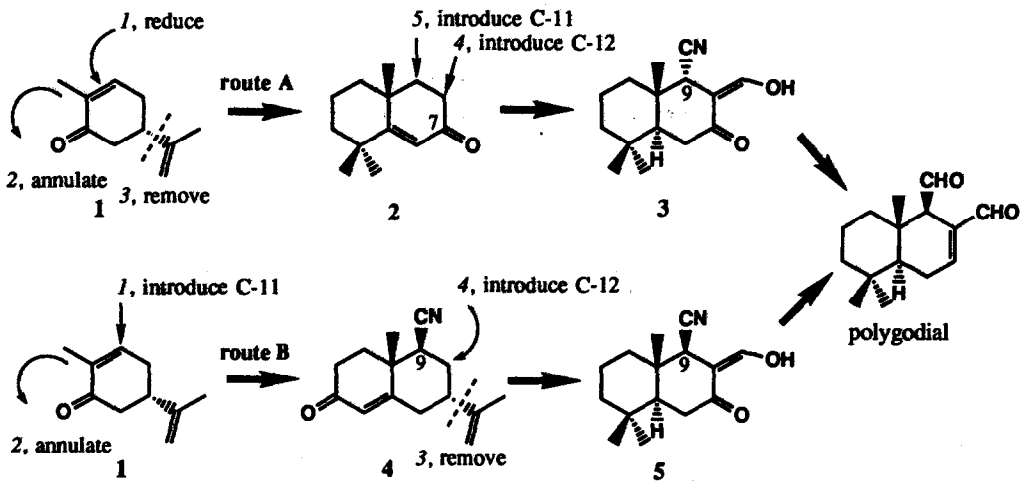


polygodial muzigadial drimenin drim-7-ene-3,11,12-triol

In our former approach, S-(+)-carvone (**1**) was first reduced, annulated, and dehydrated. After methylation the chiral handle was removed and transformed into a carbonyl group at C-7 in **2**. Next, the functionalized C-12 and C-11 carbon atoms were introduced to afford compound **3** with the wrong stereochemistry of the nitrile group at C-9. Finally a number of functional group transformations led to drimanes like polygodial (scheme 1, route A).

It seemed worthwhile to investigate a route where the introduction of a nitrile group at C-9 and the 'reduction' of the double bond in S-(+)-carvone were combined in the first step of the sequence and then proceed with the annulation to give **4**. Methylation, removal of the isopropenyl group and the introduction of C-12 could lead to compound **5**, but now with the correct stereochemistry at C-9 (scheme 1, route B).

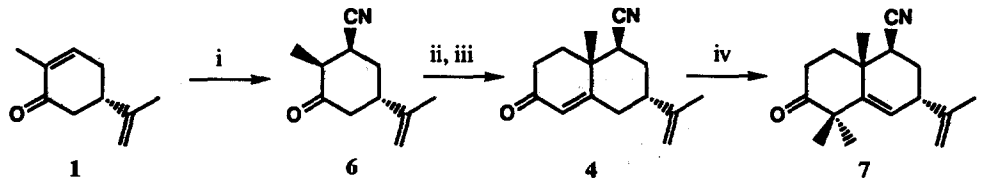
Scheme 1



The investigation of a total synthesis along these lines was strongly stimulated by two findings :

- The conjugate addition of potassium cyanide to S-(+)-carvone proceeded quite selectively in 95% yield to the adduct **6**, (scheme 2) which was simply isolated via crystallization[1d, 7].
- The Robinson annulation of **6** with methyl vinyl ketone followed by dehydration proceeded stereoselectively in 80% yield to give **4**[1d]. Methylation of enone **4** under standard basic conditions gave the keto nitrile **7**, without epimerization of the nitrile group (scheme 2).

Scheme 2

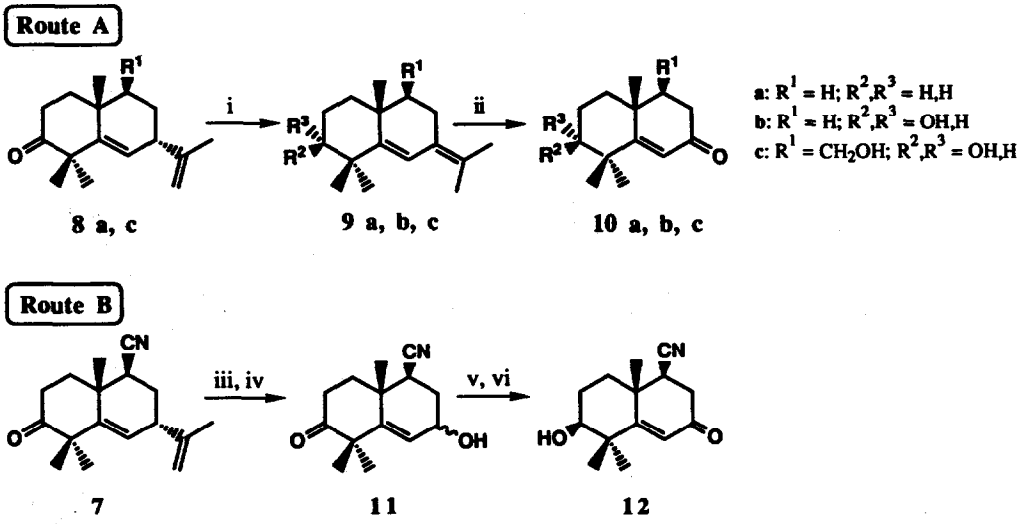


Reagents i: KCN, HOAc, EtOH, H_2O; ii: MVK, NaOMe, MeOH; iii: *p*-TsOH, toluene, reflux; iv: MeI, KO-*t*-Bu, HO-*t*-Bu.

The next step in the synthesis of drimane sesquiterpenes from keto nitrile **7** was the transformation of the isopropenyl group into a carbonyl group *via* oxidative methods. Two possible procedures for the removal of the isopropenyl group were explored. The first procedure started with the isomerization of the isopropenyl group to an isopropylidene group under basic conditions, a phenomenon previously observed during the

Wolff-Kishner reduction of similar compounds[1a], followed by selective ozonolysis of the exocyclic double bond[1a,c] (scheme 3, route A). The second procedure involved direct ozonolysis of the isopropenyl group, followed by a Criegee rearrangement[8] (scheme 3, route B).

Scheme 3



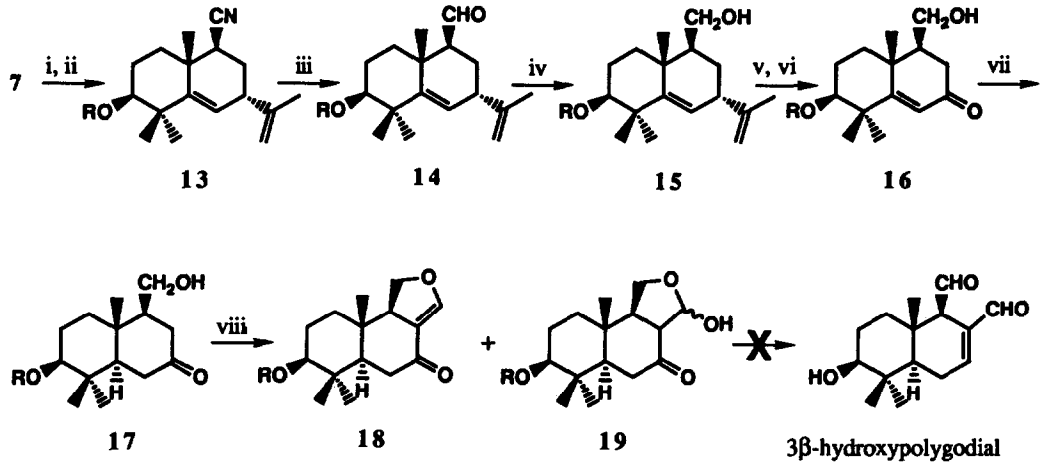
Reagents i: Hydrazine, KOH, DEG, 220 °C *or* $NaBH_4$, MeOH; KOH, DEG, 220 °C; ii: O_3, thiourea, MeOH; iii: O_3, MeOH, -78 °C; Ac_2O, Et_3N, DMAP; iv: K_2CO_3, MeOH; v: $NaBH_4$, MeOH; vi: MnO_2, acetone.

The preferred procedure strongly depends on the functional groups necessary for a rational synthesis of the targetted natural product. Drimanes without a substituted A-ring, like polygodial, are easy accessible *via* the unsaturated decalone **10a**[1a], and in these cases procedure A is the obvious choice. Under the strong basic conditions of the Wolff-Kishner reduction, decalone **8a** is converted into compound **9a**, precursor for several drimanic sesquiterpenes (scheme 3). The strong basic conditions are not compatible with functional groups like nitriles, ketones and aldehydes[1c,9], since competing reactions like saponification, epimerization, enolization or aldol condensation will occur. When these functionalities are transformed into less vulnerable groups, *i.e.*, into a hydroxy group, procedure A is suitable again for the conversion of the isopropenyl group into a carbonyl group. This method is demonstrated in scheme 4 as part of an attempted synthesis of 3β-hydroxypolygodial. Because ketones and nitriles are resistant to ozonolysis, removal of the isopropenyl group by ozonolysis followed by a Criegee rearrangement is possible in the presence of these groups. This procedure is illustrated in scheme 5, as part of the total synthesis of (-)-3β-acetoxydrimenin **24**[10].

In scheme 4 the application of procedure A is depicted as part of an attempted total synthesis of 3β-hydroxypolygodial. The keto group in **7** was reduced to an alcohol, which was then protected as its *tert*-butyl dimethylsilyl (TBDMS) ether **13**. Reduction of the nitrile group in **13** with diisobutylaluminum hydride (DIBAH) gave the aldehyde **14**, and reduction of this aldehyde with sodium borohydride afforded the alcohol **15**. Transformation of the isopropenyl group in **15** into a carbonyl group was performed *via* procedure A, to

give **16** in a moderate yield. Enone **16** was submitted to a dissolving metal reduction to give the *trans*-decalone **17**. The introduction of C-12 was now required and direct formylation was used to achieve this goal. Formylation at C-8 of **17** gave a mixture of two products, which were identified as the dihydrofuran **18** and the hemiacetal **19** in 33 % and 52 % yield, respectively. Protection of the alcohol functionality of **17** as its *tert*-butyldimethylsilyl ether, followed by submission to the same formylation conditions resulted in no reaction at all, probably due to steric hindrance. Similar products and findings were found by Lallemand *et al.*[11] in formylation reactions of monocyclic model compounds for **17**. Further elaboration of the rather unstable compounds **18** or **19** did not give satisfactory results and another route was examined for the introduction of a functional group at C-8.

Scheme 4

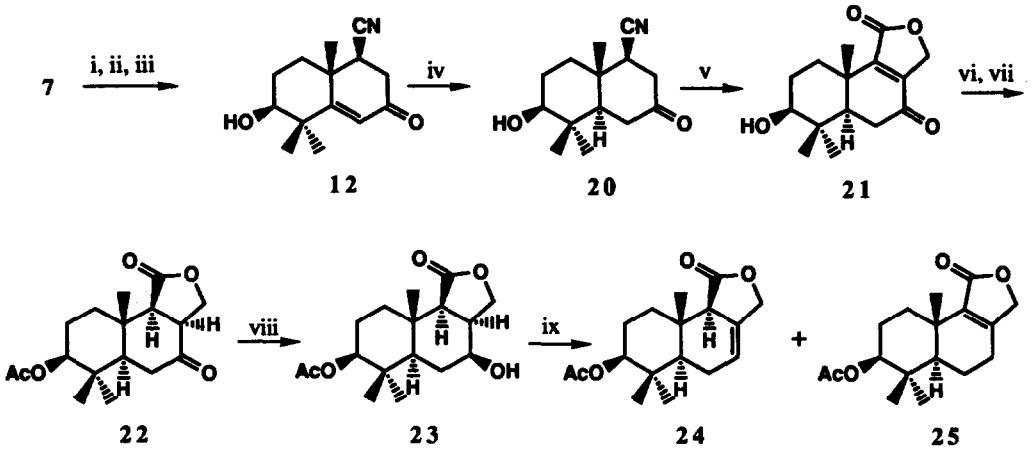


Reagents i: $NaBH_4$, MeOH; ii: TBDMSCl, DMF, imidazole; iii: DIBAH, toluene; iv: $NaBH_4$, MeOH; v: KOH, DEG, 220 °C; vi: O_3, MeOH; thiourea; vii: Li / NH_3, HO-*t*-Bu; viii HCO_2Et, NaH.

The synthesis of enantiomerically pure (-)-3β-acetoxydrimenin **24** was carried out as depicted in scheme 5. For this synthesis keto nitrile **7** was submitted to ozonolysis, followed by the addition of acetic anhydride, triethylamine and 4-N,N-dimethylaminopyridine to perform the Criegee rearrangment[8]. This gave a 1 : 1 mixture of α- and β-acetates, which after treatment with potassium carbonate in methanol also gave a 1 : 1 mixture of the α- and β-alcohols **11**. The keto group at C-3 was reduced with sodium borohydride to give a mixture of diols which was now selectively oxidized with manganese dioxide to give **12** in good yield. Enone **12** was submitted to catalytic hydrogenation, with palladium on activated carbon as catalyst, to give the saturated keto nitrile **20**. The introduction of C-12 in **20** *via* the common formylation conditions (sodium hydride, ethyl formate), also gave partial epimerization of the nitrile group and other unwanted side reactions. To avoid these problems the formylation was carried out under neutral conditions using bis-dimethylamino-*t*-butoxymethane (Bredereck's Reagent)[12] followed by hydrolysis of the resulting enamine with hydrochloric acid, which gave the α,β-unsaturated keto lactone **21** directly. Lactone **21** is a suitable intermediate for the synthesis of several natural 3β-oxygenated drimane sesquiterpenes. Acylation of **21** and hydrogenation of the

double bond of the α,β-unsaturated lactone using platinum(IV)oxide as catalyst, gave the lactone **22**. Selective reduction of the C-7 carbonyl group in **22** with sodium borohydride gave **23**. Dehydration[13] of **23** with trifluoromethanesulfonyl chloride (TfCl) in the presence of 4-N,N-dimethylaminopyridine finally led to (-)-3β-acetoxydrimenin **24** and (+)-3β-acetoxyisodrimenin **25** in 53% and 12% respectively. Sierra *et al.*[10] have converted (-)-3β-acetoxydrimenin **24** to drim-7-ene-3,11,12-triol[14]. It is obvious that also other 3-oxygenated drimanes are easily accessible *via* this synthetic route.

Scheme 5



Reagents i: O_3, MeOH, Ac_2O, Et_3N, DMAP; K_2CO_3, MeOH; ii: $NaBH_4$, MeOH; iii: MnO_2, acetone; iv: H_2, 10% Pd/C, 4 bar; v: Bredereck's reagent; HCl, H_2O, acetone; vi: Ac_2O, DMAP; vii: H_2, PtO_2, 2 bar; viii: $NaBH_4$, MeOH; ix: TfCl, DMAP.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-E 200 spectrometer or on a Bruker AMX 500. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale) in $CDCl_3$ solutions. Mass spectral data and HRMS measurements were obtained on a AEI MS 902 spectrometer. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at room temperature in chloroform as the solvent with the concentrations denoted in g/100 ml. GLC analyses were carried out on a Fisons MEGA8000 chromatograph provided with a 30 m capillaire column (DB-5 MS). For all dry reactions performed under a steady stream of nitrogen the equipment was dried in an oven at 150 °C for several hours, and allowed to cool in an atmosphere of dry nitrogen. Ether and toluene were dried by storage over sodium wire. Usually the reaction mixture was diluted with water and extracted three times with ether or ethyl acetate (EtOAc). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate ($MgSO_4$) prior to filtration and evaporation of the solvent under reduced pressure. Flash chromatography was performed on silica gel (230 - 400 mesh) and mixtures of petroleum ether (PE, boiling range 40 - 60 °C) and EtOAc were used as eluent.

(1S,3S,8aR)-3-Isopropenyl-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthalenecarbonitrile (7)

To a solution of 111.5 g (1.0 mol) of potassium *tert*-butoxide in 1500 mL of *tert*-butyl alcohol was added dropwise a solution of 110.0 g (0.48 mol) of enone **4**[1d] in 2000 mL of *tert*-butyl alcohol. After stirring at room temperature for 1.5 h, 90.2 mL (1.46 mol) of methyl iodide was added and stirring was continued for another 2 h. The reaction mixture was concentrated *in vacuo* and worked up as usual to afford an oily residue which was distilled (160 - 163 °C, 0.01 bar) to give 98.8 g (80 %) of **7** as a yellow oil.

^{1}H NMR: δ 1.09 (s, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.76 (s, 3H); 1.8 - 1.9 (m, 2H); 2.0 - 2.2 (m, 2H); 2.5 - 2.6 (m, 3H); 2.77 (t, J = 5.6 Hz, 1H); 4.53 (bs, 1H); 4.88 (bs, 1H); 5.47 (d, J = 4.8 Hz, 1H). ^{13}C NMR: δ 19.5 (q); 21.9 (q); 25.1 (t); 26.7 (q); 29.5 (q); 32.7 (t); 33.1 (t); 34.9 (d); 36.1 (s); 39.6 (d); 48.6 (s); 113.1 (t); 120.7 (s); 122.4 (d); 146.2 (s); 147.8 (s); 213.8 (s). HRMS: calcd (M^+) *m/e* 257.1779; found *m/e* 257.1767. Anal: calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44; found: C, 79.04; H, 8.95; N, 5.55. $[\alpha]_D = -32.6$ (c = 3.5).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile (13)

To a solution of 10.5 g (40.6 mmol) of **7** in 75 mL of methanol was added carefully 845 mg (22.3 mmol) of sodium borohydride. After stirring for 30 min a few drops of acetic acid were added and stirring was continued for 30 min. The reaction mixture was concentrated *in vacuo* and worked up as usual with ether. The residue was purified by flash chromatography (eluent EtOAc - PE 1: 5) to give 9.5 g (90 %) of *(1S,3S,6S,8aR)-6-Hydroxy-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile* as a white solid, mp: 80 - 81 °C.

^{1}H NMR: δ 1.05 (s, 3H); 1.16 (s, 3H); 1.31 (s, 3H); 1.76 (s, 3H); 1.2 - 1.3 (m, 1H); 1.53 (bs, 1H); 1.7 - 1.9 (m, 2H); 1.9 - 2.2 (m, 3H); 2.42 (dd, J = 2.6, 13.0 Hz, 1H); 2.73 (dd, J = 4.5 Hz, 6.9 Hz, 1H); 3.26 (m, 1H); 4.53 (br s, 1H); 4.86 (br s, 1H); 5.47 (d, J = 4.2 Hz, 1H). ^{13}C NMR: δ 21.8 (q); 22.3 (q); 22.5 (q); 25.1 (t); 26.6 (t); 26.7 (q); 36.0 (s); 36.6 (t); 37.9 (d); 40.3 (d); 41.6 (s); 77.0 (d); 112.7 (t); 121.3 (s); 122.3 (d); 146.5 (s); 147.7 (s). HRMS: calcd (M^+) *m/e* 259.1936; found *m/e* 259.1934. $[\alpha]_D = -121$ (c = 1.4).

To a solution of 14.1 g (54.4 mmol) of the above-mentioned alcohol in 200 mL of N,N-dimethylformamide was added 14.8 g (220 mol) of imidazole and 16.4 g (110 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred overnight at room temperature and worked up as usual with ether. The residue was recrystallized from methanol to give 16.9 g (83 %) of **13** as white crystals, mp: 89 - 90 °C.

^{1}H NMR: δ 0.00 (s, 3H); 0.02 (s, 3H); 0.86 (s, 9H); 1.00 (s, 3H); 1.06 (s, 3H); 1.28 (s, 3H); 1.74 (s, 3H); 1.2 (m, 1H); 1.5 - 2.2 (m, 5H); 2.38 (dd, J = 2.5 Hz, 13.1 Hz, 1H); 2.70 (dd, J = 4.6 Hz, 6.8 Hz, 1H); 3.21 (dd, J = 4.6 Hz, 11.2 Hz, 1H); 4.55 (bs, 1H); 4.84 (bs, 1H); 5.43 (d, J = 4.3 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 21.8 (q); 22.3 (q); 23.1 (q); 25.2 (t); 25.6 (3*q); 27.0 (t); 27.1 (q); 35.9 (s); 36.5 (t); 37.9 (d); 40.3 (d); 42.3 (d); 77.5 (d); 112.6 (t); 121.1 (s); 121.9 (d); 146.6 (s); 148.1 (s). HRMS: calcd (M^+) *m/e* 373.2800; found *m/e* 373.2797. Anal: calcd for $C_{23}H_{39}NOSi$: C, 73.95; H, 10.52; N, 3.75; found: C, 73.87; H, 10.51; N, 3.58. $[\alpha]_D = -74.9$ (c = 1.7).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarboxaldehyde (14)

To a solution of 16.9 g (45.2 mmol) of **13** in 350 mL of dry toluene at - 80 °C was added dropwise 80 mL of 1 M diisobutylaluminum hydride in toluene. Stirring was continued for 4 h, then water was added slowly. The aqueous layer was extracted twice with PE. The combined organic layers were washed with water and brine and dried. The solvent was filtered and evaporated *in vacuo* to give 16.9 g (99 %) of pure **14** as a pale yellow oil, which solidified upon standing, mp: 60 - 61 °C.

^{1}H NMR: δ 0.02 (s, 3H); 0.03 (s, 3H); 0.88 (s, 9H); 1.02 (s, 3H); 1.09 (s, 3H); 1.16 (s, 3H); 1.74 (s, 3H); 1.0 - 2.2 (m, 7H); 2.74 (m, 1H); 3.26 (dd, J = 4.6 Hz, 11.0 Hz, 1H); 4.56 (bs, 1H); 4.79 (bs, 1H); 5.48 (d, J = 4.4 Hz, 1H); 9.87 (s, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 21.2 (t); 21.9 (q); 22.2 (q); 23.3 (q); 25.6 (3*q); 27.1 (t); 27.6 (q); 36.5 (t); 37.2 (s); 40.4 (d); 42.5 (s); 55.7 (d); 77.6 (d); 111.7 (t); 122.9 (d); 147.6 (s); 149.3 (s); 205.7 (s). HRMS: calcd (M^+) *m/e* 376.2797; found *m/e* 376.2792. Anal: calcd for $C_{23}H_{40}O_2Si$: C, 73.36; H, 10.71; found: C, 73.09; H, 10.81. $[\alpha]_D$ = -67 (c = 1.1).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenemethanol (15)

To a solution of 4.20 g (11.2 mmol) of **14** in 75 mL of ethanol was added carefully 0.21 g (5.6 mmol) of sodium borohydride. The solution was stirred at room temperature for 2 h. A few drops of acetic acid were added and stirring was continued for 1.5 h. The mixture was worked up as usual with ether. The residue was purified by flash chromatography (eluent EtOAc - PE 1: 9) to give 4.01 g (95 %) of **15** as white crystals, mp: 92 - 94 °C.

^{1}H NMR: δ 0.01 (s, 3H); 0.02 (s, 3H); 0.86 (s, 9H); 0.97 (s, 3H); 1.01 (s, 3H); 1.07 (s, 3H); 1.75 (s, 3H); 1.0 - 1.4 (m, 3H); 1.5 - 1.9 (m, 5H); 2.68 (m, 1H); 3.19 (dd, J = 4.5 Hz, 11.1 Hz, 1H); 3.27 (dd, J = 8.9 Hz, 10.3 Hz, 1H); 3.76 (dd, J = 3.6 Hz, 10.4 Hz, 1H); 4.56 (bs, 1H);.4.76 (bs, 1H); 5.49 (d, J = 4.2 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 20.6 (q); 22.0 (q); 23.7 (q); 24.6 (t); 25.6 (3*q); 27.4 (t); 27.8 (q); 36.2 (t); 36.5 (s); 41.2 (d); 43.3 (s); 45.5 (d); 63.0 (t); 77.9 (d); 111.0 (t); 123.1 (d); 148.5 (s); 150.1 (s). HRMS: calcd (M^+) *m/e* 378.2954; found *m/e* 378.2953. Anal: calcd for $C_{23}H_{42}O_2Si$: C, 72.97; H, 11.18; found: C, 72.82; H, 11.22. $[\alpha]_D$ = -70 (c = 0.5).

(1S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,8,8-trimethyl-1-naphthalenemethanol (16)

A solution of 13.7 g (36.2 mmol) of **15** and 4.1 g (72.4 mmol) of potassium hydroxide in 250 mL of diethylene glycol was heated at 220 °C for 3 h. The reaction mixture was poured into water and worked up as usual with ether. The residue was purified by flash chromatography (eluent EtOAc - PE 1: 9) to give 10.2 g (74 %) of *(1S,6S,8aR)-6-(tert-Butyldimethylsilyloxy)-3-isopropylidene-1,2,3,5,6,7,8,8a-octahydro-5,8,8-trimethyl-1-naphthalenemethanol* as a yellow oil.

^{1}H NMR: δ 0.01 (s, 3H); 0.02 (s, 3H); 0.87 (s, 9H); 0.96 (s, 3H); 1.02 (s, 3H); 1.13 (s, 3H); 1.74 (bs, 3H); 1.77 (bs, 3H); 1.2 - 2.1 (m, 7H); 2.69 (dd, J = 3.7 Hz, 15.4 Hz, 1H); 3.25 (dd, J = 4.5 Hz, 11.2 Hz, 1H); 3.38 (dd, J = 8.9 Hz, 10.4 Hz, 1H); 3.84 (dd, J = 3.7 Hz, 10.4 Hz, 1H); 6.44 (s, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 19.4 (q); 20.6 (q); 20.7 (q); 24.2 (q); 25.7 (3*q); 26.2 (t); 27.1 (q); 27.4 (t); 36.1 (s); 36.1 (t); 42.5 (s); 49.6 (d); 63.4 (t); 77.4 (d); 119.9 (d); 125.7 (s); 127.0 (s); 150.1 (s). HRMS: calcd (M^+) *m/e* 378.2954; found *m/e* 378.2951. $[\alpha]_D$ = -48 (c = 1.2).

A solution of 9.8 g (25.9 mmol) of the above-mentioned diene in 96 mL of a mixture of methanol and dichloromethane (1: 5) was ozonized at - 80 °C for 30 min. Then nitrogen was purged through for 15 min and 1.20 g (15.7 mmol) of thiourea was added. Stirring was continued for 30 min at - 80 °C, and 2 h at room temperature. The solvent was evaporated and water and dichloromethane were added. The organic layer was washed with water and dried, filtered and evaporated *in vacuo*. The crude oil was purified by flash chromatography (eluent EtOAc - PE 3:7) to give 5.5 g (56 %) of **16** as a yellow oil which solidified on standing, mp: 121 - 123 °C.

^{1}H NMR: δ 0.00 (s, 3H); 0.01 (s, 3H); 0.84 (s, 9H); 1.06 (s, 3H); 1.11 (s, 3H); 1.15 (s, 3H); 1.2 - 2.0 (m, 5H); 2.25 (dd, J = 13.7 Hz, 17.8 Hz, 1H); 2.58 (dd, J = 4.2 Hz, 17.9 Hz, 1H); 2.70 (bs, 1H); 3.32 (dd, J = 4.6 Hz, 10.7 Hz, 1H); 3.46 (dd, J = 8.1 Hz, 10.6 Hz, 1H); 3.80 (dd, J = 4.1 Hz, 10.7 Hz, 1H); 6.01 (s, 1H). ^{13}C NMR: δ - 5.3 (q); - 4.1 (q); 17.8 (s); 20.0 (q); 23.8 (q); 25.6 (3*q); 26.4 (q); 26.8 (t); 34.0 (t); 36.5 (t); 37.8 (s); 43.4 (s); 48.9 (d); 61.8 (t); 76.1 (d); 124.8 (d); 178.5 (s); 200.4 (s). HRMS: calcd (M^+ - 57) *m/e* 295.1729; found *m/e* 295.1731. Anal: calcd for $C_{20}H_{36}O_3Si$: C, 68.14; H, 10.29; found: C, 68.44; H, 10.47. $[\alpha]_D$ = -38 (c = 0.6).

(1S,4aR,6S,8aS)-6-(*tert*-Butyldimethylsilyloxy)-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,8,8-trimethyl-1-naphthalenemethanol (17)

To a stirred solution of 120 mg (17.5 mgrat) of lithium in 40 mL of ammonia and 20 mL of dry ether was added dropwise a solution of 2.80 g (7.9 mmol) of **16** and 1.65 mL (17.5 mmol) of *tert*-butyl alcohol in 25 mL of dry ether in 30 min. After stirring for 30 min 2.0 g of solid ammonium chloride was added and the ammonia was allowed to evaporate. The mixture was worked up as usual with ether. The crude oil was purified by flash chromatography (eluent EtOAc - PE 3: 7) to give 2.10 g (75 %) of **17** as a white solid, mp: 106 - 107 °C.

^{1}H NMR: δ 0.00 (s, 3H); 0.01 (s, 3H); 0.77 (s, 3H); 0.84 (s, 12H); 0.99 (s, 3H); 1.0 - 1.4 (m, 3H); 1.4 - 1.7 (m, 3H); 1.7 - 1.9 (m, 2H); 2.1 - 2.4 (m, 2H); 2.55 (ddd, J = 1.1 Hz, 4.3 Hz, 10.1 Hz, 1H); 3.18 (dd, J = 5.6 Hz, 10.1 Hz, 1H); 3.38 (dd, J = 8.1 Hz, 10.6 Hz, 1H); 3.79 (dd, J = 4.1 Hz, 10.5 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.6 (q); 15.1 (q); 17.8 (s); 25.6 (3*q); 27.3 (q); 27.9 (q); 35.6 (s); 36.3 (t); 38.8 (t); 39.5 (s); 40.8 (t); 52.1 (d); 52.8 (d); 62.4 (t); 78.6 (d); 211.5 (s). HRMS: (M^+) *m/e* 339.2355; found *m/e* 339.2361. Anal: calcd for $C_{20}H_{38}O_3Si$: C, 67.76; H, 10.80; found: C, 67.65; H, 10.92. $[\alpha]_D$ = +2.5 (c = 1.2).

(5aR,7S,9aS,9bR)-7-(*tert*-Butyldimethylsilyloxy)-1,4,5,5a,6,7,8,9,9a,9b-decahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan (18) and (3ξ,3aξ,5aR,7S,9aS,9bS)-7-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4-oxo-6,6,9a-trimethyl-perhydronaphtho-[1,2-c]-furan (19)

To a suspension of 180 mg (6 mmol) of 80% sodium hydride in 5 mL of dry benzene was added dropwise a solution of 355 mg (1 mmol) of **17** and 160 µL (2 mmol) of ethyl formate in 5 mL of dry benzene. The mixture was stirred for 6 h at room temperature. Water was added carefully, followed by ether and 10 mL of aqueous 4 M hydrochloric acid. The aqueous layer was extracted twice with ether and the combined organic layers were washed with water, saturated aqueous sodium bicarbonate and brine. The solvent was dried, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent EtOAc - PE 1: 9) to give 120 mg (33 %) of **18** and 200 mg (52 %) of **19** as rather unstable compounds.

18: ^{1}H NMR: δ - 0.06 (s, 3H); - 0.05 (s, 3H); 0.74 (s, 3H); 0.78 (s, 12H); 0.80 (s, 3H); 1.0 - 1.2 (m, 2H); 1.3 - 1.6 (m, 4H); 2.3 (m, 1H); 2.95 (m, 1H); 3.14 (dd, J = 4.9 Hz, 10.5 Hz, 1H); 4.19 (t, J = 9.9 Hz, 1H);

4.48 (dd, J = 9.9 Hz, 10.8 Hz, 1H); 7.09 (d, J = 2.0 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.2 (q); 14.6 (q); 17.7 (s); 25.6 (3*q); 27.1 (t); 27.7 (q); 35.4 (s); 36.5 (t); 36.6 (t); 39.1 (s); 50.4 (d); 54.3 (d); 74.0 (t); 78.7 (d); 116.6 (s); 153.5 (d); 195.9 (s). HRMS: (M^+) *m/e* 364.2433; found *m/e* 364.2426. $[\alpha]_D$ = -16 (c = 1.1).

19: ^{1}H NMR: δ - 0.02 (s, 3H); - 0.01 (s, 3H); 0.63 (s, 3H); 0.78 (s, 3H); 0.83 (s, 12H); 1.0 - 1.2 (m, 2H); 1.4 - 1.7 (m, 4H); 2.2 - 2.5 (m, 3H); 2.86 (dd, J = 1.7 Hz, 10.8 Hz, 1H); 3.19 (dd, J = 4.9 Hz, 9.9 Hz, 1H); 3.8 - 4.1 (m, 2H); 5.72 (d, J = 1.2 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.7 (q); 14.8 (q); 17.8 (s); 25.6 (3*q); 27.1 (t); 27.6 (q); 34.5 (s); 36.6 (t); 37.9 (t); 39.3 (s); 48.6 (d); 53.2 (d); 57.5 (d); 67.0 (t); 78.9 (d); 99.3 (d); 210.4 (s). HRMS: (M^+ - 57) *m/e* 325.1835; found *m/e* 325.1834.

(1S,3R,8aR) and (1S,3S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthalenecarbonitrile (11)

A solution of 41.1 g (160 mmol) of ketone **7** in 78 mL of methanol and 390 mL of dichloromethane was ozonized at - 80 °C until a pale blue colour appeared. The solution was purged with nitrogen and 214 mL (2.26 mol) of acetic anhydride, 214 mL (1.54 mol) of triethylamine and 0.86 g of 4-N,N-dimethylaminopyridine were added. The resulting mixture was stirred overnight at ambient temperature, poured into 1000 mL of aqueous 6 M hydrochloric acid and stirred for 2 h. The mixture was extracted twice with dichloromethane. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate and dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the residue (42.2 g) was dissolved in 300 mL of methanol and 2.3 g of potassium carbonate was added. Stirring was continued overnight. The mixture was concentrated and worked up as usual with EtOAc. The remaining residue was purified by flash chromatography (eluent EtOAc - PE 1: 1) to give 25.8 g (111 mmol, 69 %) of a 1: 1 mixture of α- and β-alcohols **11.**

^{1}H NMR of the mixture of alcohols: δ 0.98 (s, 3H); 1.06 (s, 3H); 1.10 (s, 3H); 1.13 (s, 6H); 1.16 (s, 3H); 1.6 - 2.7 (m, 13H); 2.84 (dd, J = 5.0 Hz, 11.2 Hz, 1H); 3.3 - 3.6 (m, 2H); 4.15 - 4.30 (m, 2H); 5.48 (d, J = 1.9 Hz, 1H); 5.61 (d, J = 5.0 Hz, 1H).

(1S,6S,8aR)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,5,8a-trimethyl-1-naphthalenecarbonitrile (12)

To a solution of 30.2 g (130 mmol) of the mixture of alcohols **11** in 200 mL of methanol was added 2.43 g (64 mmol) of sodium borohydride and the mixture was stirred for 1 h. The mixture was concentrated, and worked up as usual with EtOAc. The residue (28.8 g), was dissolved in 250 mL of acetone and 31.5 g (245 mmol) of manganese dioxide was added. After stirring overnight an extra amount of 10.5 g (80 mmol) of manganese dioxide was added and stirring was continued for 18 h. The mixture was filtered over hyflo and the solvent was evaporated *in vacuo*, to give 28.4 g (94 %) of pure enone **12**, mp: 129 - 130 °C.

^{1}H NMR: δ 1.06 (s, 3H); 1.15 (s, 3H); 1.39 (s, 3H); 1.3 - 1.5 (m, 1H); 1.7 - 1.9 (m, 2H); 2.00 (dt, J = 3.2 Hz, 13.4 Hz, 1H); 2.6 (m, 2H); 2.83 (d, J = 5.1 Hz, 1H); 2.94 (dd, J = 6.5 Hz, 11.8 Hz, 1H); 3.30 (m, 1H); 5.98 (s, 1H). ^{13}C NMR: δ 21.3 (q); 22.9 (q); 25.6 (q); 26.0 (t); 35.4 (2*t); 37.0 (s); 40.3 (d); 42.9 (s); 74.9 (d); 118.4 (s); 124.3 (d); 174.9 (s); 194.6 (s). HRMS: calcd (M^+) *m/e* 233.1416; found *m/e* 233.1416. Anal: calc for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21; N, 6.00; found: C, 72.05; H, 8.13; N, 5.87. $[\alpha]_D$ = -50.2 (c = 0.3).

(1S,4aR,6S,8aS)-6-Hydroxy-3-oxo-perhydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile (20)
A mixture of 27.0 g (106 mmol) of enone **12** and 0.8 g of 10 % palladium on activated carbon in 170 mL of ethanol was hydrogenated (4 bar) for 6 h. The mixture was filtered over hyflo and the solvent was evaporated *in vacuo* to give 24.8 g (91 %) of pure **20** as a pale yellow solid, mp: 139 - 140 °C.
^{1}H NMR: δ 0.79 (s, 3H); 0.91 (s, 3H); 1.23 (s, 3H); 1.2 - 1.3 (m, 2H); 1.6 - 1.8 (m, 2H); 1.93 (bs, 1H); 2.00 (dt, J = 3.7 Hz, 13.3 Hz, 1H); 2.30 (dd, J = 14.0 Hz, 15.7 Hz, 1H); 2.40 (dd, J = 3.6 Hz, 11.5 Hz, 1H); 2.5 - 2.6 (m, 3H); 3.20 (dd, J = 4.4 Hz, 11.5 Hz, 1H). ^{13}C NMR: δ 14.3 (q); 14.5 (q); 26.5 (t); 27.0 (q); 35.8 (s); 36.5 (t); 37.9 (t); 38.9 (s); 39.4 (t); 42.6 (d); 50.1 (d); 77.6 (d); 118.5 (s); 205.8 (s). HRMS: calcd (M$^+$) *m/e* 235.1572; found *m/e* 235.1572. Anal: calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95; found: C, 71.21; H, 9.06; N, 5.89. $[\alpha]_D = -0.7$ (c = 0.4).

(5aR,7S,9aS)-7-Hydroxy-4,5,5a,6,7,8,9,9a-octahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (21)
A mixture of 4.0 g (17 mmol) of ketone **20** and 15.8 mL (76.6 mmol) of bis-dimethylamino-*tert*-butoxymethane (Bredereck's Reagent) was heated at 55 °C for 4 h, and then poured into an ice cold aqueous 1 M hydrochloric acid solution. The mixture was stirred for 1 h and worked up as usual with EtOAc. The residue, 4.30 g of a brown oil, was dissolved in 50 mL of acetone and 30 mL of aqueous 4 M hydrochloric acid. The reaction mixture was stirred for four days. Water was added and the mixture was worked up as usual with EtOAc. The residue was purified by flash chromatography (eluent EtOAc - PE 2: 3) to give 2.21 g (49 %) of **21** as a pale yellow solid, mp: 199 - 200 °C.
^{1}H NMR: δ 0.90 (s, 3H); 1.01 (s, 3H); 1.26 (s, 3H); 1.3 - 1.9 (m, 5H); 2.4 - 2.7 (m, 3H); 3.29 (dd, J = 5.2 Hz, 11.0 Hz, 1H); 4.83 (s, 2H). ^{13}C NMR: δ 15.1 (q); 18.1 (q); 26.9 (t); 27.7 (q); 31.7 (t); 35.9 (t); 36.4 (s); 38.8 (s); 50.9 (d); 67.3 (t); 77.6 (d); 149.0 (s); 151.7 (s); 170.7 (s); 195.8 (s). HRMS: calcd (M$^+$) *m/e* 264.1361; found *m/e* 264.1361. Anal: calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; found: C, 67.72; H, 7.79. $[\alpha]_D = +31.3$ (c = 0.4).

(3aS,5aR,7S,9aS,9bS)-7-Acetoxy-4-oxo-perhydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (22)
To a solution of 2.06 g (7.8 mmol) of **21** in 30 mL of pyridine was added 2.21 mL (23.4 mmol) of acetic anhydride and 25 mg of 4-N,N-dimethylaminopyridine. The reaction mixture was stirred for 2.5 h, then poured into an ice cold aqueous 2 M hydrochloric acid solution and worked up with EtOAc to give 2.26 g (95 %) of *(5aR,7S,9aS)-7-Acetoxy-4,5,5a,6,7,8,9,9a-octahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one* as a pale yellow solid, mp: 220 - 221 °C.
^{1}H NMR: δ 0.89 (s, 3H); 0.97 (s, 3H); 1.27 (s, 3H); 1.5 - 1.9 (m, 4H); 2.03 (s, 3H); 2.3 - 2.4 (m, 3H); 4.54 (dd, J = 4.9 Hz, 11.2 Hz, 1H); 4.82 (s, 2H). ^{13}C NMR: δ 16.2 (q); 18.1 (q); 21.2 (q); 23.3 (t); 27.7 (q); 31.4 (t); 35.7 (t); 36.2 (s); 37.7 (s); 50.9 (d); 67.4 (t); 79.0 (d); 149.1 (s); 151.6 (s); 170.6 (2*s); 195.4 (s). HRMS: calcd (M$^+$) *m/e* 306.1464; found *m/e* 306.1467. Anal: calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; found: C, 66.43; H, 7.13. $[\alpha]_D = +36.1$ (c= 0.4).
To a solution of 1.45 g (4.7 mmol) of the above-mentioned acetate in 75 mL of EtOAc and 10 mL of methanol was added 100 mg of platinum(IV)oxide hydrate. The mixture was hydrogenated for 2.5 h (2 bar), and then filtered over hyflo. The solvent was evaporated *in vacuo*. The crude oil was purified by flash chromatography (eluent EtOAc - PE 2: 3) to give 0.71 g (49 %) of **22** as white crystals, mp: 182 - 183 °C.

^{1}H NMR: δ 0.83 (s, 3H); 0.86 (s, 3H); 0.94 (s, 3H); 1.5 - 1.8 (m, 4H); 1.88 (dd, J = 8.6 Hz, 11.2 Hz, 1H); 2.04 (s, 3H); 2.44 (m, 2H); 2.80 (d, J = 12.5 Hz, 1H); 3.29 (ddd, J = 6.4 Hz, 9.8 Hz, 12.4 Hz, 1H); 4.3 - 4.6 (m, 3H). ^{13}C NMR: δ 14.9 (q); 15.6 (q); 21.0 (q); 23.1 (t); 27.1 (q); 35.9 (s); 35.9 (t); 36.8 (t); 37.9 (s); 44.1 (d); 48.2 (d); 52.8 (d); 66.2 (t); 79.3 (d); 170.5 (s); 175.3 (s); 208.6 (s). HRMS: calcd (M^+ - 60) *m/e* 248.1412; found *m/e* 248.1415. Anal: calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85; found: C, 66.48; H, 7.85. $[\alpha]_D$ = -77 (c= 0.5).

(3aS,4S,5aR,7S,9aS,9bS)-7-Acetoxy-4-hydroxy-perhydro-6,6,9a-trimethyl-naphtho-[1,2-c] -furan-1-one (23)

To a solution of 0.62 g (2.0 mmol) of **22** in 20 mL of methanol was added 38 mg (1 mmol) of sodium borohydride. The reaction mixture was stirred for 1 h and worked up as usual with EtOAc to give 0.59 g (95 %) of pure **23** as a white solid, mp: 215 - 217 °C.

^{1}H NMR: δ 0.89 (s, 6H); 1.04 (s, 3H); 1.1 - 1.9 (m, 6H); 2.03 (s, 3H); 2.1 - 2.3 (m, 2H); 2.41 (bs, 1H); 2.99 (m, 1H); 4.0 - 4.4 (m, 3H); 4.48 (dd, J = 5.0 Hz, 11.0 Hz, 1H). ^{13}C NMR: δ 16.7 (2*q); 21.0 (q); 22.0 (t); 26.8 (t); 28.1 (q); 35.5 (s); 37.6 (s); 37.9 (t); 40.2 (d); 49.5 (d); 54.1 (d); 68.8 (t); 69.2 (d); 79.6 (d); 170.7 (s); 177.5 (s). HRMS: calcd (M^+ - 60) *m/e* 250.1569; found *m/e* 250.1564. Anal: calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44; found: C, 65.95; H, 8.51. $[\alpha]_D$ = -36 (c = 0.4).

(5aR,7S,9aS,9bR)-7-Acetoxy-5,5a,6,7,8,9,9a,9b-octahydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (24) and (5aR,7S,9aS)-7-Acetoxy-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (25)

To a solution of 0.20 g (0.65 mmol) of **23** and 0.47 (3.8 mmol) of 4-N,N-dimethylaminopyridine in 15 mL of dry dichloromethane was added dropwise a solution of 156 µL (1.47 mmol) of trifluoromethanesulfonyl chloride in 3 mL of dichloromethane at -5 °C and the mixture was stirred for 20 min. Then the mixture was stirred for 1 h at room temperature. Water and dichloromethane were added, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with water, saturated aqueous sodium bicarbonate and brine. The solvent was dried, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent EtOAc - PE 2: 3) to give 99 mg (53 %) of **24** as white crystals, mp: 150 - 165 °C and 23 mg (12 %) of **25** as a pale yellow oil.

24 ^{1}H NMR (500 MHz): δ 0.89 (s, 6H); 0.95 (s, 3H); 1.3 - 1.8 (m, 5H); 2.06 (s, 3H); 2.16 (m, 1H); 2.53 (dt, J = 3.4 Hz, 6.8 Hz, 1H); 2.76 (m, 1H); 4.56 (dd, J = 5.0 Hz, 10.8 Hz, 1H); 4.68 (m, 2H); 5.75 (m, 1H). ^{13}C NMR: δ 14.0 (q); 15.9 (q); 21.2 (q); 23.0 (t); 23.5 (t); 27.6 (q); 33.9 (s); 35.9 (t); 37.8 (s); 49.2 (d); 53.6 (d); 69.8 (t); 80.3 (d); 120.7 (d); 129.8 (s); 170.8 (s); 174.9 (s). HRMS: calcd (M^+) *m/e* 292.1674; found *m/e* 292.1673. Anal: calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; found: C, 69.84; H, 8.25. $[\alpha]_D$ = -6.1 (c = 0.4).

25 : ^{1}H NMR: δ 0.92 (s, 6H); 1.15 (s, 3H); 1.1 - 1.9 (m, 6H); 2.05 (s, 3H); 2.35 (m, 2H); 2.60 (dt, J = 3.5 Hz, 13.6 Hz, 1H); 4.53 (dd, J = 5.3 Hz, 11.2 Hz, 1H); 4.57 (s, 2H). ^{13}C NMR: δ 16.6 (q); 17.9 (t); 20.1 (q); 21.3 (q); 23.6 (t); 25.3 (t); 28.2 (q); 32.3 (t); 34.5 (s); 37.8 (s); 51.6 (d); 70.7 (t); 80.1 (d); 135.0 (s); 159.1 (s); 172.4 (s); 176.4 (s). HRMS: calcd (M^+-60) *m/e* 232.1463, found *m/e* 232.1463. $[\alpha]_D$ = +100 (c = 0.11).

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