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Total Synthesis of (-)-Ambrox® from S-(+)-Carvone (part 6)[1]

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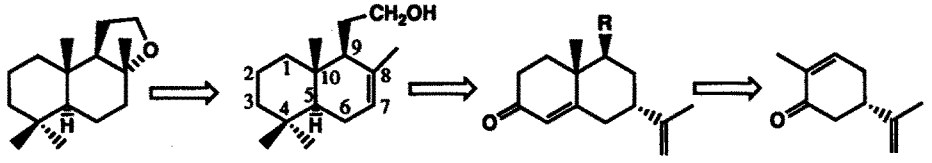
Abstract: Conjugate addition of cyanide and allyl nucleophiles to S-(+)-carvone followed by annulation with methyl vinyl ketone gave the substituted decalones 2 and 3 stereoselectively. Both decalones were transformed into (-)-Ambrox® *via* modification of the sidechain, methylation, conversion of the isopropenyl group and cyclization.

Since ancient times, ambergris has been one of the most highly valued perfumery materials[2]. Ambergris is a metabolic product of the spermwhale (*Physeter macrocephalus L.*), which accumulates as concretions in the gut. Due to excessive whaling, ambergris is disappearing from the world market. (-)-Ambrox®, the commercially most important constituent of the scarce natural ambergris, is recognized as the prototype of all ambergris odorants, both structurally and organoleptically[3]. For this reason, diverse synthetic routes to Ambrox® and its racemate have been developed. (-)-Ambrox® was previously prepared starting from geranylacetone[4], which made an optical resolution step necessary, and from naturally occurring sesquiterpenes[5] or diterpenes[6]. The racemate was prepared by a number of total syntheses employing biogenetic-type cyclizations from farnesic or monocyclofarnesic acids or derivatives of these[7].

Scheme 1



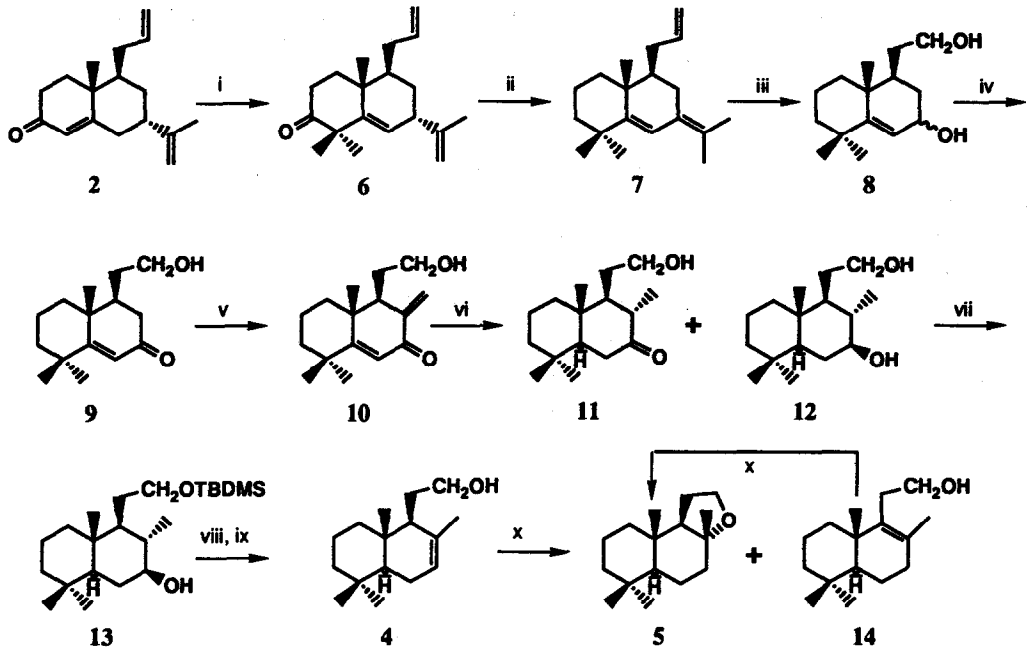
5 (-)-Ambrox® — **4** — **2: R = allyl, 3: R = CN** — **1** S-(+)-carvone

Our retrosynthetic plan to (-)-Ambrox® starting from S-(+)-carvone is shown in scheme 1. Conjugate addition of the indicated nucleophiles to S-(+)-carvone **1** followed by a Robinson annulation with methyl vinyl ketone gives the substituted decalones **2** and **3** stereoselectively[1d] with the chiral centers at C-9[8] and C-10 in the correct configuration for the preparation of (-)-Ambrox®. The allyl and nitrile substituents both can be transformed into the hydroxy ethylene substituent in **4**. The conversion of the isopropenyl group into a carbonyl group at C-7[1a,c,e] gives the opportunity to introduce a methyl group at C-8. This carbonyl group can

be used later on for the introduction of the $\Delta^{7,8}$ double bond in **4** which is necessary for the final cyclization to (-)-Ambrox®.

Decalone **2** in scheme 2 was obtained from S-(+)-carvone *via* conjugate addition of allyl magnesium chloride, followed by annulation of the corresponding silyl enol ether with methyl vinyl ketone[1d]. The required *gem* dimethyl groups were introduced using methyl iodide and standard basic conditions to give ketone **6** in 88% yield. Removal of the carbonyl group and isomerization of the olefinic bond of the isopropenyl group to the exocyclic isopropylidene group were performed in one step[1a,c] under the conditions of the Wolff-Kishner reduction in 85% yield. Ozonolysis of the allylic and exocyclic double bonds in **7** and reduction of the intermediate ozonides with sodium borohydride gave diol **8** in 80% yield. The allylic hydroxyl group was selectively oxidized with manganese dioxide to give the α,β-unsaturated ketone **9** in 90% yield.

Scheme 2

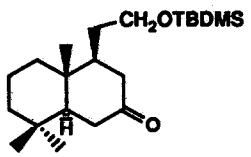


Reagents i: MeI, KO-*t*-Bu, HO-*t*-Bu; ii: Hydrazine, KOH, DEG, 220 °C; iii: O_3, MeOH, -78 °C; $NaBH_4$; iv: MnO_2, acetone; v: $(Me)_2N\text{-}CH_2\text{-}N(Me)_2$, Ac_2O; vi: Li, NH_3, EtOH; vii: TBDMSCl, DMF, imidazole; viii: MsCl, DMAP, CH_2Cl_2; $LiCO_3$, LiBr, Δ; ix: HF, acetonitrile; x: *p*-TsOH, nitromethane.

An obvious way to proceed from this point was the synthesis of hydroxyketone **11** *via* the saturated decalone **15** (figure 1), but this approach was unsuccessful. Although the trans-fused decalone **15** was obtained in good yield *via* catalytic hydrogenation of enone **8** with palladium on activated carbon in ethanol

followed by protection of the primary hydroxyl group with *tert*-butyldimethylsilyl chloride, the subsequent methylation gave very disappointing results. Under the usual kinetic methylation conditions (lithium diisopropylamide, tetrahydrofuran, hexamethylphosphoramide) a large recovery of the starting material was observed. The reaction could not be improved by using a small excess of lithium diisopropylamide (1.5 eq) and/or a higher temperature of 40 °C, because then dimethylation was a competing reaction, in addition to a large recovery of starting material. The introduction of an α-methylene group to **15** by a Mannich reaction followed by β-elimination[9] was unsuccessful too. Heating decalone **15** in a mixture of N,N,N',N'-tetramethyldiaminomethane and acetic anhydride gave a product that according to GC-MS and ^{1}H NMR analysis had an α-methylene group at both C-6 and C-8.

Figure 1



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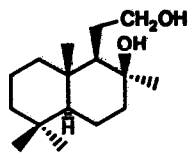

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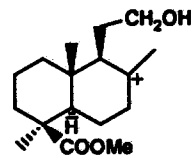


17

Enone **9** gave dienone **10** in 70% yield in the Mannich reaction[9] with N,N,N',N'-tetramethyldiaminomethane and acetic anhydride (scheme 2). Reduction of compound **10** by a large excess of lithium in ammonia and ethanol as the proton donor gave diol **12** in 73% and decalone **11** as a byproduct in 10% yield. Selective protection of the primary hydroxyl group in **12** by *tert*-butyldimethylsilyl chloride (TBDMSCl) gave the monoprotected diol **13** in 98% yield. Dehydration of **13** was performed by mesylation, substitution by bromide and dehydrobromination. Deprotection of the TBDMS ether with hydrofluoric acid gave alcohol **4** in 80% from **13**.

The unsaturated alcohol **4** was transformed into (-)-Ambrox® before *via* a six step procedure[5]. The successful dehydration of racemic alcohol **16** (figure 1) to (±)-Ambrox® by Büchi and Wüest[7a] encouraged us to try the cyclization of alcohol **4** to (-)-Ambrox® in one step, because the same tertiary carbocationic intermediate is assumed to be formed from **4** and **16**. Refluxing of **16** in nitromethane in the presence of *p*-toluenesulfonic acid gave the kinetic cyclization product Ambrox® in excess. The ratio of the thermodynamic and kinetic diastereoisomers in the cyclization of **17** [6a] proved to be only temperature dependent. Decreasing the temperature from 80 °C to 20 °C afforded the kinetic diastereomer almost exclusively.

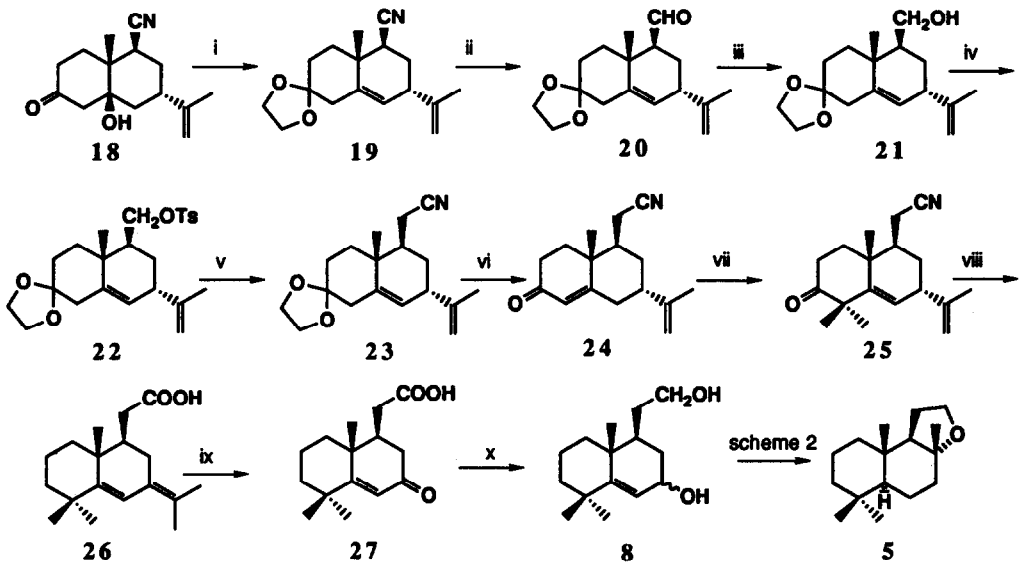
We therefore investigated the cyclization of alcohol **4** *at room temperature* in nitromethane in the presence of *p*-toluenesulfonic acid and indeed in this way (-)-Ambrox® was obtained directly in 80% yield. When the mixture was not stirred long enough, the yield of (-)-Ambrox® was lower and the isomerized alcohol **14** was found as byproduct. Alcohol **14** could be cyclized to (-)-Ambrox® too under the same acidic conditions at room temperature.

A second route to (-)-Ambrox® was developed starting from hydroxyketone **18**, which was obtained from S-(+)-carvone in two steps in an overall yield of 86%[1d]. Although the synthetic sequence involves more steps than the reaction path from **2**, it is more suitable for large scale production.

Hydroxyketone **18** was dehydrated and protected as its acetal in an "one-pot reaction" by refluxing in

toluene with a catalytic amount of *p*-toluenesulfonic acid. Hydroxyketone **18** was first transformed completely into the intermediate **3** and then glycol was added to give the acetal **19** in 90% yield. Compound **19** was reduced with diisobutylaluminum hydride (DIBAH) to give aldehyde **20** in 95% yield and further reduction with sodium borohydride gave alcohol **21** in 99%. The hydroxyl group was tosylated with *p*-toluenesulfonyl choride in pyridine to give tosylate **22** in 96% yield. The tosyl group was replaced by a nitrile group in 99% yield and then the acetal functionality was deprotected with hydrochloric acid to give enone **24** in 93% yield. Methylation with methyl iodide under standard basic conditions gave compound **25** in 80% yield. The conditions of the Wolff-Kishner reduction changed three substituents in one procedure. The C-3 carbonyl group was removed, the isopropenyl group was isomerized into an isopropylidene group and the nitrile substituent was saponified[10] to give acid **26** in 98% yield. Ozonolysis followed by reduction with sodium borohydride gave enone **27** in 90% yield. Reduction of enone **27** with lithium aluminum hydride gave **8** in 80% yield. This diol was transformed into (-)-Ambrox® according to scheme 2.

Scheme 3



Reagents i: *p*-TsOH, toluene, glycol, Δ; ii: DIBAH, toluene; iii: $NaBH_4$; iv: TsCl, pyridine; v: NaCN, DMF; vi: HCl, H_2O; vii: MeI, KO-*t*-Bu, HO-*t*-Bu; viii: Hydrazine, KOH, DEG, 220 °C; ix: O_3, MeOH; x: $NaBH_4$.

Although the synthesis of Ambrox® itself from S-(+)-carvone is not a short one, the approach is flexible and a number of other ambergris derivatives with attractive organoleptic properties[11] can also be synthesized *via* this route.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-E 200 or a Bruker AMX 500 spectrometer. Routine ^{1}H NMR spectra (90 MHz) were recorded on a Varian EM-390 spectrometer. 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 fused silica 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. Dry tetrahydrofuran was obtained by distillation of the commercial material from sodium benzophenone ketyl. Ether was dried by storage over sodium wire. Usually aqueous solutions were extracted three times with ether. The combined organic extracts were washed with brine and dried on magnesium sulfate ($MgSO_4$) prior to filtration and evaporation of the solvent under reduced pressure. Flash chromatography was performed on Merck silica gel (230 - 400 mesh) and mixtures of petroleum ether (PE, boiling range 40 - 60 °C) and ethyl acetate (EtOAc) were used as eluent.

(4aR,5S,7S)-3,4,4a,5,6,7-Hexahydro-7-isopropenyl-5-(prop-2'-enyl)-1,1,4a-trimethyl-naphthalene-2(1H)-one (6)

To a solution of 5.0 g (45 mmol) of potassium-*tert*-butoxide in *tert*-butyl alcohol (80 ml) was added dropwise a solution of 4.47 g (18.3 mmol) of enone **2**[1d] in *tert*-butyl alcohol (20 ml) at room temperature. After stirring for 30 min, 3.4 ml (7.8 g, 55 mmol) of methyl iodide was added in one portion and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and worked up as usual to afford an oily residue which was purified by flash chromatography (eluent PE/EtOAc = 97/3) to give 4.40 g (16.2 mmol, 88%) of ketone **6** as a pale yellow oil.

^{1}H NMR: δ 0.74 (s, 3H); 1.23 (s, 3H); 1.27 (s, 3H); 1.73 (s, 3H); 1.3 - 1.8 (m, 5H); 1.9 - 2.8 (m, 5H); 4.54 (s, 1H); 4.79 (s, 1H); 4.93 (m, 1H); 5.00 (s, 1H); 5.50 (dd, J = 4.8 Hz, 1.0 Hz, 1H); 5.63 (m, 1H). ^{13}C NMR: δ 17.2 (q); 22.0 (q); 25.6 (t); 26.9 (q); 30.1 (q); 31.3 (t); 33.4 (t); 33.9 (t); 37.4 (s); 39.1 (d); 40.9 (d); 48.4 (s); 111.3 (t); 115.6 (t); 123.0 (d); 137.7 (d); 148.0 (s); 150.4 (s); 216.1 (s). HRMS: calcd (M^+) *m/e* 272.2140; found *m/e* 272.2143. $[\alpha]_D = -109$ (c = 0.3).

(1S,8aR)-3-Isopropylidene-1,2,3,5,6,7,8,8a-octahydro-1-(prop-2'-enyl)-4a,8,8-trimethylnaphthalene (7)

A solution of 4.40 g (16.2 mmol) of ketone **6**, 5 ml of hydrazine hydrate and 2.70 g (48 mmol) of potassium hydroxide in diethylene glycol (80 ml) was heated for 2 h at 120 °C and then the excess of hydrazine hydrate and water was removed by distillation. The temperature was raised to 220 °C and after 3 h cooled, poured into water and worked up as usual. The residue was purified by flash chromatography (eluent PE) to afford 3.57 g (13.8 mmol, 85%) of triene **7** as a colourless oil.

^{1}H NMR: δ 1.04 (s, 3H); 1.14 (s, 6H); 1.70 (s, 3H); 1.78 (s, 3H); 0.8 - 2.0 (m, 10H); 2.2 - 2.6 (m, 2H); 5.01

(m, 2H); 5.73 (m, 1H). ^{13}C NMR: δ 18.3 (t); 19.3 (q); 19.9 (q); 20.4 (q); 28.2 (t); 31.1 (q); 32.3 (q); 34.1 (t); 35.9 (s); 37.0 (s); 38.3 (t); 40.8 (t); 46.5 (d); 115.1 (t); 118.3 (d); 124.6 (s); 127.5 (s); 138.6 (d); 151.4 (s). HRMS: calcd (M^+) *m/e* 258.2347; found *m/e* 258.2349. $[\alpha]_D = -64.6$ (c = 0.3).

(1S,3R/S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthaleneethanol (8)

A solution of 3.05 g (11.8 mmol) of triene **7** in 100 ml of methanol/dichloromethane (3/1) was ozonized at -78 °C. The excess of ozone was expelled by purging the solution with nitrogen for 15 min. Then 0.90 g (23.7 mmol) of sodium borohydride was added at -78 °C. The cooling bath was removed and the mixture was stirred for 3 h at room temperature. Water was added and the mixture was worked up as usual to give 2.25 g (9.5 mmol, 80%) of diol **8** as white crystals, mp 122-126 °C after flash chromatography (eluent PE/EtOAc = 3/2).

^1H NMR: (with a drop of $CDOD_3$) δ 1.03 (s, 6H); 1.09 (s, 3H); 0.70 - 1.95 (m, 11H); 2.79 (bs, 2H); 3.45 - 3.80 (m, 2H); 4.12 - 4.30 (m, 1H); 5.42 - 5.48 (m, 1H). ^{13}C NMR: δ 18.4 (t); 20.6 (q); 30.0 (q); 32.4 (t); 32.9 (q); 33.3 (t); 35.8 (s); 37.7 (s); 38.2 (t); 41.0 (t); 42.8 (d); 61.4 (t); 68.0 (d); 122.9 (d); 153.6 (s). HRMS: calcd (M^+) *m/e* 238.1933; found *m/e* 238.1924. Anal: calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00; found: C, 75.78; H, 11.14. $[\alpha]_D = +10.9$ (c = 0.4).

(1S,8aR)-1,2,3,5,6,7,8,8a-Octahydro-3-oxo-5,5,8a-trimethyl-1-naphthaleneethanol (9)

A mixture of 2.00 g (8.4 mmol) of diol **8** and 7.3 g (84 mmol) of manganese dioxide in acetone was stirred for 8 h. After filtration over hyflo the acetone was evaporated and the residue was purified by flash chromatography (eluent PE/EtOAc = 3/2) to afford 1.78 g (7.5 mmol, 90%) of enone **9** as a colourless oil.

^1H NMR: δ 1.13 (s, 3H); 1.15 (s, 3H); 1.18 (s, 3H); 1.00 - 2.55 (m, 12H); 3.50 - 3.80 (m, 2H); 5.99 (s, 1H). ^{13}C NMR: δ 17.8 (t); 19.5 (q); 30.5 (q); 31.7 (q); 31.8 (t); 37.1 (s); 37.2 (t); 38.7 (s); 39.0 (t); 39.5 (t); 43.2 (d); 60.6 (t); 123.8 (d); 179.8 (s); 200.2 (s). HRMS: calcd (M^+) *m/e* 236.1776; found *m/e* 236.1776. $[\alpha]_D = -36.7$ (c = 0.4).

(1R,8aR)-2-Methylene-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,5,8a-trimethyl-1-naphthleneethanol (10)

To a solution of 0.62 g (2.64 mmol) of hydroxyketone **9** in 2 ml of N,N,N',N'-tetramethyldiaminomethane was added 2 ml of acetic anhydride. The reaction mixture was heated for 2 h at 90 °C under a nitrogen atmosphere. Water was added and the mixture was worked up as usual. The residue was dissolved into methanol and stirred for 1 h at room temperature with 0.18 g (1.3 mmol) of potassium carbonate. The mixture was worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 7/3) to give 0.64 g (1.85 mmol, 70%) of **10** as a colourless oil.

^1H NMR: δ 1.06 (s, 3H); 1.17 (s, 6H); 1.10 - 2.00 (m, 9H); 2.53 (dd, J = 2.0 Hz, 12.5 Hz, 1H); 3.45 - 3.90 (m, 2H); 5.24 (d, J = 2.0 Hz, 1H); 6.13 (s, 2H). ^{13}C NMR: δ 18.2 (t); 20.9 (q); 27.6 (t); 30.4 (q); 31.5 (q); 37.3 (s); 37.5 (t); 39.6 (t); 41.3 (s); 49.4 (d); 61.1 (t); 118.5 (t); 123.6 (d); 144.6 (s); 179.7 (s); 190.6 (s). HRMS: calcd (M^+) *m/e* 248.1776; found *m/e* 248.1779. $[\alpha]_D = -145.1$ (c = 0.3).

(1S,2S,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-3-oxo-2,5,5,8a-tetramethyl-1-naphthaleneethanol (11)
(1S,2S,3S,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-3-hydroxy-2,5,5,8a-tetramethyl-1-naphthaleneethanol (12)

To a solution of dienone **10** (0.40 g,1.6 mmol) in a mixture of anhydrous ether (1 ml), ethanol (1 ml) and ammonia (20 ml), lithium (0.30 g, 43 mgrat) was added slowly in small pieces under a nitrogen atmosphere. The mixture was stirred for 3 h at -33 °C, while a persistent blue color remained. Then solid ammonium chloride was introduced to quench the excess of lithium. After evaporation of the ammonia, water was added and the mixture was worked up as usual. Flash chromatography (eluent PE/EtOAc= 3/2) gave 0.04 g (0.16 mmol, 10%) of hydroxyketone **11** as a colourless oil and 0.30 g (1.17 mmol, 73%) of diol **12** as white crystals, mp 120 - 122 °C.

11: ^{1}H NMR: δ 0.80 (s, 3H); 0.81 (s, 3H); 0.98 (s, 3H); 1.01 (d, J = 6.5 Hz, 3H); 0.90 - 1.95 (m, 10H); 2.10 - 2.50 (m, 4H); 3.38 - 3.68 (m, 2H). ^{13}C NMR: δ 12.8 (q); 13.6 (q); 18.4 (t); 21.1 (q); 32.7 (q); 32.7 (t); 33.7 (s); 38.1 (s); 38.5 (t); 38.9 (t); 41.7 (t); 47.8 (d); 54.0 (d); 54.1 (d); 63.5 (t); 213.1 (s) . HRMS: calcd (M^+) *m/e* 252.2089; found *m/e* 252.2091. $[\alpha]_D$ = -12.3 (c = 1.0).

12: ^{1}H NMR: δ 0.81 (s, 6H); 0.84 (s, 3H); 1.01 (d, J = 6.2 Hz, 3H); 0.40 - 0.55 (m, 1H); 0.80 - 1.92 (m, 14H); 3.12 (ddd, J = 6.2 Hz, 12.0 Hz, 12.5 Hz, 1H); 3.40 - 3.70 (m, 2H). ^{13}C NMR: δ 14.2 (q); 16.2 (q); 18.5 (t); 21.7 (q); 31.2 (t); 32.0 (t); 33.1 (s); 33.2 (q); 37.8 (s); 38.8 (t); 41.9 (t); 42.0 (d); 51.6 (d); 52.1 (d); 64.2 (t); 76.7 (d) . HRMS: calcd (M^+-18) *m/e* 236.2140; found *m/e* 236.2134. $[\alpha]_D$ = + 16.2 (c = 0.3).

(2S,3S,4S,4aR,8aS)-4-[2'-*tert*-Butyldimethylsilyloxy)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-3,4a,8,8-tetra-methyl-2-naphthalenol (13)

To a solution of 0.190 g (0.748 mmol) of diol **12** in 20 ml of N,N-dimethylformamide was added 0.135 g (0.898 mmol) of *t*-butyldimethylsilyl chloride and 0.15 g (2.2 mmol) of imidazole. The mixture was stirred at room temperature for 1 h. Water was added and the mixture was worked up as usual. The monosilylated alcohol **13** was obtained pure after evaporation of the solvent (0.270 g, 0.734 mmol, 98%) as white crystals, mp 86 - 87 °C.

^{1}H NMR: δ 0.03 (s, 6H); 0.30 - 0.46 (m, 1H); 0.80 (s, 6H); 0.84 (s, 3H); 0.88 (s, 9H); 1.13 (d, J = 9.4 Hz, 3H); 1.05 - 1.92 (m, 13H); 3.09 (ddd, J = 5.4 Hz, 10.5 Hz, 11.4 Hz, 1H); 3.33 - 3.67 (m, 2H). ^{13}C NMR: δ -5.2 (2 * q); 14.2 (q); 16.3 (q); 18.4 (s); 18.5 (t); 21.7 (q); 26.0 (3*q); 31.2 (t); 32.1 (t); 33.1 (s); 33.3 (q); 37.8 (s); 38.8 (t); 42.0 (d); 42.0 (t); 51.5 (d); 52.2 (d); 64.6 (t); 76.8 (d). HRMS: calcd (M^+-57) *m/e* 311.2406; found *m/e* 311.2408. Anal: calcd for $C_{22}H_{44}O_2Si$: C, 71.69; H, 12.03; found: C, 71.89; H, 12.38. $[\alpha]_D$ = +15.3 (c = 0.8).

(1S,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthaleneethanol (4)

A mixture of 0.27 g (0.734 mmol) of **13**, 0.7 g (5.6 mmol) of 4-N,N-dimethylaminopyridine and 0.3 ml (3.9 mmol) of methanesulfonyl chloride in 10 ml of dichloromethane was stirred at room temperature for 1 h. Water was added and the mixture was worked up as usual. After evaporation of the solvent 0.3 g (3.4 mmol) of lithium bromide and 0.26 g (3.4 mmol) of lithium carbonate in 2 ml of N,N-dimethylformamide were added and the mixture was heated at 150 °C for 2 h. Water was added and the mixture was worked up as usual. Flash chromatography with PE as the eluent gave 0.15 g (0.42 mmol, 58%) of *(1S,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-[2'-tert-butyldimethyl-silyloxy)ethyl]-naphthalene.*

Further elution (eluent PE/EtOAc =7/3) gave 0.05 g (0.21 mmol, 29%) of alcohol **4**. The TBDMS ether was dissolved in 5 ml of acetonitrile and 5 drops of 48% aqueous hydrofluoric acid were added and the mixture was stirred at room temperature for 1 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (5 ml) and extracted twice with ether. The extract was washed with water, dried and evaporated. Flash chromatography (eluent PE/EtOAc =7/3) gave a second crop of alcohol **4** of 0.089 g (0.38 mmol, 51%).
TBDMS ether: ^{1}H NMR: δ 0.05 (s, 6H); 0.75 (s, 3H); 0.84 (s, 3H); 0.87 (s, 3H); 0.91 (s, 9H); 1.0 - 2.15 (m, 15H); 3.35 - 3.82 (m, 2H); 5.39 (bs, 1H). ^{13}C NMR: δ -5.2 (2 * q); 13.5 (q); 18.4 (s); 18.7 (t); 21.8 (q); 22.1 (q); 23.8 (t); 26.0 (3*q); 30.4 (t); 32.9 (s); 33.1 (q); 36.5 (s); 39.1 (t); 42.3 (t); 50.1 (d); 50.6 (d); 64.7 (t); 122.3 (d); 134.9 (s). HRMS: calcd (M^+-57) *m/e* 293.2301; found *m/e* 293.2301. $[\alpha]_D$ = -6.7 (c = 0.7).
4: ^{1}H NMR: δ 0.74 (s, 3H); 0.82 (s, 3H); 0.85 (s, 3H); 1.64 (bs, 3H); 0.75 - 2.03 (m, 12H); 2.21 (s, 1H); 3.42 - 3.60 (m, 1H); 3.65 - 3.84 (m, 1H); 5.38 (m, 1H). ^{13}C NMR: δ 13.5 (q); 18.7 (t); 21.8 (q); 22.0 (q); 23.7 (t); 29.7 (t); 32.9 (s); 33.1 (q); 36.4 (s); 39.1 (t); 42.2 (t); 50.0 (d); 50.7 (d); 64.2 (t); 122.6 (d); 134.5 (s). HRMS: calcd (M^+) *m/e* 236.2140; found *m/e* 236.2142. $[\alpha]_D$ = -11.8 (c = 0.9).

(3aR,5aS,9aS,9bR)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (Ambrox®) (5)
A mixture of 0.050 g (0.21 mmol) of **4** and 0.03 g (0.16 mmol) of *p*-toluenesulfonic acid in 3 ml of nitromethane was stirred at room temperature for 18 h. Ether was added and the mixture was washed with saturated aqueous sodium bicarbonate and dried ($MgSO_4$). Flash chromatography (eluent PE/EtOAC =19/1) removed the small amount of iso-ambrox (< 5% according to GLC) and gave 0.040 g (0.17 mmol, 80%) of Ambrox® as white crystals, mp 74 - 75 °C (ref. [6a]: mp 74 - 76 °C).

A mixture of 0.089 g (0.375 mmol) of **4** and 0.06 g (0.32 mmol) of *p*-toluenesulfonic acid in 5 ml of nitromethane gave after stirring for 8 h and the same work-up and purification procedure 0.051 g (0.214 mol, 57%) of Ambrox® and after further elution (eluent PE/EtOAc = 4/1) 0.020 g (0.085 mmol, 23%) of isomerized alcohol **14**. Stirring of alcohol **14** in 5 ml of nitromethane with 0.03 g (0.16 mmol) of *p*-toluenesulfonic acid for 48 h gave a second crop of Ambrox® after the same work-up and purification procedure of 0.014 g (0.06 mmol, 16%).
Ambrox®: ^{1}H NMR (500MHz): δ 0.81 (s, 3H); 0.82 (s, 3H); 0.86 (s, 3H); 0.94 (dd, J = 12.4 Hz, 2.8 Hz, 1H); 1.02 (td, J = 12.7 Hz, 3.7 Hz, 1H); 1.07 (s, 3H); 1.17 (td, J = 14.1 Hz, 4.6 Hz, 1H); 1.22 - 1.50 (m, 6H); 1.60 - 1.78 (m, 4H); 1.92 (dt, J = 11.6 Hz, 3.3 Hz, 1H); 3.80 (q, J = 8.2 Hz, 1H); 3.83 - 3.94 (m, 1H). ^{13}C NMR: δ 15.0 (q); 18.4 (t); 20.6 (t); 21.1 (2*q); 22.6 (t); 33.0 (s); 33.5 (q); 36.1 (s); 39.7 (t); 39.9 (t); 42.4 (t); 57.2 (d); 60.1 (d); 64.9 (t); 79.9 (s). HRMS: calcd (M^+) *m/e* 236.2140; found *m/e* 236.2144. Anal: calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94; found: C, 80.98; H, 12.02. $[\alpha]_D$ = -24.6 (c = 0.5) (ref. [6a]: $[\alpha]_D$ = -22.1 (c = 0.7)).
14: ^{1}H NMR (90 MHz, major signals): δ 0.90 (s, 3H); 0.93 (s, 3H); 0.96 (s, 3H); 1.65 (s, 3H); 3.60 (t, J = 8 Hz, 2H)).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalenecarbonitrile (19)
A solution of 23.0 g of hydroxyketone **18**[1d] (93.1 mmol) in 200 ml of toluene was heated under reflux with a water separator in the presence of 1.5 g of *p*-toluenesulfonic acid. After 1.5 h 10 ml of ethylene glycol was

added and refluxing was continued for 2 h. Saturated sodium bicarbonate was added and the mixture was worked up as usual. The residue was recrystallized from methanol to afford 22.8 g (83.5 mmol, 90%) of acetal **19** as white crystals, mp 99 - 100 °C.

^{1}H NMR: δ 1.23 (s, 3H); 1.74 (s, 3H); 1.30 - 2.25 (m, 7H); 2.40 - 2.72 (m, 3H); 3.91 (bs, 4H); 4.70 (s, 1H); 4.90 (s, 1H); 5.20 (d, J = 4.9 Hz, 1H). ^{13}C NMR: δ 19.2 (q); 21.9 (q); 25.6 (t); 30.6 (t);35.3(d); 35.9 (s); 36.3 (t); 40.3 (d); 41.4 (t); 64.0 (t); 64.2 (t); 108.5 (s); 114.0 (t); 121.2 (s); 123.6 (d); 138.4 (s); 145.5 (s). HRMS: calcd (M^+) *m/e* 273.1729 ; found *m/e* 273.1729. Anal: calcd for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12; found: C, 74.40; H, 8.52; N, 4.88. $[\alpha]_D = -118.4$ (c = 0.3).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalene-carboxaldehyde (20)

To 10.0 g (36.6 mmol) of **19** in 250 ml of dry toluene was added dropwise under nitrogen 37 ml of 1.2 M diisobutylaluminum hydride in toluene at -78 °C. After 1 h 5 ml of water was added dropwise and the solution was stirred at room temperature for a 0.5 h. Then 5 ml of aqueous 4N sodium hydroxide was added dropwise. After 1 h $MgSO_4$ was added and stirring was continued for a 0.5 h. Purification by a short column of silica (eluent PE/EtOAc =9/1) gave 9.55 g (34.6 mmol,95%) of aldehyde **20** as white crystals, mp 104 - 105 °C.

^{1}H NMR: δ 1.14 (s, 3H); 1.79 (s, 3H); 1.65 - 2.45 (m, 8H); 2.50 (dt, J = 2.2 Hz, 14.1 Hz, 1H); 2.69 (bs, 1H); 3.99 (s, 4H); 4.78 (s, 1H); 4.92 (s, 1H); 5.31 (d, J = 5.6 Hz, 1H); 9.93 (s, 1H). ^{13}C NMR: δ 18.47 (q);21.50 (t); 21.98 (q); 30.64 (t); 36.35 (t); 36.65 (s); 40.42 (d); 40.97 (t); 53.67 (d); 64.00 (t); 64.15 (t); 108.56 (s); 113.11 (t); 124.65 (d); 139.48 (s); 146.40 (s); 205.02 (d). HRMS: calcd (M^+) *m/e* 276.1725; found *m/e* 276.1725. Anal: calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; found: C, 73.98; H, 8.97. $[\alpha]_D = -114.9$ (c = 0.4).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalene-methanol (21)

To 8.72 g (31.6 mmol) of **20** in 200 ml of ethanol was added 1.0 g of sodium borohydride (26 mmol) at 0 °C. After 30 min the ethanol was partly evaporated and water was added. The residue was worked up as usual. Recrystallization of the residue from PE/EtOAc gave 8.70 g (31.3 mmol, 99%) of **21** as white crystals, mp 82 - 83 °C.

^{1}H NMR: δ 0.99 (s, 3H); 1.80 (s, 3H); 1.35 - 2.05 (m, 8H); 2.14 (dd, J = 2.8 Hz, 13.9 Hz, 1H); 2.50 (dt, J = 2.2 Hz, 13.9 Hz, 1H); 2.69 (bs, 1H); 3.36 (dd, J = 8.0 Hz, 10.5 Hz, 1H); 3.77 (dd, J = 3.5 Hz, 10.6 Hz, 1H); 3.97 (bs, 4H); 4.78 (bs, 1H); 4.89 (bs, 1H); 5.31 (d, J = 4.9 Hz, 1H). ^{13}C NMR: δ 17.2 (q); 22.1 (q); 24.8 (t); 30.9 (t); 36.0 (t); 36.2 (s); 41.1 (t); 41.2 (d); 43.3 (d); 63.3 (t); 63.9 (t); 64.0 (t); 109.0 (s); 112.4 (t); 125.0 (d); 140.2 (s); 147.1 (s) . HRMS: calcd (M^+) *m/e* 278.1882; found *m/e* 278.1883. Anal: calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41; found: C, 72.96; H, 9.48. $[\alpha]_D = -105.9$ (c = 0.4).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-tosyloxymethyl-naphthalene (22)

To 5.33 g (19.2 mmol) of **21** in 50 ml of pyridine was added 5.0 g of tosylchloride (26.2 mmol, 1.36 eq). After 2 h 50 ml of water was added and the mixture was extracted with ether (3 x 100 ml). The combined organic layers were washed with a saturated bicarbonate solution and with brine and dried, filtrated and

evaporated. Purification by flash chromatography (eluent PE/EtOAc = 17/3) gave 7.99 g (18.49 mmol,96%) of **22** as white crystals, mp 78 - 79 °C.
^{1}H NMR: δ 0.93 (s, 3H); 1.74 (s, 3H); 1.20 - 1.90 (m, 7H); 2.16 (dd, J = 2.6 Hz, 4.0 Hz, 1H); 2.47 (s, 3H); 2.45 - 2.70 (m, 2H); 3.94 (bs, 4H); 3.83 - 4.05 (m, 1H); 4.16 (dd, J = 4.4 Hz, 9.7 Hz, 1H);4.70 (s, 1H); 4.84 (s, 1H); 5.27 (d, 4.6 Hz, 1H); 7.36 (d, J = 8.2 Hz, 2H); 7.79 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 17.2 (q); 21.4 (q); 21.9 (q); 24.6 (t); 30.7 (t); 35.8 (t); 36.1 (s); 40.0 (d); 40.8 (d); 41.1 (t); 63.9 (t); 64.1 (t); 71.4 (t); 108.7 (s); 112.7 (t); 124.9 (d); 127.6 (2*d); 129.6 (2*d); 132.9 (s); 139.5 (s); 144.4 (s); 146.5 (s). HRMS: calcd (M^+) *m/e* 432.1970; found *m/e* 432.1969. Anal: calcd for $C_{24}H_{32}O_5S$: C, 66.64; H, 7.46; found: C, 66.59; H, 7.65. $[\alpha]_D$ = -76.4 (c = 0.3).

(1R,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthaleneacetonitrile (23)
A mixture of 12.40 g (28.7 mmol) of **22** and 3.0 g (61 mmol) of sodium cyanide in 100 ml of N,N-dimethylformamide was heated to 90 °C for 3 h. Water was added and the mixture was worked up as usual. Purification by flash chromatography (eluent PE/EtOAc =17/3) gave 8.14 g (28.3 mmol,99%) of **23** as white needles, mp 66 - 67 °C.
^{1}H NMR: δ 1.00 (s, 3H); 1.83 (s, 3H); 1.20 - 1.95 (m, 7H); 2.05 - 2.30 (m, 2H); 2.43 - 2.80 (m, 3H); 3.96 (bs, 4H); 4.78 (s, 1H); 4.92 (s, 1H); 5.33(d, J = 4.5 Hz, 1H) ^{13}C NMR: δ 16.8 (q); 18.4 (t); 21.9 (q); 27.2 (t); 30.8 (t); 35.6 (t); 36.8 (s); 38.3 (d); 41.1 (t); 41.2 (d); 64.0 (t); 64.1 (t); 108.7 (s); 112.9 (t); 119.6 (s); 125.0 (d); 139.3 (s); 146.4 (s). HRMS: calcd (M^+) *m/e* 287.1885; found *m/e* 287.1884. Anal: calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87; found: C, 74.87; H, 8.82; N, 4.67. $[\alpha]_D$ = -116.7 (c = 0.5).

(1R,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-6-oxo-1-naphthaleneacetonitrile (24)
To a solution of 3.54 g(12.3 mmol) of **23** in 50 ml of acetone was added 1 ml of an aqueous 4N hydrochloric acid solution. The mixture was stirred for 1 h. The mixture was concentrated *in vacuo*. Water was added and the mixture was worked up as usual. Flash chromatography (eluent PE/EtOAc = 7/3) gave 2.78 g (11.4 mmol, 93 %) of **24** as pale yellow crystals, mp 69 - 70°C.
^{1}H NMR: δ 1.14 (s, 3H); 1.71 (s, 3H); 1.65 - 2.75 (m, 12H); 4.73 (s, 1H); 4.88 (s, 1H); 5.82 (s, 1H). ^{13}C NMR: δ 16.3 (q); 18.0 (t); 22.3 (q); 29.0 (t); 33.4 (t); 35.0 (t); 35.5 (t); 38.3 (s); 38.7 (d); 39.2 (d); 112.9 (t); 118.8 (s); 126.2 (d); 145.5 (s); 167.3 (s); 197.5 (s). HRMS: calcd (M^+) *m/e* 243.1623; found *m/e* 243.1623. Anal: calcd for $C_{16}H_{21}O_1N$: C, 78.97; H, 8.70; N, 5.76; found: C, 78.55; H, 8.74; N, 5.67. $[\alpha]_D$ = + 112.2 (c = 0.3).

(1R,3S,8aR)-3-Isopropenyl-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthaleneacetonitrile (25)
To 100 ml of *tert*-butyl alcohol was added 7.0 g (62.4 mmol) of potassium *tert*-butoxide. Then 6.55 g (28.6 mmol) of enone **24** was added and the mixture was stirred at room temperature. After 1 h 6 ml (96.4 mmol) of methyl iodide was added in one portion and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and worked up as usual. Flash chromatography of the residue (eluent PE/EtOAc = 19/1) gave 5.88 g (22.9 mmol, 80%) of **25** as white crystals, mp 99 - 100 °C.
^{1}H NMR: δ 0.79 (s, 3H); 1.26 (s, 3H); 1.31 (s, 3H); 1.81 (s, 3H); 1.55 - 2.03 (m, 5H); 2.12 (dd, J = 9.4 Hz,

16.4 Hz, 1H); 2.40 - 2.73 (m, 3H); 2.80 (t, J = 5.0 Hz, 1H); 4.59 (bs, 1H); 4.88 (bs, 1H); 5.57 (d, J = 5.0 Hz, 1H). ^{13}C NMR: δ 17.0 (q); 18.6 (t); 22.0 (q); 26.7 (t); 26.8 (q); 30.1 (q); 31.4 (t); 33.0 (t); 37.1 (s); 37.6 (d); 40.5 (d); 48.5 (s); 112.2 (t); 119.2 (s); 123.3 (d); 147.0 (s); 149.1 (s); 214.8 (s). HRMS: calcd (M^+) *m/e* 271.1936; found *m/e* 271.1935. Anal: calcd for $C_{18}H_{25}O_1N$: C, 79.66; H, 9.28; N, 5.16; found: C, 79.47; H, 9.47; N, 5.08. $[\alpha]_D$ = -66.6 (c = 0.4).

(1R,8aR)-3-Isopropylidene-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthaleneacetic acid (26)

A solution of 4.00 g (14.8 mmol) of ketone **25**, 5 ml of hydrazine hydrate and 3.0 g (53.6 mmol) of potassium hydroxide in diethylene glycol (150 ml) was heated for 3 h at 120 °C and then the excess of hydrazine hydrate and water was removed by distillation. The mixture was heated to 220 °C for 18 h and then cooled, poured into water and acidified with hydrochloric acid. The mixture was extracted with ether (3 x 200 ml). The combined ethereal layers were extracted with an aqueous 1 N sodium hydroxide solution (3 x 50 ml). The last obtained combined aqueous layers were acidified with hydrochloric acid and extracted with ether. The last obtained ethereal layers were washed with water, dried and evaporated to give 4.00 g (14.5 mmol, 98%) of carboxylic acid **26**, which was used immediately for the next reaction, without further purification.

^1H NMR (90 MHz, major signals): δ 1.00 (s, 3H); 1.20 (s, 6H); 1.72 (s, 3H); 1.82 (s, 3H); 6.40 (s, 1H); 8.50 - 9.30 (bs, 1H).

(1R,8aR)-1,2,3,5,6,7,8,8a-Octahydro-3-oxo-5,5,8a-trimethyl-1-naphthaleneacetic acid (27)

A solution of 4.00 g (14.5 mmol) of carboxylic acid **26** in methanol (50 ml) was ozonolysed at -78 °C. The excess of ozone was expelled by purging the solution with nitrogen for 15 min. Then 0.65 g (14.5 mmol) of sodium borohydride was added at -78 °C. The cooling bath was removed and the mixture was stirred for 3 h at room temperature. Water was added and the mixture was acidified with hydrochloric acid and extracted with ether (3 x 50 ml). The combined ethereal layers were washed with water, dried and evaporated to give 3.26 g (13 mmol, 90%) of carboxylic acid **27** which was used without further purification.

^1H NMR (90 MHz, major signals): δ 1.16 (s, 6H);1.21 (s, 3H); 6.05 (s, 1H), 7.5-8.4 (bs, 1H).

(1S,3R/S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthaleneethanol (8)

A solution of 3.00 g (12 mmol) of **27** in 50 ml of dry ether was added dropwise to 0.85 g (22 mmol) of lithium aluminum hydride under a nitrogen atmosphere and the mixture was stirred for 18 h. Then 0.9 ml of water was added, after 30 min followed by 0.9 ml of a 4N sodium hydroxide solution. The mixture was stirred for 30 min and 2.7 ml of water was added, after 30 min followed by $MgSO_4$. The mixture was filtered after 2 h and the solvent was evaporated *in vacuo* , purified by flash chromatography (eluent PE/EtOAc = 3/2) to give 2.28 g (9.6 mmol, 80%) of diol **8** as white crystals, mp 122 - 126 °C.

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