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The synthesis of Ambrox®-like compounds starting from (+)-larixol. Part 2

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Abstract—Several Ambrox®-like compounds were synthesized in an enantiomerically pure form, and in relatively short procedures, starting from (+)-larixol. Triol **5** and enone **6** are important intermediates in these syntheses. The formation of Δ^6-Ambrox®-type ethers was achieved by a new cyclization approach via ionization of the C(6)-allylic alcohol in ring B. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Labdane diterpenoids[1] are easily available from Nature and they are used frequently as starting material for the synthesis of (−)-Ambrox® and related flavour compounds.[2] (−)-Sclareol[3] has been studied extensively for this purpose, but larixol (**1**) and larixyl acetate are also easily available from Nature.[4,5] These labdanes may provide for suitable synthons for the synthesis of Ambrox® related compounds[6] as well, especially for those that are modified at C(6) like 6-oxo-Sclareolide (**2**), 6-oxo-Ambrox® (**3**) and Δ^6-Ambroxene (**4**) (Fig. 1). It is known that small structural changes such as the introduction of a double bond, a hydroxyl functionality, or a ketone in Ambrox® can change the odour properties. Derivatives functionalized in ring B at position C(5), C(6) and C(7)[6,7] are amber odoriferous, in some cases even more intense than the non functionalized analogues. 6α-Hydroxy-Ambrox® has been used as a key intermediate in such syntheses before[6] and now we report on the use of triol **5** and enone **6** as attractive intermediates for the synthesis of Ambrox® related compounds.

2. Results and discussion

(+)-Larixol (**1**) was isolated from the resin of venice larch

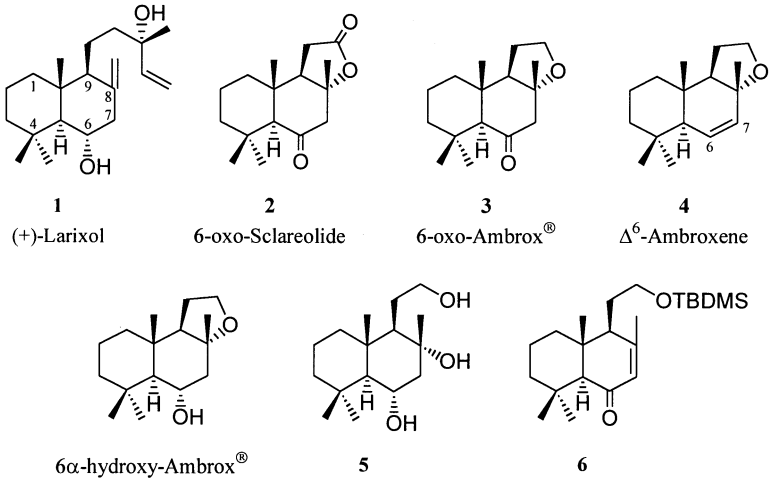

Figure 1.

Keywords: larixol; Ambrox®-like compounds; Δ^6-Ambroxene.
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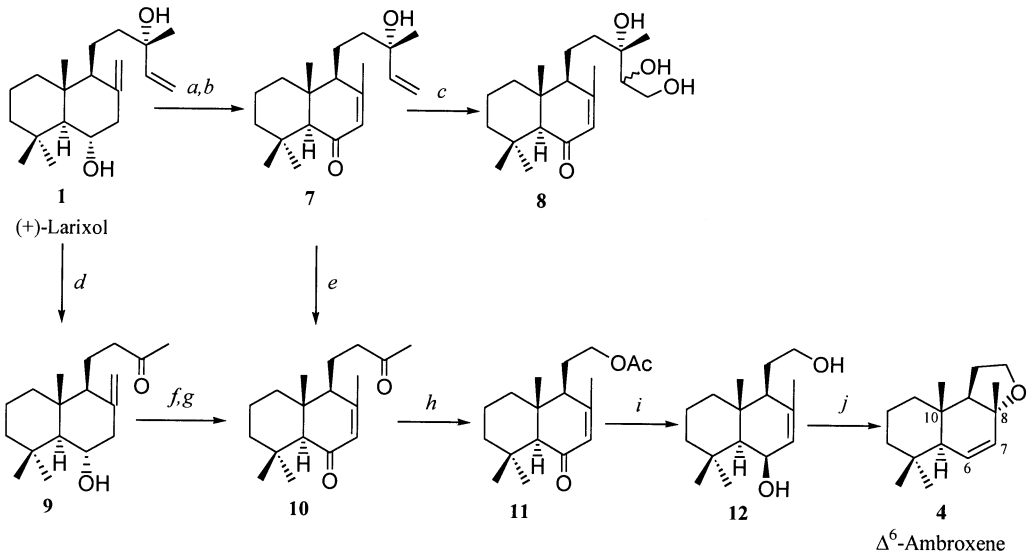
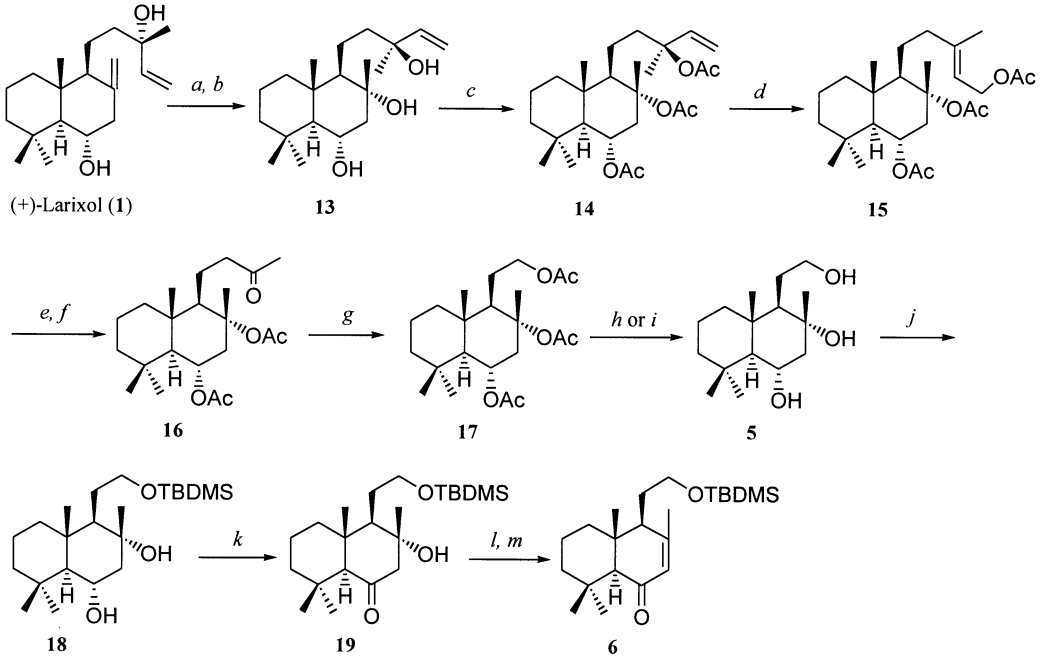


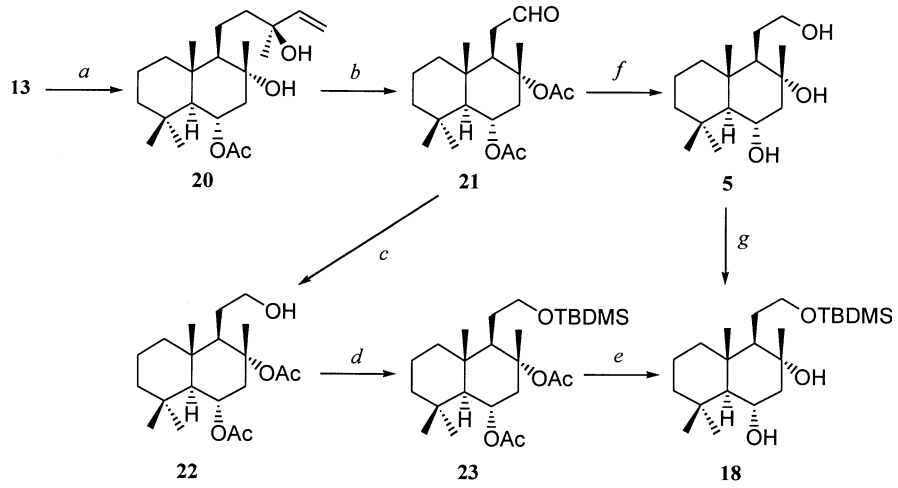
Scheme 1. *Reagents and conditions:* (*a*) PCC, CH_2Cl_2, 95%; (*b*) $NaOCH_3$, MeOH, 98%; (*c*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 56%; (*d*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 68%; (*e*) $KMnO_4$, BTEACl, CH_2Cl_2, rt,))), 68%; (*f*) PCC, CH_2Cl_2, 89%; (*g*) NaOMe, MeOH, 92%; (*h*) *m*-CPBA, $BF_3{\cdot}OEt_2$, 30%; (*i*) $LiAlH_4$, THF, 0°C to rt; (*j*) *p*-TsOH, CH_3NO_2, 37% (2 steps).

turpentine,[4,6,8] and as our first goal the synthesis of Δ^6-Ambroxene was undertaken as depicted in Scheme 1.

To get the known conjugated enone **10**,[9,10] a more efficient route was developed and starting from (+)-larixol (**1**) two reaction sequences have been investigated. The hydroxyl group at C(6) was oxidized with pyridinium chlorochromate (PCC) followed by base catalyzed isomerization of the double bond to give the conjugated enone **7** in high yield. The standard $KMnO_4$ oxidation (3 equiv. $KMnO_4$, 0°C) of the side chain in **7** did not give the desired methyl ketone **10**, but triol **8** as the main product.[6] However, sonication of **7** at room temperature gave the desired diketone **10** in 68% yield. An alternative procedure is to oxidize first the side chain of larixol with $KMnO_4$ to methyl ketone **9**,[6] followed by oxidation of the hydroxyl group at C(6) and isomerization of the double bond. In this way diketone **10** was obtained in 56% overall yield.[11] However, also in our hands the Bayer–Villiger oxidation of **10** to **11**, using various conditions, could only be accomplished in a moderate 30% yield, along with unreacted starting material (ca. 50%).[10b] Also the reduction of **11** to diol **12** could not be



Scheme 2. *Reagents and conditions:* (*a*) oxone, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 81%; (*b*) $LiAlH_4$, THF, 0°C to rt, 94%; (*c*) AcCl, *N*,*N*-dimethylaniline, 93%; (*d*) $PdCl_2(CH_3CN)_2$, THF, 98%; (*e*) O_3, CH_2Cl_2/MeOH 1:1, −78°C; (*f*) PPh_3, −78°C, 95% (2 steps); (*g*) *m*-CPBA, CH_2Cl_2, 83%; (*h*) $LiAlH_4$, THF, 0°C to rt, 94%; (*i*) NaOMe, MeOH, 85%; (*j*) TBDMSiCl, DMF, imidazole, N_2, 95%; (*k*) PDC, CH_2Cl_2, 3 Å molecular sieves, 86%; (*l*) $SOCl_2$, py, DMAP, 0°C to rt; (*m*) NaOMe, MeOH, 82% (2 steps).

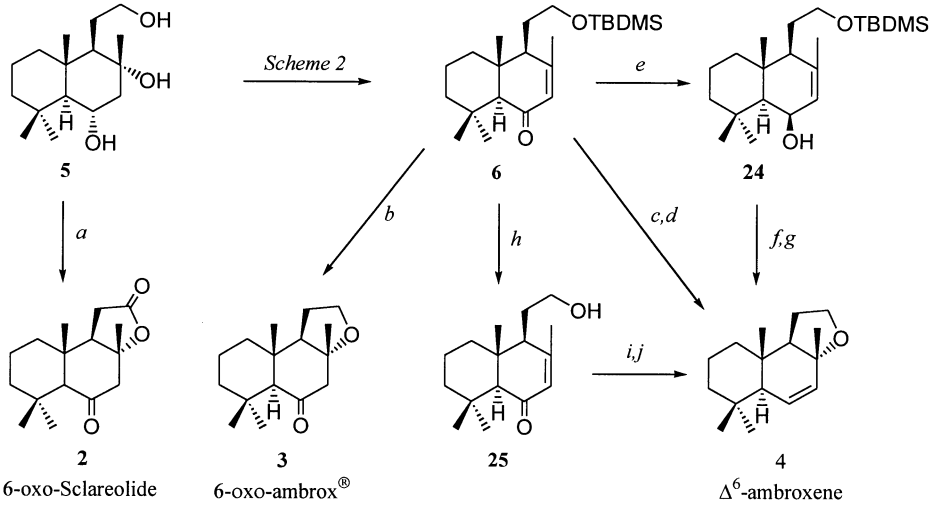


Scheme 3. *Reagents and conditions:* (*a*) Ac_2O, py, DMAP, CH_2Cl_2, 91%; (*b*) cat. OsO_4, $NaIO_4$, THF, 84%; (*c*) $NaBH_4$, MeOH, 80%; (*d*) TBDMSiCl, imidazole, DMF, N_2, 92%; (*e*) NaOMe, MeOH, 50°C, 5 h, 34%; (*f*) $LiAlH_4$, THF, 0°C to rt, 93%; (*g*) TBDMSiCl, imidazole, DMF, N_2, 95%.

effected in a good yield, and acid catalyzed cyclization of **12** gave the desired compound **4** in an overall of 37% yield. The configuration of **4** was determined by $^1H,^1H$-NOESY-NMR, whereby a clear nOe was observed between the protons of the C(8)-methyl-group and the C(10)-methyl-group. For these reasons this route to diol **12** was not elaborated further, but the good result in the cyclization reaction encouraged us to look for a better synthesis of **12**. The reduction of the carbonyl group in enone **6** (Scheme 2) could provide a solution for this problem.

The oxidative breakdown of the side chain to a hydroxyethyl group can be accomplished in several ways and a modified version of one of the routes described before[6] is depicted in Scheme 2. In this route the exocyclic double bond of larixol (**1**) was first converted to compound **13** by epoxidation with oxone followed by reduction of the epoxide with $LiAlH_4$.[12] Its structure was determined unambiguously by spectroscopy and X-ray.[13] Peracetylation,[3i] palladium catalyzed isomerization[14] of the allylic acetate in the side chain and ozonolysis afforded methyl ketone **16**, which upon Baeyer–Villiger oxidation gave triacetate **17** in good yield. In general it was noticed that the Baeyer–Villiger reaction of acetates proceed in good yields while other functional groups (e.g. **11**) regularly cause difficulties and low yields. Conversion of the acetates into triol **5** and selective monosilylation[15] of the primary hydroxyl group in the side chain gave the protected diol **18**. Oxidation of the secondary hydroxyl group at C(6) with pyridinium dichromate (PDC),[16] and regioselective elimination of the tertiary hydroxyl group at C(8), with thionylchoride in pyridine,[17] then gave the desired enone **6** in 34% overall yield, starting from (+)-larixol. This enone **6** is also an important intermediate in the total synthesis of the polyoxygenated diterpenes crotomachlin and 8-*epi*-crotomachlin.[18]

Another synthesis of the selectively protected **18** is depicted in Scheme 3. The C(6)-hydroxyl group in **13** could be protected selectively as its acetate, with acetic anhydride in pyridine,[19] and now a sclareol type oxidation[20] of **20** with a catalytic amount of OsO_4 and an excess of $NaIO_4$ afforded in high yield the aldehyde **21**, which upon



Scheme 4. *Reagents and conditions:* (*a*) PCC, CH_2Cl_2, 76%; (*b*) TBAF, dry THF, 18 h, 59%; (*c*) $LiAlH_4$, dry THF, 0°C to rt; (*d*) *p*-TsOH, CH_3NO_2, 40% (2 steps); (*e*) DIBAL-H, dry THF, 0°C, N_2, 90%; (*f*) TBAF, dry THF; (*g*) *p*-TsOH, CH_3NO_2, 87% (2 steps); (*h*) TBAF, dry THF, 1 h, 93%; (*i*) DIBAL-H, dry THF, 0°C, N_2; (*j*) *p*-TsOH, CH_3NO_2, 71% (2 steps).

reduction with $LiAlH_4$ gave triol **5** in a overall yield of 54%, starting from (+)-larixol. This triol could be converted into **18** as described before (Scheme 2). An alternative route to **18** was performed via selective reduction of the aldehyde group in **21**, by the use of $NaBH_4$, followed by protection of the hydroxyl group and transesterification of the acetates with sodium methoxide. However, complete transesterification proved difficult and easily led to mixtures of partly acylated and especially desilylated products, so for practical reasons the route via selective protection of **5** was our preference.

The obtained intermediates, triol **5** and enone **6**, are good starting points for the synthesis of C(6) modified Ambrox®-like compounds (Scheme 4). Oxidation of triol **5** with PCC gave 6-oxo sclareolide (**2**) in 76% yield. Deprotection of the hydroxyl group in the side chain in enone **6** gave cyclization to 6-oxo Ambrox® (**3**).[21,22]

A selective synthesis of Δ^6-Ambroxene (**4**) from enone **6** proved to be possible in one pot, but a two step procedure gave better results. Reduction of the carbonyl group at C(6) with $LiAlH_4$ was accompanied by deprotection of the hydroxyl group in the side chain, and acid catalyzed cyclization of diol **12** afforded Δ^6-Ambroxene (**4**) in a moderate 40% yield. A more than 90% yield of **24** was obtained when the reduction of the enone was performed with DIBAL-H in toluene. Deprotection of the hydroxyl group in **24** by TBAF,[18] followed by acid catalyzed cyclization then gave Δ^6-Ambroxene (**4**) in 78% overall yield, based on **6**. This reaction sequence also could be reversed, so deprotection of the hydroxyl group followed by reduction with DIBAL-H and acid catalyzed cyclization also led to Δ^6-Ambroxene (**4**) in a slightly lower 71% overall yield.

3. Conclusions

Starting from (+)-larixol (**1**), the synthesis of enone **6**, which has been used before as an intermediate in the synthesis of crotomachlin,[18] can be achieved in an enantiomerically pure form in a relatively short procedure of 10 or 8 steps (Schemes 2 or 3, respectively).

The Ambrox®-like compounds **2**, **3** and **4** were also obtained in enantiomerically pure form, starting from (+)-larixol (**1**). The selective synthesis of **4** should be noted because this compound can not be obtained easily by selective elimination of the hydroxyl group at C(6). Such type of eliminations lead to mixtures of alkenes with the Δ^5-compound as the main product.[6] The cyclization via ionization of the allylic alcohol in ring B is a new approach in the formation of Ambrox®-type ethers. The 6-oxo compounds **2** and **3** did not have any smell, but Δ^6-Ambroxene (**4**) exhibits a pleasant Ambrox®-like odour.

4. Experimental[23]

4.1. General procedures

4.1.1. (+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (7). To a stirred solution of (+)-larixol[6] (**1**) (2.5 g, 8.18 mmol) in CH_2Cl_2 (60 mL) were added 3 Å molecular sieves (2.0 g) followed by pyridinium chlorochromate (PCC) (2.63 g, 12.25 mmol) and 10 drops of acetic acid. After 1 h the mixture was filtered over silica gel and flushed with ethyl acetate. Purification of the crude product by flash column chromatography (PE/EA 3:1) gave *(+)-(4S,4aR,8aS)-4-((3S)-3-hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-methyleneoctahydro-1(2H)-naphthalenone* (2.35 g, 7.75 mmol, 95%) as a colorless oil. $[\alpha]_D^{20}$=+74.6 (*c* 3.0) (lit.[24] +76); IR (liquid film) ν_{max} 3467, 2930, 1715, 1652, 1464, 1293, 1233 cm^{-1}; ^1H NMR δ 0.63 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 1.28 (s, 3H), 1.14–1.86 (m, 15H), 4.68 (d, *J*=1.1 Hz, 1H), 4.85 (d, *J*=1.1 Hz, 1H), 5.06 (dd, *J*=1.3, 10.7 Hz, 1H), 5.20 (dd, *J*=1.3, 17.2 Hz, 1H), 5.91 (dd, *J*=10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 18.2 (t), 18.9 (t), 21.6 (q), 27.9 (q), 32.6 (s), 32.8 (q), 38.9 (t), 41.1 (t), 41.4 (s), 42.7 (t), 55.9 (t), 57.3 (d), 66.4 (d), 73.4 (s), 110.1 (t), 111.9 (t), 143.4 (s), 145.1 (d), 208.2 (s); HRMS: M^+, found 304.2400. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 304 (M^+, 4), 287 (23), 286 (100), 258 (23), 206 (52), 151 (63), 135 (36), 109 (28), 68 (30).

The C(6)-ketone (2.0 g, 6.58 mmol), obtained above, was isomerized into the conjugated ketone **7** by treatment with a 0.125 M solution of sodium methoxide in methanol (40 mL) at room temperature for 2 h. The methanol was evaporated and an 1 M aqueous solution of HCl (200 mL) was added. Extraction with ether followed by the usual work-up gave the crude product which was purified by flash column chromatography (PE/EA 2:1) to give compound **7** (1.96 g, 6.45 mmol, 98%) as a light yellow oil. $[\alpha]_D^{20}$=+43.5 (*c* 3.6) (lit[24]+144, lit.[25] +70); IR (liquid film) ν_{max} 3429, 3088, 2912, 1651 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.05 (s, 3H), 1.08 (s, 3H), 1.25 (s, 3H), 1.12–1.92 (m, 13H), 1.85 (s, 3H), 5.03 (dd, *J*=1.2, 10.7 Hz, 1H), 5.17 (dd, *J*=1.2, 17.3 Hz, 1H), 5.68 (t, *J*=1.4 Hz, 1H), 5.86 (dd, *J*=10.7, 17.3 Hz, 1H); ^{13}C NMR δ 14.6 (q), 18.2 (t), 21.4 (t), 21.5 (q), 22.1 (q), 27.8 (q), 32.3 (s), 33.4 (q), 38.7 (t), 43.2 (t), 43.4 (s), 44.6 (t), 56.6 (d), 63.6 (d), 73.4 (s), 112.3 (t), 128.4 (d), 144.6 (d), 159.0 (s), 200.4 (s); HRMS: M^+, found 304.2394. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 286 [(M^+−18), 17], 219 (19), 218 (34), 135 (100), 109 (28), 95 (21), 73 (89), 43 (31).

4.1.2. (+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-((3*S*)-3,4,5-trihydroxy-3-methylpentyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (8). To an ice-cooled stirred solution of **7** (1.00 g, 3.29 mmol) and benzyltriethylammonium chloride (1.10 g, 4.94 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (0.77 g, 4.94 mmol) in small portions over 15 min and the mixture allowed to warm up to room temperature and stirred for an additional 14 h until complete conversion of the starting material. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution (75 mL) and with a 3% aqueous solution of oxalic acid (75 mL). Extraction of the now colorless reaction mixture with ethyl acetate (3×75 mL) was followed by usual work-up. Purification was performed by flash column chromatography (eluent EA/MeOH 9:1) and gave compound **8** as a white crystalline solid (0.62 g, 1.84 mmol, 56%). Mp 108–110°C; $[\alpha]_D^{20}$=+21.0 (*c* 1.1); IR (KBr) ν_{max} 3422, 2928, 1669, 1384, 1293, 1234,

1087 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.90 (s, 3H), 1.12–1.94 (m, 15H), 3.48 (t, J=4.2 Hz, 1H), 3.76 (d, J=4.2 Hz, 2H), 5.72 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.0 (t), 21.0 (t), 21.4 (q), 21.9 (q), 22.2 (q), 33.3 (q), 38.6 (t), 41.8 (t), 43.0 (t), 43.4 (s), 43.5 (s), 56.7 (d), 63.3 (t), 63.5 (d), 74.5 (s), 74.8 (d), 128.3 (d), 159.1 (s), 200.6 (s); HRMS: M^+, found 338.2449. $C_{20}H_{34}O_4$ requires 338.2457; MS *m/e* (%) 338 (M^+, 10), 320 (13), 277 (17), 219 (49), 218 (73), 135 (100), 109 (18), 43 (22); Anal. found C, 70.82; H, 10.12%. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.13%.

4.1.3. (+)-4-((1*S*,4*S*,4a*S*,8a*R*)-4-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl)-2-butanone (9). To an ice-cooled stirred solution of (+)-larixol[6] (**1**) (1.0 g, 3.27 mmol) and benzyltriethylammonium chloride (2.2 g, 9.81 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (1.54 g, 9.81 mmol) in small portions in 15 min. The mixture was allowed to warm to room temperature and stirring was continued until completion of the reaction. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and with a 3% aqueous solution of oxalic acid. Extraction of the now colorless reaction mixture with ethyl acetate was followed by usual work-up. Purification by flash column chromatography (eluent PE/EA 3:1) gave methyl ketone **9** (0.62 g, 2.22 mmol, 68%) as a white crystalline solid. Mp 77–79°C; $[\alpha]_D^{20}$=+43.4 (*c* 2.0); IR (KBr) ν_{max} 3467, 2926, 1713, 1644, 1361 cm^{-1}; ^1H NMR δ 0.69 (s, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.07–2.06 (m, 14H), 2.10 (s, 3H), 2.66 (dd, J=4.9, 12.1 Hz, 1H), 3.82 (dt, J=4.9, 10.6 Hz, 1H), 4.49 (d, J=1.2 Hz, 1H), 4.88 (d, J=1.2 Hz, 1H); ^{13}C NMR δ 15.9 (q), 17.7 (t), 19.1 (t), 22.3 (q), 30.1 (q), 33.9 (s), 36.6 (q), 39.2 (t), 39.4 (s), 42.8 (t), 43.6 (t), 49.0 (t), 55.4 (d), 60.4 (d), 71.6 (d), 108.2 (t), 145.3 (s), 209.2 (s); HRMS: (M^+-H_2O), found 260.2131. $C_{18}H_{28}O$ (M^+-18) requires 260.2140; MS *m/e* (%) 260 [(M^+-18), 76], 202 (53), 153 (52), 109 (55), 95 (38), 93 (72), 43 (100); Anal. found C, 78.12; H, 11.28%. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.86%.

4.1.4. (+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxobutyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (10). A solution of enone **7** (0.50 g, 1.64 mmol), benzyltriethylammonium chloride (1.12 g, 4.93 mmol) and $KMnO_4$ (0.78 g, 4.93 mmol) in dichloromethane (25 mL) was sonicated at 30–40°C until completion of the reaction. After 90 min the dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and with a 3% aqueous solution of oxalic acid. Extraction of the now colorless reaction mixture with ethyl acetate (3×40 mL) was followed by usual work-up. Purification by flash column chromatography (eluent PE/EA 5:1) gave methyl ketone **10** (0.62 g, 2.22 mmol, 68%) as a colorless oil. (Lit.[10b] Mp 59°C) $[\alpha]_D^{20}$=+34.8 (*c* 0.5) (lit.[10b] +43); IR (film) ν_{max} 2928, 2870, 1716, 1669, 1464, 1379, 1359, 1234, 1163 cm^{-1}; ^1H NMR δ 0.84 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.86 (s, 3H), 1.12–2.05 (m, 10H), 2.15 (s, 3H), 2.41–2.77 (m, 2H), 5.74 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.1 (t), 20.5 (t), 21.4 (q), 22.1 (q), 30.0 (q), 32.2 (s), 33.4 (q), 38.9 (t), 43.0 (t), 43.4 (s), 45.3 (t), 55.5 (d), 63.5 (d), 128.8 (d), 158.0 (s), 200.3 (s), 207.9 (s); HRMS: M^+, found 276.2082. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 276 (M^+, 1), 261 (2), 135 (19), 109 (13), 95 (5), 73 (100), 69 (6), 57 (27), 43 (30).

4.1.5. (+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxobutyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (10). A mixture of methyl ketone **9** (1.0 g, 3.60 mmol), PCC (1.16 g, 5.40 mmol), four drops of acetic acid and 3 Å molecular sieves (0.5 g) in CH_2Cl_2 (25 mL) was stirred at room temperature for 1 h. The black mixture was filtered over silica gel, flushed with ethyl acetate and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave the pure ketone *(+)-(4S,4aR,8aS)-4a,8,8-trimethyl-3-methylene-4-(3-oxobutyl)octahydro-1(2H)-naphthalenone* (0.88 g, 3.20 mmol, 89%) as white crystals. Mp 72–74°C; $[\alpha]_D^{20}$=+80.4 (*c* 1.0); IR (KBr) ν_{max} 2940, 2873, 1702, 1645, 1390, 1228 cm^{-1}; ^1H NMR δ 0.65 (s, 3H), 0.96 (s, 3H), 1.14 (s, 3H), 2.12 (s, 3H), 1.20–2.20 (m, 13H), 2.67 (dd, J=4.0, 9.6 Hz, 1H), 4.88 (br s, 1H), 5.29 (br s, 1H); ^{13}C NMR δ 15.7 (q), 17.5 (t), 18.4 (t), 26.1 (q), 28.1 (q), 29.8 (q), 32.5 (s), 38.8 (t), 41.1 (t), 42.5 (s), 42.6 (t), 55.7 (t), 55.8 (d), 57.4 (d), 109.9 (t), 141.2 (s), 207.8 (s), 208.9 (s); HRMS: M^+, found 276.2074. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 276 (M^+, 54), 258 (20), 151 (57), 124 (20), 123 (94), 109 (100), 107 (26), 95 (40), 81 (45), 43 (57); Anal. found C, 78.53; H, 10.50%. $C_{18}H_{28}O_2$ requires C, 78.21; H, 10.21%.

A solution of the above ketone (0.50 g, 1.81 mmol) in a 0.2 M solution of sodium methoxide in MeOH (12 mL) was stirred at room temperature for 2 h. After evaporation of the solvent, ether (30 mL) was added and the mixture was acidified with a 4 M solution of hydrochloric acid (5 mL). The mixture was extracted, washed with brine, dried and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave enone **10** (0.46 g, 1.67 mmol, 92%) as a colorless oil. Spectral data were identical with the above-mentioned.

4.1.6. (+)-2-((1*S*,4a*S*,8a*R*)-2,5,5,8a-tetramethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenyl)ethyl acetate (11). A mixture of enone **10** (0.270 g, 1.0 mmol), *m*-CPBA (0.370 g, 1.5 mmol), boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (1.5 mmol, 0.19 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for four days. The mixture was diluted with ether, washed with a 10% aqueous solution of $Na_2S_2O_3$ and with a saturated aqueous sodium bicarbonate solution, brine, dried and evaporated. Flash column chromatography (eluent PE/EA 5:1) gave acetate **11** (0.088 g, 0.30 mmol, 30%) as a colorless oil besides unreacted starting material **10** (0.139 g, 0.50 mmol, 50%). $[\alpha]_D^{20}$=+15.0 (*c* 0.7); IR (film) ν_{max} 2928, 1741, 1671, 1463, 1382, 1238, 1041 cm^{-1}; ^1H NMR δ 0.78 (s, 3H), 1.06 (s, 3H), 1.09 (s, 3H), 1.12–1.85 (m, 10H), 1.87 (s, 3H), 2.01 (s, 3H), 3.99–4.29 (m, 2H), 5.72 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.1 (t), 21.0 (q), 21.5 (q), 22.1 (q), 26.1 (t), 32.3 (s), 33.4 (q), 38.7 (t), 42.8 (s), 43.1 (t), 52.4 (d), 63.4 (d), 65.0 (t), 128.9 (d), 157.3 (s), 171.0 (s), 199.8 (s); HRMS: M^+, found 276.2082. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 292 (M^+, 14), 232 (48), 203 (14), 150 (13), 149 (100), 135 (15), 109 (26), 108 (57), 95 (16), 43 (19).

4.1.7. (−)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,5a,6,7,8,9,9a,9b-decahydronaphtho[2,1-*b*]furan (Δ^6-Ambroxene) (4). To a stirred solution of enone **11**

(0.05 g, 0.171 mmol) in dry THF (10 mL) was added $LiAlH_4$ (0.033 g, 0.86 mmol) at 0°C. After stirring overnight at room temperature the mixture was diluted with Et_2O and carefully treated with an 1 M aqueous solution of hydrochloric acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to obtain the crude *(1R,4S,4aR,8aS)-4-(2-hydroxyethyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (12)*. This oil was not purified but directly converted into **4** by treatment with *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) in nitromethane (5 mL) at room temperature for 4 h. Ether (25 mL) was added and the mixture was washed with saturated aqueous sodium bicarbonate and brine and worked up as usual. Flash column chromatography on silica gel (eluent PE/EA 5:1) gave **4** (0.015 g, 0.064 mmol, 37%) as a clear oil. $[\alpha]_D^{20}=-46.0$ (*c* 0.4); IR (film) ν_{max} 2925, 1729, 1462, 1367, 1164, 1073, 1049 cm^{-1}; ^1H NMR (C_6D_6) 0.80 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.24 (s, 3H), 0.81–2.48 (m, 10H), 3.80–3.91 (m, 2H), 5.74 (dd, *J*=2.8, 10.1 Hz, 1H), 5.87 (dd, *J*=2.8, 10.1 Hz, 1H); ^{13}C NMR (C_6D_6) 14.1 (q), 18.8 (t), 22.2 (q), 25.6 (t), 27.5 (q), 32.7 (s), 33.3 (q), 36.5 (s), 38.8 (t), 41.8 (t), 53.1 (d), 58.2 (d), 65.8 (t), 80.2 (s), 127.5 (d), 132.8 (d); HRMS: M^+, found 234.1983. $C_{16}H_{26}O$ requires 234.1984; MS *m/e* (%) 234 (M^+, 11), 220 (16), 219 (100), 201 (14), 147 (13), 135 (5), 123 (17), 119 (6), 69 (5), 43 (5).

4.1.8. (+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (13). To a stirred solution of (+)-larixol[6] (**1**) (6.0 g, 19.61 mmol) in CH_2Cl_2 (100 mL), acetone (100 mL), H_2O (180 mL), [18]crown-6 (0.6 g) and sodium hydrogen carbonate (24 g) was added a solution of oxone (18.08 g, 29.41 mmol) in H_2O (100 mL) at 0°C. After stirring at 0°C for 90 min the mixture was diluted with a saturated aqueous sodium hydrogen carbonate solution. The aqueous mixture was extracted with ethyl acetate and the combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine. Usual work up gave a crude oil which was purified by flash column chromatography (eluent PE/EA 1:1) to give the monoepoxide *(+)-(1S,4S,4aR,8aS)-4((3S)-3-hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-spiro-2′-oxiran-decahydro-1-naphtalenol* (5.11 g, 15.88 mmol, 81%) as a white crystalline solid. Mp 114–115°C; $[\alpha]_D^{20}=+16.3$ (*c* 1.7); IR (KBr) ν_{max} 3442, 3048, 2932, 2857, 1455, 1237 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 0.94–2.05 (m, 16H), 2.59 (d, *J*=4.3 Hz, 1H), 2.79 (dd, *J*=1.8, 4.2 Hz, 1H), 4.01 (dt, *J*=4.8, 10.9 Hz, 1H), 5.04 (dd, *J*=1.3, 10.7 Hz, 1H), 5.20 (dd, *J*=1.3, 17.2 Hz, 1H), 5.84 (dd, *J*=10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.0 (t), 18.3 (t), 22.3 (q), 28.1 (q), 33.8 (s), 36.6 (q), 39.2 (t), 40.2 (s), 43.6 (t), 43.7 (t), 47.0 (t), 51.2 (t), 53.7 (d), 57.7 (s), 60.3 (d), 69.9 (d), 73.6 (s), 111.8 (t), 145.0 (d); HRMS: (M^+-31), found 291.2323. $C_{19}H_{31}O_2$ (M^+-31) requires 291.2324; MS *m/e* (%) 291 [(M^+-31), 8], 233 (60), 109 (91), 69 (90), 43 (59), 31 (100); Anal. found C, 74.19; H, 10.85%. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%.

To a stirred suspension of $LiAlH_4$ (1.3 g, 34.21 mmol) in freshly distilled THF (100 mL) was added the obtained epoxide (5.5 g, 17.08 mmol) in small portions at 0°C. After stirring overnight at room temperature the mixture was carefully treated with ethyl acetate (75 mL) and diluted with a 1 M solution of hydrochloric acid in water (200 mL). The aqueous mixture was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine and worked up as usual. The residue was crystallized from EA/CH_2Cl_2 1:1 to give 6α-hydroxy sclareol (**13**) (5.2 g, 16.05 mmol, 94%) as white crystals. Mp 158–159°C; $[\alpha]_D^{20}=+43.4$ (*c* 1.3, EtOH); IR (KBr) ν_{max} 3427, 2923, 2542, 2474, 1457, 1388 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD) δ 0.72 (s, 3H), 0.90 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H), 0.95–1.60 (m, 13H), 2.00 (dd, *J*=3.9, 11.9 Hz, 1H), 3.26 (br s, 3H), 3.70 (dt, *J*=3.8, 10.9 Hz, 1H), 4.99 (dd, *J*=1.6, 10.9 Hz, 1H), 5.13 (dd, *J*=1.6, 17.4 Hz, 1H), 5.77 (dd, *J*=10.9, 17.4 Hz, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 15.9 (q), 17.8 (t), 18.7 (t), 21.5 (q), 24.7 (q), 28.6 (q), 33.3 (s), 35.9 (q), 39.2 (s), 39.4 (t), 43.5 (t), 44.3 (t), 51.1 (d), 53.3 (t), 60.7 (d), 68.3 (d), 73.9 (s), 74.0 (s), 111.6 (t), 144.1 (d); HRMS: (M^+-H_2O), found 306.2560. $C_{20}H_{34}O_2$ (M^+-18) requires 306.2559; MS *m/e* (%) 306 [(M^+-18), 1], 292 (6), 191 (53), 187 (56), 150 (53), 123 (81), 109 (72), 87 (100), 43 (99); Anal. found C, 73.71; H, 11.37%. $C_{20}H_{36}O_3$ requires C, 74.02; H, 11.18%.

4.1.9. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-((3*S*)-3-(acetyloxy)-3-methyl-4-pentenyl)-2,5,5,8a-tetramethyl-decahydro-2-naphthalenyl acetate (14). 6α-Hydroxy sclareol (**13**) (0.50 g, 1.54 mmol) was dissolved in *N*,*N*-dimethylaniline (15 mL) and acetyl chloride (8.83 g, 112.5 mmol) was added dropwise and stirred overnight. The reaction mixture was acidified cautiously with a 4 M aqueous solution of sulfuric acid and worked up as usual. The residual yellow oil was purified by flash column chromatography on silica gel (eluent PE/EA 3:1) to yield triacetate **14** (0.66 g, 1.43 mmol, 93%) as white crystals. Mp 100–102°C; $[\alpha]_D^{20}=+38.8$ (*c* 2.2); IR (KBr) ν_{max} 2931, 1737, 1732, 1372, 1258, 1239, 1021 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.88 (s, 3H), 0.97 (s, 3H), 1.49 (s, 3H), 1.01–1.92 (m, 16H), 1.93 (s, 3H), 1.98 (s, 3H), 1.99 (s, 3H), 2.74 (dd, *J*=4.1, 12.0 Hz, 1H), 5.03 (dt, *J*=4.1, 11.0 Hz, 1H), 5.07 (dd, *J*=0.9, 17.5 Hz, 1H), 5.15 (dd, *J*=0.9, 10.9 Hz, 1H), 5.92 (dd, *J*=10.9, 17.5 Hz, 1H); ^{13}C NMR δ 16.6 (q), 17.9 (t), 19.4 (t), 21.7 (q), 21.8 (q), 21.9 (q), 22.1 (q), 22.7 (q), 23.6 (q), 33.1 (s), 35.9 (q), 39.4 (t), 39.4 (s), 42.1 (t), 43.3 (t), 44.9 (t), 57.7 (d), 57.9 (d), 70.0 (d), 83.0 (s), 85.8 (s), 113.2 (t), 141.7 (d), 169.7 (s), 169.9 (s), 170.1 (s); HRMS: M^+, found 450.2977. $C_{26}H_{42}O_6$ requires 450.2981; MS *m/e* (%) 450 (M^+, 1), 435 (1), 270 (68), 262 (63), 202 (69), 190 (88), 189 (100), 43 (83); Anal. found C, 69.07; H, 9.48%. $C_{26}H_{42}O_6$ requires C, 69.30; H, 9.40%.

4.1.10. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-((3*E*)-5-(acetyloxy)-3-methyl-3-pentenyl)-2,5,5,8a-tetramethyl-decahydro-2-naphthalenyl acetate (15). A mixture of triacetate **14** (1.0 g, 2.22 mmol) and $PdCl_2(CH_3CN)_2$ (25 mg, 0.10 mmol) in freshly distilled THF (25 mL) was stirred at room temperature for 1 h. Ether (40 mL) was added and the mixture was washed with brine and worked up as usual. Flash column chromatography (eluent PE/EA 6:1) gave **15** (0.98 g, 2.18 mmol, 98%) as a sticky solid. Mp 58–61°C; $[\alpha]_D^{20}=+38.2$ (*c* 2.5); IR (KBr) ν_{max} 2931, 1735, 1367, 1025 cm^{-1}; ^1H NMR δ 0.78 (s, 3H), 0.81 (s, 3H), 0.94 (s,

3H), 1.47 (s, 3H), 1.65 (s, 3H), 1.12–1.87 (m, 13H), 1.88 (s, 3H), 1.95 (s, 3H), 2.00 (s, 3H), 2.72 (dd, J=4.1, 12.0 Hz, 1H), 4.52 (d, J=7.2 Hz, 2H), 5.04 (dt, J=4.1, 11.1 Hz, 1H), 5.27 (dt, J=1.2, 7.2 Hz, 1H); ^{13}C NMR δ 16.0 (q), 16.5 (q), 17.9 (t), 21.0 (q), 21.7 (q), 21.8 (q), 21.9 (q), 22.7 (q), 24.2 (t), 33.5 (s), 35.9 (q), 38.2 (t), 39.1 (t), 39.6 (s), 43.4 (t), 44.1 (t), 55.2 (d), 57.5 (d), 61.3 (t), 73.2 (d), 118.2 (d), 142.6 (s), 144.1 (s), 169.9 (s), 170.0 (s), 171.0 (s); HRMS: ($M^+-C_2H_4O_2$), found 390.2767. $C_{24}H_{38}O_4$ requires 390.2770; MS *m/e* (%) 390 [(M^+-60), 1], 330 (6), 270 (12), 190 (100), 140 (34), 119 (19), 81 (11), 69 (10).

4.1.11. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-2,5,5,8a-tetramethyl-1-(3-oxobutyl)decahydro-2-naphthalenyl acetate (16). A solution of compound **15** (2.0 g, 4.44 mmol) in a mixture of CH_2Cl_2 and MeOH 1:1 (60 mL) was ozonolyzed at −78°C. The excess of ozone was expelled by flushing with N_2 and PPh_3 (2.33 g, 8.88 mmol) was added at −78°C. The mixture was allowed to warm up to room temperature. After stirring overnight the solvents were evaporated and the residue was purified by flash column chromatography (eluent PE/EA 3:1) to yield **16** (1.6 g, 4.22 mmol, 95%) as a white solid. Mp 128–129°C; $[\alpha]_D^{20}$=+42.8 (c 1.1); IR (KBr) ν_{max} 2931, 1722, 1708, 1369, 1248, 1025 cm^{-1}; ^{1}H NMR δ 0.81 (s, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.51 (s, 3H), 1.21–1.85 (m, 12H), 1.90 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.51 (dd, J=7.0, 10.5 Hz, 1H), 2.74 (dd, J=4.1, 12.1 Hz, 1H), 5.06 (dt, J=4.1, 11.0 Hz, 1H); ^{13}C NMR δ 16.5 (q), 17.9 (t), 19.4 (t), 21.7 (q), 21.9 (q), 22.0 (q), 22.8 (q), 29.9 (q), 33.2 (s), 35.9 (q), 39.4 (s), 39.6 (t), 43.2 (t), 44.9 (t), 46.2 (t), 57.1 (d), 57.8 (d), 69.9 (d), 85.9 (s), 169.9 (s), 170.0 (s), 208.8 (s); HRMS: ($M^+-C_2H_4O_2$), found 320.2354. $C_{20}H_{32}O_3$ requires 320.2351; MS *m/e* (%) 320 [(M^+-60), 4], 260 (100), 242 (23), 202 (58), 189 (69), 187 (55), 153 (25), 119 (54), 43 (34); Anal. found C, 69.52; H, 9.68%. $C_{22}H_{36}O_5$ requires C, 69.44; H, 9.54%.

4.1.12. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-(acetyloxy)ethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (17). A solution of methyl ketone **16** (0.20 g, 0.52 mmol) and *m*-CPBA (0.18 g, 1.04 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 7 days. Ether was added and the mixture was washed with a 2% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine, respectively, and worked up as usual. Flash column chromatography (eluent PE/EA 6:1) of the residual oil gave triacetate **17** (0.17 g, 0.42 mmol, 83%) as white crystals. Mp 142–144°C; $[\alpha]_D^{20}$=+25.4 (c 0.9); IR (KBr) 2934, 1729, 1718, 1706, 1239, 1026 cm^{-1}; ^{1}H NMR δ 0.82 (s, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.53 (s, 3H), 1.18–1.86 (m, 11H), 1.92 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.80 (dd, J=4.1, 12.1 Hz, 1H), 3.94–4.18 (m, 2H), 5.08 (dt, J=4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.7 (q), 17.9 (t), 21.6 (q), 21.8 (q), 21.9 (q), 22.0 (q), 22.8 (q), 24.8 (t), 33.2 (s), 35.9 (q), 39.0 (s), 39.4 (t), 43.2 (t), 44.9 (t), 54.0 (d), 57.8 (d), 65.6 (t), 69.8 (d), 85.2 (s), 169.9 (s), 170.0 (s), 171.0 (s); HRMS: ($M^+-C_2H_4O_2$), found 336.2296. $C_{20}H_{32}O_4$ requires 336.2301; MS *m/e* (%) 336 [(M^+-60), 1], 276 (30), 217 (19), 216 (68), 201 (35), 189 (21), 119 (20), 109 (20), 69 (25), 43 (100); Anal. found C, 66.99; H, 9.30%. $C_{22}H_{36}O_6$ requires C, 66.64; H, 9.15%.

4.1.13. (+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (5). Triacetate **17** (0.25 g, 0.63 mmol) was dissolved in freshly distilled THF (20 mL), cooled to 0°C and $LiAlH_4$ (0.144 mg, 3.79 mmol) was added in small portions. The reaction mixture was allowed to come to room temperature. After stirring overnight, the mixture was carefully treated with ethyl acetate, and then diluted with a 4 M aqueous solution of hydrochloric acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and worked up as usual. The crude oil was purified by flash column chromatography on silica gel (eluent PE/EA 1:1) to give **5** (0.016 g, 0.059 mmol, 94%) as white crystals. Mp 156–158°C; $[\alpha]_D^{20}$=+31.4 (c 0.8, EtOH); IR (KBr) ν_{max} 3462, 3287, 2925, 2872, 1463, 1378, 1247, 1051 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 0.73 (s, 3H), 0.87 (s, 3H), 1.02 (s, 3H), 1.10 (s, 3H), 1.05–1.56 (m, 10H), 1.90 (dd, J=3.4, 11.9 Hz, 1H), 2.48 (d, J=1.7 Hz, 1H), 3.33 (t, J=7.7 Hz, 2H), 3.48–3.55 (m, 1H), 4.09 (br s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 20.3 (q), 22.0 (t), 25.7 (q), 29.0 (q), 31.6 (t), 37.5 (s), 40.1 (q), 43.1 (s), 43.4 (t), 47.5 (t), 57.7 (t), 62.2 (d), 64.7 (d), 67.4 (t), 72.3 (d), 76.2 (s); HRMS: ($M^+-15-18$), found 237.1852. $C_{15}H_{25}O_2$ requires 237.1855; MS *m/e* (%) 270 (M^+, 2), 255 (1), 151 (6), 109 (7), 95 (6), 87 (100), 69 (9), 43 (11); Anal. found C, 71.38; H, 11.35%. $C_{16}H_{30}O_3$ requires C, 71.07; H, 11.18%.

Triacetate **17** (0.10 g, 0.25 mmol) was treated with a 0.2 M solution of sodium methoxide in methanol (13 mL) at room temperature. After 2 days the MeOH was evaporated, water was added and the mixture was acidified with a 4 M aqueous solution of hydrochloric acid (5 mL). The aqueous mixture was extracted with ethyl acetate. The combined organic layers were worked up as usual. Purification of the crude oil by flash column chromatography on silica gel (eluent PE/EA 1:1) gave triol **5** (0.057 g, 0.21 mmol, 85%) as white crystals, identical in all aspects with the product obtained before.

Aldehyde **21** was dissolved in freshly distilled THF and treated with $LiAlH_4$. Work up as usual and purification gave crystalline triol **5** in 93% yield. The analytical data were as mentioned above.

4.1.14. (+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (18). A mixture of triol **5** (0.77 g, 2.85 mmol), *tert*-butyldimethylsilyl chloride (0.47 g, 3.13 mmol) and imidazole (0.31 g, 4.56 mmol) in DMF (30 mL) was stirred at room temperature. After 1 h the mixture was diluted with ether, washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 5:2) to give silyl ether **18** (1.04 g, 2.71 mmol, 95%) as white crystals. Mp 160–162°C; $[\alpha]_D^{20}$=+9.8 (c 0.8); IR (KBr) ν_{max} 3420, 2924, 1471, 1362, 1257 cm^{-1}; ^{1}H NMR δ 0.04 (s, 6H), 0.78 (s, 3H), 0.86 (s, 9H), 0.94 (s, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 1.25–1.67 (m, 13H), 2.17 (dd, J=3.7, 12.0 Hz, 1H), 3.41 (dt, J=4.3, 9.7 Hz, 1H), 3.71–3.84 (m, 2H); ^{13}C NMR δ −5.4 (2×q), 16.5 (q), 18.1 (t), 18.2 (s), 22.0 (q), 25.8 (q), 25.9 (3×q), 27.6 (t), 33.7 (s), 36.4 (q), 39.3 (s), 39.5 (t), 43.5 (t), 54.4 (t), 58.4 (d), 61.2 (d), 64.7 (t), 69.0 (d), 71.5 (s);

HRMS: (M^+-CH_3), found 369.2825. $C_{21}H_{41}O_3Si$ requires 369.2821; MS *m/e* (%) 369 [(M^+-15), 1], 241 (30), 217 (36), 191 (100), 151 (40), 109 (27), 95 (26), 75 (51), 69 (33), 32 (43), 31 (54).

4.1.15. (+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)-silyl]oxy}ethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (18). A solution of compound **23** (1.00 g, 2.25 mmol) in a 0.2 M solution of sodium methoxide in MeOH (25 mL) was stirred at 50°C for 5 h. After evaporation of the solvent ether was added and the mixture was acidified with a 4 M solution of hydrochloric acid (5 mL). The mixture was extracted, washed with brine, dried and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave **18** (0.294 g, 0.765 mmol, 34%) as white crystals, identical in all aspects with the product obtained before. Further elution (eluent PE/EA 1:1) gave triol **5** (0.273 g, 1.012 mmol, 45%) as white crystals with analytical data as mentioned before.

4.1.16. (+)-(3*R*,4*R*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)-silyl]oxy}ethyl)-3-hydroxy-3,4a,8,8-tetramethyloctahydro-1(2*H*)-naphthalenone (19). A mixture of silylether **18** (0.8 g, 2.08 mmol), PDC (1.18 g, 3.13 mmol), and 3 Å molecular sieves (0.5 g) in CH_2Cl_2 (30 mL) was stirred at room temperature. After 90 min the black mixture was filtered over silica gel, flushed with ethyl acetate and the solvent was evaporated. Purification of the residue by flash column chromatography (eluent PE/EA 10:1) gave pure **19** (0.68 g, 1.79 mmol, 86%) as white crystals. Mp 86–88°C; $[\alpha]_D^{20}=+3.3$ (*c* 0.8); IR (KBr) ν_{max} 3425, 2933, 1713, 1491, 1387, 1252, 1088 cm^{-1}; ^1H NMR δ 0.11 (s, 6H), 0.76 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 1.22–1.84 (m, 10H), 2.19 (s, 1H), 2.52–2.63 (m, 2H), 3.49–3.58 (m, 1H), 3.83–3.90 (m, 1H); ^{13}C NMR δ −5.4 (2×q), 16.2 (q), 18.2 (t), 18.3 (s), 21.6 (q), 25.3 (q), 25.9 (3×q), 27.8 (t), 32.1 (s), 32.3 (q), 39.8 (t), 41.5 (s), 42.6 (t), 59.6 (d), 60.4 (t), 64.5 (t), 66.1 (d), 74.8 (s), 209.7 (s); HRMS: ($M^+-C_4H_9$), found 325.2199. $C_{18}H_{33}O_3Si$ requires 325.2196; MS *m/e* (%) 325 [(M^+-57), 100], 267 (35), 201 (36), 123 (86), 109 (40), 105 (90), 95 (30), 81 (26), 75 (58), 73 (29).

4.1.17. (+)-(4*S*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]-oxy}ethyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (6). To a solution of **19** (0.63 g, 1.65 mmol) and DMAP (25 mg, 0.20 mmol) in dry pyridine (15 mL) was added $SOCl_2$ (0.3 mL, 4.12 mmol) at 0°C. The reaction mixture was allowed to warm up slowly to room temperature. After stirring for 2 h the mixture was quenched with ice and extracted with ethyl acetate. The organic solution was washed with water, saturated aqueous $NaHCO_3$, and brine and worked up as usual. The crude oil was isomerized into the conjugated ketone **6** by treatment with a 1 M solution of sodium methoxide (3 mL) in methanol (25 mL) at room temperature during 2 h. The methanol was evaporated and 1 M aqueous solution of HCl (100 mL) was added. Extraction with ether followed by usual work up gave the crude product which was purified by flash column chromatography (eluent PE/EA 25:1) to give compound **6** (0.49 g, 1.346 mmol, 82%) as a colorless oil, which crystallizes upon standing. Mp 48–50°C; $[\alpha]_D^{20}=+7.3$ (*c* 1.2); IR (film) ν_{max} 2928, 1672, 1462, 1385, 1255, 1098 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.83 (s, 3H), 0.90 (s, 9H), 1.14 (s, 3H), 1.17 (s, 3H), 1.18–2.14 (m, 8H), 1.89 (s, 3H), 2.04 (s, 1H), 2.16 (br s, 1H), 3.56–3.79 (m, 2H), 5.76 (br s, 1H); ^{13}C NMR δ −5.5 (2×q), 14.4 (q), 17.9 (t), 18.3 (s), 21.2 (q), 22.0 (q), 25.7 (3×q), 29.9 (t), 32.2 (q), 33.2 (q), 38.5 (t), 42.8 (s), 42.9 (t), 51.9 (d), 63.3 (d), 63.7 (t), 128.4 (d), 158.6 (s), 200.2 (s); HRMS: M^+, found 364.2801. $C_{22}H_{40}O_2Si$ requires 364.2798; MS *m/e* (%) 364 (M^+, 1), 308 (24), 307 (100), 249 (20), 232 (70), 173 (15), 149 (54), 147 (26), 95 (18), 75 (23), 73 (16); Anal. found C, 72.13; H, 10.94%. $C_{22}H_{40}O_2Si$ requires C, 72.07; H, 11.55%.

4.1.18. (+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-3-Hydroxy-4-((3*S*)-3-hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyldeca-hydro-1-naphthalenyl acetate (20). A solution of **13** (1.5 g, 4.63 mmol) in CH_2Cl_2 (10 mL) and pyridine (8 mL) was treated with acetic anhydride (1.75 mL, 1.90 g, 18.63 mmol) and DMAP (25 mg, 0.20 mmol) and stirred at 0°C. After stirring for 150 min at room temperature the mixture was acidified with a 4 M solution of hydrochloric acid (100 mL). The pyridine was evaporated, extra water (50 mL) was added and the aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with a 4 M solution of hydrochloric acid and worked up as usual. Flash column chromatography (eluent PE/EA 3:1) gave white crystalline acetate **20** (1.54 g, 4.21 mmol, 91%). Mp 126–128°C; $[\alpha]_D^{20}=+52.9$ (*c* 2.1); IR (KBr) ν_{max} 3423, 2924, 2869, 1727, 1716, 1469, 1266, 1239 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.86 (s, 3H), 1.02 (s, 3H), 1.26 (s, 6H), 1.08–1.74 (m, 14H), 2.04 (s, 3H), 2.07 (dd, *J*=3.9, 11.7 Hz, 1H), 2.54 (br s, 2H), 5.07 (dd, *J*=3.3, 10.8 Hz, 1H), 5.23 (dd, *J*=1.4, 17.2 Hz, 1H), 5.87 (dd, *J*=10.8, 17.2 Hz, 1H); ^{13}C NMR δ 16.2 (q), 18.0 (t), 19.0 (t), 22.0 (2×q), 25.6 (q), 29.2 (q), 33.3 (s), 36.1 (q), 39.5 (t), 39.7 (s), 43.5 (t), 44.3 (t), 50.0 (t), 58.4 (d), 61.0 (d), 70.9 (d), 74.1 (s), 74.2 (s), 112.0 (t), 144.9 (d), 170.3 (s); HRMS: (M^+-H_2O), found 348.2669. $C_{22}H_{36}O_3$ (M^+-18) requires 348.2664; MS *m/e* (%) 348 [(M^+-18), 2], 288 (44), 191 (48), 190 (81), 121 (43), 109 (50), 69 (48), 43 (100); Anal. found C, 72.44; H, 10.69%. $C_{22}H_{38}O_4$ requires C, 72.09; H, 10.45%.

4.1.19. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-2,5,5,8a-tetramethyl-1-(2-oxo-ethyl)decahydro-2-naphthalenyl acetate (21). A solution of **20** (1.5 g, 4.10 mmol) and $NaIO_4$ (50.0 g, 233.8 mmol) in THF (200 mL) and water (30 mL) was treated with a 2.5 wt% OsO_4 solution in *tert*-BuOH (0.5 mL). The mixture was warmed to 45°C and stirred overnight. The reaction mixture was filtered and diluted with a saturated aqueous Na_2SO_3 solution and extracted with ethyl acetate. The combined organic layers were dried and evaporated. Purification was performed by flash column chromatography (eluent PE/EA 3:2) to yield aldehyde **21** (1.21 g, 3.44 mmol, 84%) as a white crystalline solid. Mp 114–116°C; $[\alpha]_D^{20}=+31.2$ (*c* 0.5); IR (KBr) ν_{max} 2929, 1719, 1710, 1239, 1045 cm^{-1}; ^1H NMR δ 0.87 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.57 (s, 3H), 1.07–1.89 (m, 11H), 1.90 (s, 3H), 2.05 (s, 3H), 2.94 (dd, *J*=4.1, 12.2 Hz, 1H), 5.14 (dt, *J*=4.1, 11.2 Hz, 1H), 9.69 (t, *J*=2.1 Hz, 1H); ^{13}C NMR δ 16.9 (q), 17.9 (t), 21.4 (q), 21.8 (q), 21.9 (q), 22.5 (q), 33.2 (s), 35.9 (q), 38.5 (s), 39.8 (t), 40.4 (t), 43.0 (t), 45.2 (t), 52.4 (d), 57.8 (d), 69.6 (d), 84.3 (s), 169.5 (s), 170.0 (s), 201.7 (d); HRMS: (M^+-CH_3),

found 337.2006. $C_{19}H_{29}O_5$ requires 337.2015; MS *m/e* (%) 337 [(M^+-15), 1], 293 (4), 233 (64), 190 (70), 109 (29), 43 (100); Anal. found C, 67.95; H, 9.15%. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15%.

4.1.20. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (22). To a solution of aldehyde **21** (0.100 g, 0.28 mmol) in methanol (10 mL) was added sodium borohydride (0.044 g, 1.14 mmol) at 0°C. The reaction mixture was stirred for an additional hour at room temperature, and the methanol was evaporated. Water and 4 M aqueous hydrochloric acid were added to the residue and the aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The crude oil was purified by flash column chromatography (eluent PE/EA 2:1) to give compound **22** (0.080 g, 0.226 mmol, 80%) as a clear oil. $[\alpha]_D^{20}=+43.0$ (*c* 0.9); IR (film) ν_{max} 3501, 3000, 2931, 2872, 1732, 1715 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 1.57 (s, 3H), 1.96 (s, 3H), 2.03 (s, 3H), 1.20–2.05 (m, 12H), 2.86 (dd, *J*=4.0, 12.1 Hz, 1H), 3.60–3.69 (m, 2H), 5.12 (dt, *J*=4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.3 (q), 18.0 (t), 21.1 (q), 21.9 (q), 22.0 (q), 24.4 (t), 25.1 (q), 33.3 (s), 36.0 (q), 39.2 (s), 39.5 (t), 43.3 (t), 50.2 (t), 57.2 (d), 58.3 (d), 66.3 (t), 70.7 (d), 72.8 (s), 170.2 (s), 171.2 (s); HRMS: ($M^+-C_2H_4O_2$), found 294.2220. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 [(M^+-60), 15], 219 (46), 176 (32), 129 (89), 109 (36), 95 (33), 87 (75), 69 (40), 43 (100); Anal. found C, 67.37; H, 9.66%. $C_{20}H_{34}O_5$ requires C, 67.77; H, 9.67%.

4.1.21. (+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (23). A mixture of alcohol **22** (0.50 g, 1.41 mmol), *tert*-butyldimethylsilyl chloride (0.276 g, 1.83 mmol) and imidazole (0.250 g, 3.67 mmol) in DMF (30 mL) was stirred at room temperature. After 1 h the mixture was diluted with ether, washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 15:1) to give silyl ether **23** (0.607 g, 1.297 mmol, 92%) as white crystals. Mp 87–89°C; $[\alpha]_D^{20}=+40.4$ (*c* 1.1), IR (KBr) ν_{max} 2930, 2857, 1729, 1368, 1251, 1072 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.78 (s, 3H), 0.83 (s, 9H), 0.84 (s, 3H), 0.99 (s, 3H), 1.50 (s, 3H), 1.88 (s, 3H), 1.96 (s, 3H), 0.82–1.82 (m, 11H), 2.78 (dd, *J*=4.1, 12.0 Hz, 1H), 3.42–3.65 (m, 2H), 5.04 (dt, *J*=4.1, 11.2 Hz, 1H); ^{13}C NMR δ −5.1 (2×q), 16.7 (q), 17.9 (t), 18.4 (s), 21.6 (q), 21.9 (q), 22.9 (q), 25.6 (q), 26.1 (3×q), 29.4 (t), 33.2 (s), 36.0 (q), 39.0 (s), 39.5 (t), 43.3 (t), 45.1 (t), 54.0 (d), 57.9 (d), 64.9 (t), 70.0 (d), 85.6 (s), 169.9 (s), 170.0 (s); HRMS: ($M^+-C_4H_8O_4$), found 348.2844. $C_{22}H_{40}OSi$ requires 348.2848; MS *m/e* (%) 348 [(M^+-120), 9], 291 (49), 217 (76), 201 (28), 191 (100), 190 (50), 119 (30), 117 (27), 75 (32), 73 (28), 69 (24), 43 (23).

4.1.22. (−)-(1*R*,4*S*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)-silyl]oxy}ethyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (24). To a solution of **6** (0.02 g, 0.055 mmol) in dry toluene (3 mL) at −78°C under N_2 was added DIBAL-H (0.15 mL of an 1.5 M solution in toluene; 0.22 mmol). After stirring for 1 h, the excess of DIBAL-H was quenched with ethyl acetate and an 1 M solution of HCl. The mixture was then extracted with ethyl acetate and the organic layers were washed with brine, dried and evaporated to afford **24** as an oil. The residue was purified by flash column chromatography (eluent PE/EA 25:1) to obtain **24** (0.018 g, 0.049 mmol, 90%) as a colorless oil. $[\alpha]_D^{20}=-32.1$ (*c* 1.2); IR (film) ν_{max} 3474, 2927, 2859, 1668, 1462, 1386, 1255, 1098, 1029, 938 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.89 (s, 9H), 1.01 (s, 3H), 1.04 (s, 3H), 1.30 (s, 3H), 1.73 (s, 3H), 0.82–2.00 (m, 11H), 3.47–3.59 (m, 1H), 3.67–3.93 (m, 1H), 4.36 (br s, 1H), 5.59 (br d, *J*=4.9 Hz, 1H); ^{13}C NMR δ −5.2 (2×q), 16.3 (q), 18.4 (s), 19.0 (t), 22.1 (q), 24.8 (q), 26.0 (3×q), 30.6 (t), 32.7 (q), 34.2 (s), 36.3 (s), 41.4 (t), 44.7 (t), 51.3 (d), 54.3 (d), 64.6 (t), 66.2 (d), 125.6 (d), 138.0 (s); HRMS: (M^+-H_2O), found 348.2843. $C_{22}H_{40}OSi$ requires 348.2848; MS *m/e* (%) 348 [(M^+-18), 12], 291 (41), 201 (29), 191 (25), 190 (100), 173 (19), 147 (18), 138 (16), 119 (28), 75 (30), 73 (26).

4.1.23. (+)-(4*S*,4a*R*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (25). To a solution of **6** (0.49 g, 1.34 mmol) in dry THF (25 mL) was added TBAF (1.34 mL of an 1.1 M solution in THF, 1.47 mmol). After 1 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic layers were washed with brine, dried and concentrated to yield the crude product as an oil. This oil was purified by flash column chromatography (eluent PE/EA 2:1) to afford **25** (0.31 g, 1.25 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}=+12.9$ (*c* 1.5); IR (film) ν_{max} 3437, 2927, 1667, 1460, 1379, 1235, 1166, 1038 cm^{-1}; ^1H NMR δ 0.83 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.91 (s, 3H), 1.17–2.29 (m, 11H), 3.60–3.88 (m, 2H), 5.76 (br s, 1H); ^{13}C NMR δ 14.2 (q), 17.9 (t), 21.2 (q), 21.9 (q), 27.8 (s), 29.7 (t), 33.2 (q), 38.5 (t), 42.8 (s), 43.0 (t), 51.8 (d), 63.3 (d), 63.4 (t), 128.5 (d), 158.3 (s), 200.2 (s); HRMS: M^+, found 250.1927. $C_{16}H_{26}O_2$ requires 250.1933; MS *m/e* (%) 250 (M^+, 21), 167 (13), 149 (56), 127 (8), 126 (100), 109 (14), 95 (56), 81 (7), 69 (8), 41 (9).

4.1.24. (−)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,5a,6,7,8,9,9a,9b-decahydronaphtho[2,1-*b*]furan (Δ^6-Ambroxene) (4). To a solution of **24** (0.25 g, 0.068 mmol) in dry THF (3 mL) was added TBAF (0.07 mL of an 1.1 M solution in THF, 0.075 mmol). After 1 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic layers were washed with brine, dried and concentrated to yield the crude diol **12** (20 mg). This residue was not purified, but directly converted into **4** by treatment with *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) in nitromethane (5 mL) at room temperature. After 4 h the mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine and worked up as usual. Flash column chromatography on silica gel (eluent PE/EA 5:1) gave compound **4** (0.0138 g, 0.059 mmol, 87%) as a clear oil. For analytical data see before.

To a solution of **25** (0.05 g, 0.20 mmol) in dry toluene (5 mL) at −78°C under N_2 was added DIBAL-H (0.067 mL of a 1.5 M solution in toluene, 1.00 mmol). After stirring for 1 h, the excess of DIBAL-H was quenched with ethyl acetate and an 1 M solution of aqueous HCl was added. The mixture was then extracted with ethyl acetate.

The organic layers were washed with brine, dried and evaporated to afford **12** as an oil which was not purified, but directly converted into **4** as described above. Compound **4** (0.024 g, 0.102 mmol, 71%) is obtained as a clear oil with analytical data in all aspects as before.

The conversion of **6** into **4** via **12** was performed as described above, compound **4** (0.018 g, 0.077 mmol, 40%) is obtained as a clear oil with analytical data as before.

4.1.25. (+)-(3a*R*,5a*S*,9a*R*,9b*R*)-3a,6,6,9a-Tetramethyldecahydronaphtho[2,1-*b*]furan-2,5-dione (2). To a solution of **5** (0.05 g, 0.18 mmol) in CH_2Cl_2 (1.5 mL), with 3 Å molecular sieves (0.5 g) and AcOH (4 drops) was added PCC (0.025 g, 0.72 mmol). After stirring for 7 h the reaction mixture was diluted with ethyl acetate, filtered through silica gel (eluent ethyl acetate) and the solvents were evaporated to afford the crude product (60 mg) as a yellow oil. This oil was purified by flash column chromatography (eluent PE/EA 3:1) to yield 6-oxo-Sclareolide (**2**) (0.036 g, 0.136 mmol, 76%) as white crystals. Mp 163–165°C; $[\alpha]_D^{20}=+11.7$ (*c* 0.3); IR (KBr) ν_{max} 2932, 1779, 1710, 1393, 1294, 1235, 1139, 1025 cm^{-1}; ^1H NMR δ 0.93 (s, 3H), 0.95 (s, 3H), 1.17 (s, 3H), 1.29 (s, 3H), 1.04–1.72 (m, 6H), 2.17 (s, 1H), 2.33–2.93 (m, 5H); ^{13}C NMR δ 15.7 (q), 17.4 (t), 20.9 (q), 21.7 (q), 28.3 (t), 31.9 (q), 32.3 (s), 37.7 (s), 39.6 (t), 42.3 (t), 57.0 (t), 58.6 (d), 67.7 (d), 84.9 (s), 175.1 (s), 206.0 (s); HRMS: M^+, found 264.1726. $C_{16}H_{24}O_3$ requires 264.1725; MS *m/e* (%) 264 (M^+, 42), 249 (16), 181 (36), 151 (100), 123 (30), 109 (47), 95 (21), 81 (16), 69 (16), 43 (22).

4.1.26. (−)-(3a*R*,5a*S*,9a*R*,9b*R*)-3a,6,6,9a-Tetramethyldecahydronaphtho[2,1-*b*]furan-5(2*H*)-one (3). To a solution of **6** (0.10 g, 0.27 mmol) in dry THF (3.4 mL) was added TBAF (0.03 mL of an 1.1 M solution in THF, 0.033 mmol). After 14 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic solution was washed with brine, dried and concentrated to yield the crude product (50 mg) as a yellow oil. This oil was purified by flash column chromatography on silica gel (eluent PE/EA 5:1) to afford ketone **3** (0.04 g, 0.16 mmol, 59%) as a crystalline solid. Mp 66–68°C; $[\alpha]_D^{20}=-34.1$ (*c* 1.3); IR (KBr) ν_{max} 2927, 1705, 1451, 1388, 1361, 1267 cm^{-1}; ^1H NMR δ 0.88 (s, 3H), 0.96 (s, 3H), 1.06 (s, 3H), 1.13 (s, 3H), 1.09–1.94 (m, 8H), 2.13 (dd, *J*=6.2, 13.0 Hz, 2H), 2.65 (dd, *J*=6.2, 17.3 Hz, 2H), 3.95–4.07 (m, 2H); ^{13}C NMR δ 15.9 (q), 18.0 (t), 21.3 (q), 21.5 (q), 22.2 (t), 32.2 (s), 32.2 (q), 36.8 (s), 40.3 (t), 42.8 (t), 58.0 (t), 60.0 (d), 65.4 (t), 66.9 (d), 81.0 (s), 209.4 (s); HRMS: M^+, found 250.1935. $C_{16}H_{26}O_2$ requires 250.1933; MS *m/e* (%) 250 (M^+, 12), 236 (14), 235 (100), 151 (15), 123 (16), 111 (23), 109 (16), 43 (12); Anal. found C, 77.17; H, 10.74%. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%.

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