Tetrahedron Vol 44, No 7, pp 1925 to 1932, 1988
Printed in Great Britain

0040-4020/88 $3.00+.00

Synthesis of Dodecahydro-3a,6,6,9a-tetramethyl naphtho[2,1-b]furan via Alkoxy Radical Fragmentation.*

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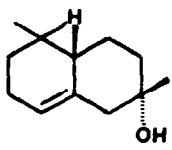
(*Received in USA* 20 *November* 1987)

Abstract: Alkoxy radicals of several sclareol derivatives undergo β-fragmentation reactions to provide decahydro-1-(2-haloethyl)-2,5,5,8a-tetramethyl-2-naphthalenol acetates (9b,c) which are converted to dodecahydro-naphthofuran 5 and ambreinolide 6.

Ambergris[1], highly valued since ancient times, is a concretion formed in the intestinal tract of the blue sperm whale. Used in perfumery as an ethanolic tincture obtained after one to three years of aging, ambergris combines a unique odor with fixative properties to comprise a vital ingredient of many fine fragrances. In recent times due to a nearly worldwide ban on the use of whale products, the fragrance industry has relied on the efforts of chemists to provide substitutes for ambergris. Some components[2] of the tincture of ambergris which make an important contribution to the overall odor include (-)-α-ambrinol (1), (+)-dihydro-γ-ionone (2), (+)-amber aldehyde (3), γ-homocyclogeranyl chloride (4) and dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (5). (+)-Ambreinolide (6), also a component of ambergris[3], is odorless. Previous work[4] from these laboratories resulted in methodology for the preparation of (±)-α-ambrinol and (±)-dihydro-γ-ionone. This report describes new processes for the conversion of sclareol (8a) to naphthofuran 5.

* Dedicated to Prof. Dr. Helmut Doerfel on the occasion of his 60th birthday.



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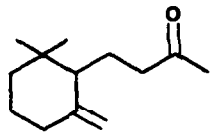

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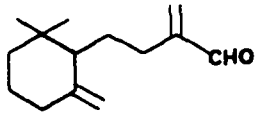

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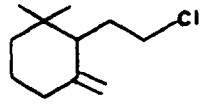

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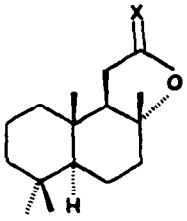
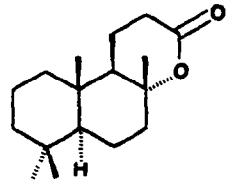


5 X = H_2
7 X = O



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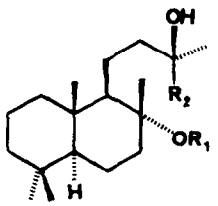
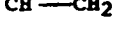
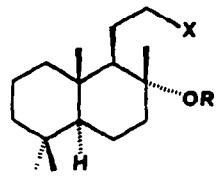
Naphthofuran 5 possesses a powerful amber odor and commands a high price for perfumery use. At the outset of this work, the commercial method for production of 5 used chromate or permanganate oxidation[5] of sclareol (8a) to sclareolide (7). Hydride reduction to diol 9a followed by dehydration provides furan 5.[6] Recently[7], we have reported that diol 9a may be obtained in high yield from sclareol by fermentation. Alternatively, acid catalyzed cyclization of homofarnesic acid (or its derivatives) affords racemic sclareolide.[8] Degradation[9] of l-abietic acid via several intermediates also leads to (-)-furan 5.



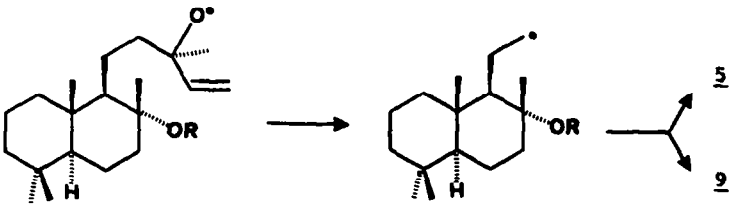
8a R_1 = H, R_2 = CH=CH_2
8b R_1 = Ac, R_2 = CH=CH_2
8c R_1 = Ac, R_2 = CH_2CH_3
8d R_1 = Ac, R_2 =





9a X = OH, R = H
9b X = I, R = Ac
9c X = Cl, R = Ac
9d X = CN, R = Ac

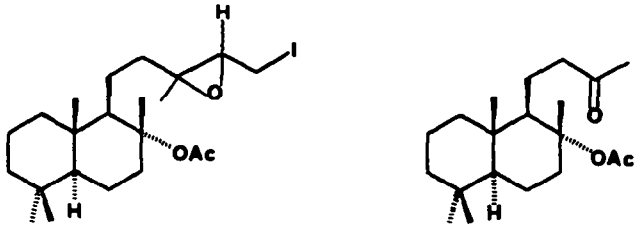
Sclareol, readily available from clary sage and possessing the appropriate stereochemistry, is an attractive starting material for the synthesis of 5. Upon consideration of alternative methods for side chain degradation of sclareol, attention focused on reactions of alkoxy radicals. β-Fragmentation of tertiary alkoxy radicals is widely considered[10,11] to proceed to give the most stable carbon radical and carbonyl components. It was envisioned that if alkoxy radical 10 could be generated, then it would likely fragment to radical 11. Oxidation of radical 11 could then occur along with either cyclization to furan 5 or trapping by a nucleophile to afford compounds of type 9. Hydrogen abstraction at C-1 by radical 10 was deemed unlikely due to steric congestion around C-1. A recent account[12] based on the same concept described the preparation of 5 from sclareol hydroperoxide.



10 11

Initially, the fragmentation of sclareol 8a was attempted using ceric ammonium nitrate or lead tetraacetate, but lead only to complex mixtures. Photolysis of the dinitrite of sclareol produced a similar result. Subsequently, the reactions of several readily available sclareol derivatives were investigated. Oxidation of sclareol monoacetate 8b with lead tetraacetate and iodine provided iodo acetate 9b in 50% yield along with iodo epoxide 12 (32% yield) as a mixture of stereoisomers. Iodo epoxide 12 could be converted back to 8b by reduction with zinc and acetic acid in 81% yield. Alkaline hydrolysis of iodo acetate 9b affords (-)-furan 5 in 81% yield (20% overall yield from 8a).

Replacement of lead tetraacetate with iodosobenzenediacetate,[13] gave a 35% yield of 9b and a 48% yield of 12. It is likely that 12 results from an ionic mechanism involving attack of the hydroxy group on an iodine/olefin complex. In order to preclude formation of compound 12, the fragmentation reaction ($Pb(OAc)_4/I_2$) was applied to dihydrosclareol monoacetate (8c). In this instance, however, the alkoxy radical fragmented with little regioselectivity leading to a 73% yield of a 5/3 ratio of iodo acetate 9b and the known[14a] keto acetate 13. Reaction of 8c with $PhI(OAc)_2/I_2$ gave 9b and 13 in 32 and 25% yield respectively.

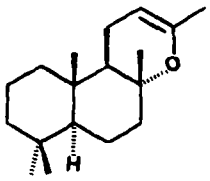


12 13

Oxidation ($VO(acac)_2$/tBuOOH) of sclareol acetate 8b, provides epoxide 8d in 87% yield. Fragmentation of epoxide 8d with either $Pb(OAc)_4$ or $PhI(OAc)_2$ and iodine lead to a 50-55% yield of iodo acetate 9b. No other products from the reaction of epoxide 8d were isolated. Attempts to effect the fragmentation reaction of sclareol derivatives 8b and 8c via the corresponding hypochlorite or hypobromite using various literature procedures[10,15] failed.

A related approach utilizes the well-known[10-12] reduction of hydroperoxides to generate alkoxy radicals. Acid catalyzed addition of hydrogen peroxide to sclareol oxide (14)[14a] affords hydroperoxide 15 in high yield. Admixture of crude 15 with ferrous chloride and a catalytic amount of cupric chloride provides a 73% yield of 9c from 14. Hydrolysis of chloride 9c furnishes (-)-furan 5 in 78% yield (34% overall yield from sclareol [14b]). No products resulting from hydrogen abstraction at C-1 were isolated from reactions of alkoxy radicals derived from 8b-8d and 15.

Iodo acetate 9b may be used to contruct other labdane-type derivatives. Heating a mixture of iodo acetate 9b and sodium cyanide in DMF provides the known[16] acetoxy nitrile 9d in 84% yield which upon hydrolysis and lactonization furnishes (+)-ambreinolide (6) in 87% yield (18% overall yield from sclareol).



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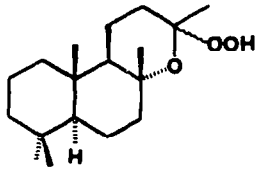

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Experimental

General. Benzene was dried over 4Å molecular sieves prior to use. Sclareol, purchased from R.J. Reynolds Tobacco Co., was recrystallized from hexane prior to use. All other reagents and solvents were of reagent grade and were used as received.

IR spectra were obtained with a Perkin-Elmer 710B spectrophotometer. Routine ^{1}H-NMR spectra were recorded with a Varian Associates T-60A NMR instrument. The ^{1}H-NMR spectral data reported at 250 MHz were recorded on a Bruker WM250 NMR instrument and the ^{13}C-NMR spectra were obtained on the same instrument at 62.5 MHz. Mass spectra were obtained with a Hewlett-Packard 5985 mass spectrophotometer. Column chromatography was performed with Merck 60 brand of silica gel. GLC analyses were obtained with a Hewlett-Packard Model 5840 or a Perkin-Elmer model 920 gas chromatography, using either a 6 ft., 2mm i.d. glass column packed with 3% OV-17 on Chromosorb W, 100-120 mesh or a 10 ft., 2 mm i.d. glass column packed with 2% Carbowax 20M on Chromosorb G, 100-120 mesh. Where indicated, percentages refer to computer calculated peak areas without correction for response. GLC and mass spectral data were provided courtesy of the Fritzsche, Dodge and Olcott, Instrumental Laboratory.

Elemental microanalyses were performed by Childers Laboratories, Milford, N.J. or Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Melting points were determined with a Thomas Model 40 micro hot-stage apparatus and are uncorrected. Optical rotations were obtained in chloroform solution at ambient temperature unless otherwise noted using a Perkin-Elmer 241 polarimeter.

[1R-[1α(R*),2β,4aβ,8aα]]-2-Acetyloxy-α-ethenyldecahydro-α,2,5,5,8a-pentamethyl-1-naphthalenepropanol (sclareol monoacetate, 8b). A mixture of sclareol 8a (92.4g, 0.3 mol) and N,N-dimethylaniline (160 mL) was reacted with acetyl chloride (53.5 mL, 0.75 mol) in a manner similar to that described by Ohloff[17] to provide 108g of crude sclareol diacetate. A solution of potassium hydroxide (19.8g, 0.3 mol) in water (70 mL) was added to a mixture of the unpurified sclareol diacetate and 95% ethanol (900 mL). The mixture was stirred at 25°C for 48h. Potassium hydroxide (3.91g, 0.06 mol) was added and the mixture was stirred for 22h at 25°C. The mixture was concentrated under reduced pressure to a volume of about 300 mL. Water (300 mL) was added and the mixture extracted with hexane/ethyl acetate (4:1, 4 x 200 mL). The extracts were washed with water (2 x 75 mL), brine (50 mL) and dried (Na_2SO_4). Evaporation

of solvents followed by crystallization of the residue from hexane/ethyl acetate provided in two crops 58.75g of material (mainly 8b according to TLC analysis). Further recrystallization gave 53.07g (50% yield) of sclareol monoacetate 8b, mp 122-123°C, $[\alpha]_D$ -34.3° (c, 1.546); lit.[18] mp 121-122°C, $[\alpha]_D^{25}$ -35.4° (c, 2.35). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.76 (3H, s), 0.81 (3H, s), 0.84 (3H, s), 1.28 (3H, s), 1.44 (3H, s), 1.92 (3H, s) 0.8-1.8 (16H, m), 5.12 (2H, dd, J = 14 Hz and 11 Hz), 5.95 (1H, dd, J = 14 Hz and 11 Hz); ^{13}C-NMR δ 15.71 (q), 18.36 (t), 19.87 (t), 20.03 (t), 20.57 (q), 21.44 (q), 22.88 (q), 27.87 (q), 33.11 (s), 33.32 (q), 38.89 (t), 39.59 (s), 39.74 (t), 41.98 (t), 45.37 (t), 55.72 (q), 58.90 (d), 73.43 (s), 88.24 (s), 111.62 (t), 145.11 (d), 169.91 (s); IR ($CHCl_3$) ν_{max} 3575, 3350, 2940, 1725, 1460, 1385, 1360 cm^{-1}; MS m/e 290, 275, 272, 257, 205, 191, 177, 81, 43.

[1R-(1α(R*),2β,4aβ,8aα)]-2-Acetyloxy-α-oxiranyldecahydro-α,2,5,5,8a-pentamethyl-1-naphthalenepropanol (8d). To a mixture of sclareol monoacetate 8d (7.00g, 0.02 mol) vanadium (IV) bis(2,4-pentanedionate) oxide (0.100g, 0.38 mmol) and methylene chloride (60 mL) heated at reflux was added a solution of t-butyl hydroperoxide (3 mL, 0.027 mol, Lucidol 90) in methylene chloride (30 mL) over a 1h period. The mixture was heated at reflux for 2h and then a solution of t-butyl hydroperoxide (1 mL, 0.009 mol) in methylene chloride (15 mL) was added over a 0.5h period. The mixture was heated at reflux for an additional 2h and then stirred at 25°C. A 10% sodium sulfite solution (75 mL) was added and the mixture was stirred for 1.5h at 25°C. The phases were separated and the aqueous phase was extracted with methylene chloride (2 x 25 mL). The combined organic layers were washed with 10% sodium sulfite solution (2 x 30 mL) (negative starch iodide test), saturated sodium bicarbonate solution and dried (Na_2SO_4). Evaporation of solvents provided 7.038g of a nearly colorless solid. Crystallization from hexane/ethyl acetate gave 6.399g (87% yield) of epoxide 8d, mp 129.5-131°C; $[\alpha]_D$ -35.75° (c, 3.43). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.74 (3H, s), 0.79 (3H, s), 0.82 (3H, s), 1.25 (3H, s), 1.41 (3H, s), 1.88 (3H, s), 0.9-1.8 (16H, m), 2.51-2.93 (4H, m); ^{13}C-NMR δ 15.68 (q), 18.34 (t), 19.07 (t), 20.01 (t), 20.64 (q), 21.40 (q), 22.79 (q), 25.84 (q), 33.07 (s), 33.28 (q), 38.82 (t), 39.55 (s), 39.66 (t), 41.90 (t), 41.95 (t), 44.03 (t), 55.70 (d), 57.72 (d), 69.41 (s), 88.08 (s), 169.85 (s); IR ($CHCl_3$) ν_{max} 3530, 2940, 1720, 1460, 1385, 1360, 1260 cm^{-1}; MS, m/e 306, 291, 273, 109, 95, 81, 43. Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09, H, 10.45. Found: C, 72.17; H, 10.45.

[1R-[1α(S*),2β,4aβ,8aα]]-2-Acetyloxy-α-ethyldecahydro-α-2,5,5,8a-pentamethyl- 1-naphthalenepropanol (8c). A mixture of sclareol monoacetate 8b (3.50g, 0.01 mol), platinum oxide (0.225g), sodium nitrite (0.01g) and ethanol (40 mL) was shaken under a hydrogen atmosphere (40 psi) for 2.5h. The mixture was filtered through Celite and the solids were washed with ethanol. The solvent was evaporated and the residue crystallized from hexane to give 2.69g (76% yield) of dihydro-sclareol monoacetate 8c, mp 92-94°C, $[\alpha]_D$ -27.35° (c, 1.547); (lit.[14,19] mp 93-94.5°C) ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.78, (3H, s), 0.84 (3H, s), 0.87 (3H, s), 0.90 (3H, t, J = 7.5 Hz), 1.16 (3H, s), 1.47 (3H, s), 1.93 (3H, s), 0.8-1.9 (18H, m), 2.60-2.68 (1H, m). IR ($CHCl_3$) ν_{max} 3580, 3450, 2950, 1720, 1455, 1385, 1360, 1260 cm^{-1}; MS, m/e 352, 292, 274, 259, 245, 204, 137, 109, 95, 43.

Reaction of Sclareol Monoacetate with Iodosobenzene Diacetate. To a mixture of sclareol monoacetate 8b (1.050g, 0.003 mol), iodosobenzene diacetate (0.966g, 0.003 mol), calcium carbonate (1.2g, 0.012 mol) and benzene (60 mL) heated at reflux was added dropwise over a 45 min period a solution of iodine (0.762g, 0.003 mol) in benzene (25 mL). The mixture was heated at reflux for 1.5h, cooled, decanted from solids, washed with 5% sodium thiosulfate solution (2 x 50 mL), saturated sodium bicarbonate solution (2 x 30 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue Kugelrohr distilled (bath 60°C, 0.5 mm) to remove most of the iodobenzene. Chromatography (eluant: hexane:ethyl acetate; 20:1) of the residue gave 0.429g (35% yield) of [1R-(1α,2β,4aβ,8aα)]-decahydro-1-(2-iodoethyl)- 2,5,5,8a-tetramethyl-2-naphthalenol acetate (9b). Crystallization from hexane provided a pure sample; mp 94-99°C with decomposition; $[\alpha]_D$ -4.28° (c, 1.33). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.77 (3H, s), 0.81 (3H, s), 0.85 (3H, s), 1.46 (3H, s), 1.93 (3H, s), 0.85-2.1 (13H, m), 2.62-2.73 (1H, m), 3.09-3.35 (2H, m); ^{13}C-NMR δ 7.59 (t), 15.78 (q), 18.32 (t), 19.92 (t), 20.48 (q), 21.43 (q), 22.91 (q), 31.84 (t), 33.16 (s), 33.31 (q), 38.95 (t), 39.26 (t), 39.73 (t), 41.83 (t), 55.66 (d), 61.17 (d), 87.26 (s), 169.73 (s),; IR ($CHCl_3$) ν_{max} 2940, 1720, 1450, 1385, 1360, 1250 cm^{-1}; MS, m/e 346, 331, 279, 219, 137, 109, 95, 43. Anal. Calcd for $C_{18}H_{31}I_2$: C, 53.20; H, 7.69; I, 31.23. Found: C, 53.76; H, 7.99; I, 30.91. The reaction also provided 0.639g (48% yield) of [1R-[1R-(2α,2β,4aβ,8aα)]]- 1-(5-iodo-3,4-epoxy-3-methylpentyl)-decahydro-2,5,5,-8a-tetramethyl-2-naphthalenol acetate (12) as a mixture of isomers. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.78 (3H, s), 0.81 (3H, s), 0.86 (3H, s), 1.28 and 1.34 (3H, 2s), 1.46 and 1.47 (3H, 2s), 1.930 and 1.932 (3H, 2s), 0.8-2.0 (15H, m), 2.6-2.75 (1H, m), 2.9-3.4 (3H, m); IR ($CHCl_3$) ν_{max} 2930, 1720, 1455, 1385, 1360, 1255 cm^{-1}; MS, m/e 416, 401, 384, 289, 245, 204, 137, 109, 95, 43.

Reduction of Iodo Epoxide 12 with Zinc. Zinc dust (0.070g, 1.07 mmol) was added to a solution of iodo epoxide 12 in methanol (15 mL) and acetic acid (1 mL). The mixture was stirred at 25°C for 17h. The mixture was poured onto water (20 mL) and extracted with hexane/ethyl acetate (9:1, 4 x 10 mL).

The extracts were washed with saturated sodium bicarbonate solution (2 x 15 mL), brine and dried (Na_2SO_4). Evaporation of solvent gave 0.113g of a colorless solid. Recrystallization from hexane/ethyl acetate gave 0.101g (81% yield) of sclareol monoacetate (8b) mp 122-123°C. Spectral data was identical to that of authentic 8b (see above).

Reaction of Sclareol Acetate with Lead Tetraacetate. To a mixture of lead tetraacetate [5.32g, 0.012 mol, washed with hexane (2 x 50 mL)], calcium carbonate (2.40g, 0.024 mol), sclareol monoacetate 8b (2.10g, 0.006 mol) and benzene (150 mL) heated at reflux was added a solution of iodine (1.524g, 0.006 mol) in benzene (90 mL) over a 1.5h period. The mixture was heated at reflux for 1h, cooled and filtered. The filtrate was washed with 5% sodium thiosulfate solution (2 x 50 mL), saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. Chromatography (eluant:hexane:ethyl acetate; 20:1) gave 1.209g (50% yield) of iodo acetate (9b) and 0.906g (32% yield) of iodo epoxide (12). The compounds were characterized as described above.

Reaction of Sclareol Epoxide Monoacetate with Iodosobenzene Diacetate. To a mixture of epoxide (8d) (0.732g, 0.002 mol) iodosobenzenediacetate (1.288g, 0.004 mol), calcium carbonate (0.8g, 0.008 mol), and benzene (40 mL) heated at reflux was added dropwise over a 45 min period a solution of iodine (0.508g, 0.002 mol) in benzene (25 mL). The mixture was heated at reflux for 1.5h and cooled. Work-up and chromatography as described above provided 0.433g (53% yield) of iodo acetate 9b.

Reaction of Sclareol Epoxide Monoacetate with Lead Tetraacetate. To a mixture of lead tetraacetate [2.66g, 0.006 mol, washed with hexane (2 x 30 mL)], calcium carbonate (1.20g, 0.012 mol), benzene (75 mL) and epoxide 8d heated at reflux was added a solution of iodine (0.726g, 0.003 mol) in benzene (35 mL) over a 1h period. The mixture was heated at reflux for 1h, cooled and filtered. Work-up and chromatography as described above gave 0.665g (55% yield) of iodo acetate 9b.

Reaction of Dihydro-sclareol Monoacetate with Lead Tetraacetate. To a mixture of lead tetraacetate (3.547g, 8 mmol), calcium carbonate (1.60g, 16 mmol), dihydro-sclareol monoacetate 8c (1.418g, 4 mmol) and benzene (200 mL) heated at reflux was added a solution of iodine (1.016g, 4 mmol) in benzene (50 mL) over a 1.5h period. The mixture was heated at reflux for 1h, cooled and filtered. Work-up and chromatography as described above gave 0.794g (49% yield) of iodo acetate 9b and 0.388g (29% yield) of keto acetate 13 as a slightly colored solid. Recrystallization of 13 from hexane gave 0.190g of material, mp 119-122°C, $[\alpha]_D$ -25.54 (c, 1.66); lit.[14a] mp 119.5-122°C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.78 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 1.47 (3H, s), 0.75-1.80 (13H, m), 1.93 (3H, s), 2.14 (3H, s), 2.49-2.71 (3H, m); ^{13}C-NMR δ 15.56 (q), 18.4 (t), 19.76 (t), 20.65 (q), 21.46 (q), 22.86 (q), 29.72 (q), 33.18 (s), 33.34 (q), 38.97 (t), 39.65 (s), 39.85 (t), 41.97 (t), 46.57 (t), 55.77 (d), 58.22 (d), 88.04 (s), 169.79 (s), 208.51 (s); IR ($CHCl_3$) ν_{max} 2940, 1720, 1455, 1385, 1360 cm^{-1}; MS, m/e 280, 262, 244, 229, 204, 109, 95, 81, 43.

Reaction of Dihydro-sclareol Monoacetate with Iodosobenzene Diacetate. To a mixture of 8c (1.056g, 3 mmol), calcium carbonate (1.20g, 12 mmol), iodosobenzene diacetate (1.732g, 6 mmol) and benzene (60 mL) heated at reflux was added dropwise over a 45 min period a solution of iodine (0.762g, 3 mmol) in benzene (40 mL). The mixture was heated at reflux for 1.5h and cooled (28°C). Work-up and chromatography as described above provided 0.388g (32% yield) of iodo acetate 9b and 0.242g (25% yield) of keto acetate 13.

[1R-(1α,2β,4aβ,8aα)]-Decahydro-1-(2-chloroethyl)-2,5,5,8a-tetramethyl-2-naphthalenol Acetate (9c). Acetic acid (2 mL) was added to a mixture of sclareol oxide (14)[14] (0.262g, 0.001 mol), tetrahydrofuran (8 mL) and 30% hydrogen peroxide (6 mL). The mixture was stirred at 25°C for 4h. The mixture was poured onto water (10 mL) and extracted with hexane/ethyl acetate (9:1, 4 x 10 mL). The extracts were washed with water (2 x 5 mL), saturated sodium bicarbonate solution (2 x 10 mL) and dried (Na_2SO_4). Evaporation of solvents provided 0.327g of the hydroperoxide intermediate as a colorless solid. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.080 (6H, s), 0.87 (3H, s), 1.38 (3H, s), 1.43 (3H, s), 0.8-2.2 (16H, m) 7.52 (1H, s).

A solution of the hydroperoxide intermediate (0.001 mol, crude product from above) in methanol (10 mL) was added dropwise over a 30 min period to a solution of ferrous chloride (0.398g, 0.002 mol) and cupric chloride (0.034g, 0.0002 mol) in methanol (6 mL) at 25°C. The mixture was stirred at 25°C for 15 min. The mixture was poured onto water (20 mL) and extracted with hexane:ethyl acetate (9:1, 4 x 15 mL). The extracts were washed with water (2 x 10 mL), saturated sodium bicarbonate solution (2 x 10 mL) and dried (Na_2SO_4). The solvents were evaporated and the residue chromatographed to provide 0.229g (73% yield) of chloro acetate 9c. Recrystallization from hexane provided an analytical sample, mp 99-101.5°C, $[\alpha]_D$ -15.76° (c, 1.76). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.73 (3H, s), 0.78 (3H, s), 0.81 (3H, s), 1.43 (3H, s), 1.87 (3H, s), 0.7-2.05 (13H, m), 2.6-2.7 (1h, m), 3.36-3.59 (2H, m); ^{13}C-NMR δ 15.56 (q), 18.28 (t), 19.87 (t), 20.39 (q), 21.37 (q), 22.65 (q), 29.88 (t), 33.07 (s), 33.22 (q), 38.87 (t), 39.09 (s), 39.68 (t), 41.78 (t), 45.76 (t), 55.59 (d), 56.93 (d), 87.00 (s), 169.30 9s); IR ($CHCl_3$) ν_{max} 2930, 1725, 1460, 1440, 1390, 1370, 1255 cm^{-1}; MS, m/e 272, 256, 254, 241, 239, 137, 124, 109. Anal. Calcd for $C_{18}H_{31}ClO_2$: C, 68.65; H, 9.92; Cl, 11.26. Found: C, 68.82; H, 10.08; Cl, 11.12.

[3aR-(3aα,5aβ,9aα,9bβ)]-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]-furan (5). A mixture of the iodo-acetate 9b (0.610g, 0.0015 mol), potassium hydroxide (0.593g, 0.009 mol) and isopropanol:water (6:1, 50 mL) was heated at reflux for 18h. The mixture was cooled and concentrated under reduced pressure. The residue was added to water and extracted with hexane (4 x 20 mL). The extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvents were evaporated and the residue chromatographed (eluant;hexane:ethyl acetate; 20:1). Kugelrohr distillation (bath 120°C, 1 mm) gave 0.286g (81% yield, 99.5% pure according to GLC analysis) of naphthofuran 5, mp 74.5-76°C; $[\alpha]_D$ -29.90° (c, 3.01 benzene); lit.[6] mp 75-76°C, $[\alpha]_D$ -28.0° (benzene) ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.83 (6H, s), 0.88 (3H, s), 1.08 (3H, s), 0.8-2.0 (14H, m), 3.75-3.96 (2H, m); ^{13}C-NMR δ15.06 (q), 18.47 (t), 20.72 (t), 22.69 (2q), 33.10 (s), 36.27 (s), 39.36 (t), 40.06 (t), 42.54 (t), 57.36 (d), 60.22 (d), 64.94 (t), 79.84 (s); IR (melt) ν_{max} 2930, 1480, 1460, 1390, 1375 cm^{-1}; MS, m/e 236, 221, 204, 137, 97.

[3aR-(3aα,5aβ,9aα,9bβ)]-Dodecahydro-3a,6,6,9a-tetramethyl-naphtho[2,1-b]-furan. A mixture of chloro acetate 9c (0.124g, 0.36 mmol), potassium hydroxide (0.118g), isopropanol (10 mL) and water (1.5 mL) was reacted above to provide after work-up and Kugelrohr distillation 0.077g (92% yield, 85% pure according to GLC analysis) of naphthofuran 5.

[1R-(1α,2β,4aβ,8aα)]-3-(2-Acetoxy-dodecahydro-2,5,5,5a-tetramethyl-1-naphthalenyl)propanenitrile (9d). A mixture of iodo acetate 9b (0.929g, 2.29 mmol), sodium cyanide (0.561g, 11.4 mmol) and dimethylformamide was heated at 100-105°C for 3.5h. The mixture was cooled (25°C) poured onto water (80 mL) and extracted with hexane: ethyl acetate (9:1, 4 x 20 mL). The extracts were washed with saturated sodium bicarbonate solution (2 x 20 mL) and dried (Na_2SO_4). Evaporation of solvents afforded 0.680g of crude product as a nearly colorless solid. Recrystallization from hexane provided in two crops 0.586g (84% yield) of acetoxy nitrile 9d, mp 83-84°C; $[\alpha]_D$ -12.34° (c, 2.269); lit.[16] mp 84-86°C, $[\alpha]_D$ -10.1° (c, 2,250). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.77 (3H, s), 0.82 (3H, s), 0.86 (3H, s), 1.48 (3H, s), 1.95 (3H, s), 0.9-1.8 (13H, m), 2.43 (2H, t, J = 6.7 Hz), 2.72-2.85 (1H, m); ^{13}C-NMR δ 15.66 (q), 18.34 (t), 19.15 (t), 19.92 (t), 20.26 (q), 21.45 (q), 21.86 (t), 22.81 (q), 33.19 (s), 33.31 (q), 39.08 (t), 39.40 (s), 39.78 (t), 41.76 (t), 55.60 (d), 58.43 (d), 87.38 (s), 119.85 (s), 169.59 (s); IR (CCl_4) ν_{max} 2935, 2225, 1730, 1450, 1385, 1360 cm^{-1}; MS, m/e 278, 263, 245, 230, 193.

[4aR-(4aα,6aβ,10aα,10bβ)]-Dodecahydro-4a,7,7,10a-tetramethyl-3H-naphtho-[2,1-b]pyran-3-one (6). A mixture of acetoxy nitrile 9d (0.471g, 1.54 mmol), isopropanol (50 mL), water (10 mL) and potassium hydroxide (0.81g, 12.4 mmol) was heated at reflux for 18h. The mixture was cooled (25°C) and concentrated under reduced pressure to about 20 mL. The cooled (ice bath) mixture was acidified with 6N hydrochloric acid solution and extracted with ether (4 x 20 mL). The extracts were washed with brine (3 x 10 mL) and dried (Na_2SO_4). Evaporation of solvent gave a viscous oil (0.406g) which solidified upon standing. Recrystallization from hexane provided in two crops 0.356g (87% yield, GLC purity 99.9%) of ambreinolide (6), mp 140-141°C; $[\alpha]_D$ 30.1° (c, 1.093) lit.[16] mp 142-144°C; $[\alpha]_D^{20}$ 33.3° (c, 2.565). ^{1}H-NMR (250 MHz, $CDCl_3$)δ 0.78 (3H, s), 0.81 (3H, s), 0.86 (3H, s), 1.35 (3H, s), 0.8-2.05 (14H, m), 2.42-2.75 (2H, m); ^{13}C-NMR δ 15.02 (q), 15.87 (t), 18.41 (t), 19.67 (t), 21.43 (q), 22.85 (q), 28.98 (t), 33.15 (s), 33.29 (q), 37.29 (s), 39.21 (t), 41.31 (t), 41.82 (t), 53.69 (d), 56.06 (d), 83.55 (s), 171.14 (s); IR ($CHCl_2$) ν_{max} 2930, 1710, 1455, 1380 cm^{-1}; MS, m/e 264, 249, 193. 177.

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