The chemistry of thujone. XX.[1] New enantioselective syntheses of Ambrox and *epi*-Ambrox

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Abstract: The development of a new synthetic approach to (−)-Ambrox® (**37**) and *epi*-Ambrox® (**29**) using thujone (**1**) as a chiral synthon, is presented. Thujone (**1**), a readily available starting material obtained from Western red cedar, can be efficiently converted to β-cyperone (**2**) and the latter is then chemically elaborated to the key intermediate, the enone **6**. A carbonyl transposition of **6** to enone **9** also allows a formal synthesis of (−)-Polywood® (**18**).

Key words: thujone, β-cyperone, (−)-Ambrox®, *epi*-Ambrox®, synthesis.

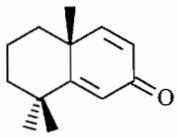
Résumé : On présente une nouvelle approche à la synthèse du (−)-Ambrox® (**37**) et de l'*epi*-Ambrox® (**29**) utilisant la thujone (**1**) comme synthon chiral. La thujone (**1**), un produit facilement disponible à partir des cèdres rouges de l'ouest, peut être transformé d'une façon efficace en β-cypérone (**2**) qui peut, par la suite, être converti en énone **6**, un intermédiaire clé. Une transposition du carbonyle de l'énone **6** en énone **9** permet de réaliser aussi une synthèse formelle du (−)-Polywood® (**18**).

Mots clés : thujone, β-cypérone, (−)-Ambrox®, *épi*-Ambrox®, synthèse.

[Traduit par la rédaction]

The ambergris fragrances are well established as an important family of perfumes. Extensive reviews, which detail studies correlating their structure with smell, synthetic efforts, etc., are available (2–4). In particular, the classic members, (−)-Ambrox® (**37**) and (+)-iso-Ambrox® (**38**), form the basis of commercial products, for example, Fixateur 404 (trade name of Firmenich), which has been marketed in the perfumery industry for more than 30 years. In a previous study (5), we presented one of our synthetic approaches to these compounds from the readily available chiral synthon thujone (**1**). We now wish to detail our most recent studies, which afford alternative and novel enantioselective syntheses to (−)-Ambrox® (**37**) and (−)-*epi*-Ambrox® (**29**) from thujone.

In developing a possible route to the above, our consideration turned to the conjugated enone **6** (Scheme 1) available from β-cyperone (**2**), via a previously published procedure (6–8). To functionalize decalone **6** in a manner that would allow eventual synthesis of Ambrox® (**37**), it was evident that a two-carbon unit had to be attached at position C9. Based on unsuccessful attempts to achieve 1,4-addition products with **7** and only very moderate yields with the *cis*-decalone **8**, an alternative ketone transposition process (**6** → **9**, Scheme 2) appeared as an attractive alternative route. Based on the relatively inefficient published procedures (9–11), the route summarized in Scheme 2 was selected.



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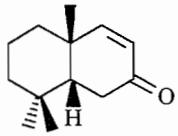

8

For this purpose, it was important to maintain the double bond functionality during the transposition steps, in order to ensure the regioselective alkylation at position C9, since competing alkylation is expected at C7 when both C7 and C9 positions are accessible for alkylation (12–14). As noted in the conversion of **6** to **10**, an oxidation at C8 is essential. For this purpose, the reaction involving α-hydroxylation of α,β-unsaturated ketones, by means of manganese(III) acetate originally described by Williams and Hunter (15), and subsequently improved by Watt and coworkers (16–18), was selected. When the reported conditions were applied to **6**, only low to moderate yields (35–60%) of the acetoxylated product were obtained even though special care was taken in drying the manganese(III) acetate. Since manganese(III) acetate is commercially available in its hydrated form, the reported drying method (phosphorus pentoxide and high vacuum for several days) proved to be insufficient for our purpose. Indeed, when azeotropic removal of water was carried out, the lower yields obtained by Watt (16, 17), could be improved and a mixture of the desired acetoxyketones **10/11** (R = Ac) were consistently obtained in 86% yield (Scheme 3). The mechanism proposed is consistent with that presented earlier (18).

α-Acetoxylation of enone **6** resulted in an inseparable mixture of isomers **10/11** in a 4:1 ratio. Assignment of the structures was done from the analysis of the C8 proton signal in the ^{1}H NMR spectrum. The proton at position C8 of the major

Received August 19, 1996.[2]

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[1] For Part XIX, see ref. 1.
[2] Revision received May 21, 1997.
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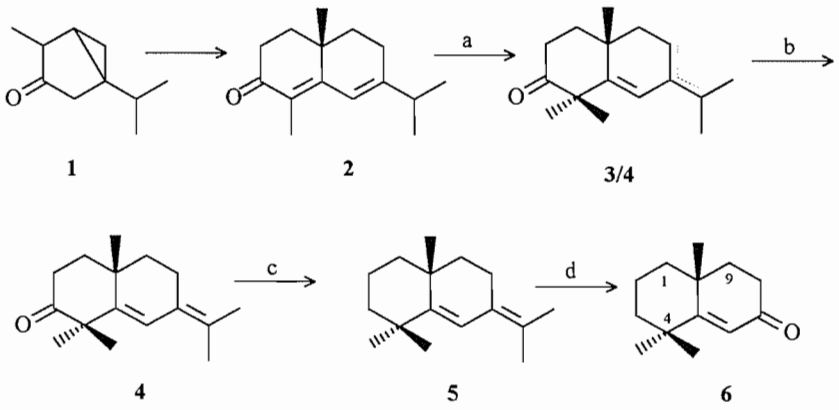
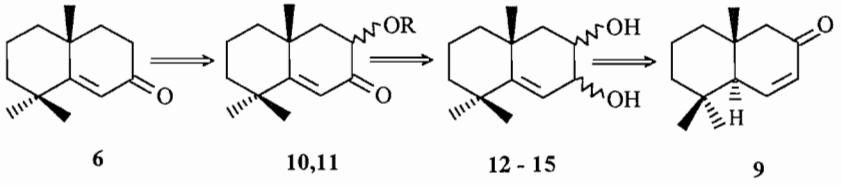
Scheme 1. Synthesis of enone **6** from thujone (**1**).



(a) NaOMe, DMSO; MeI; (b) I_2, hexane, reflux; (c) $H_2N–NH_2$, KOH, DEG; (d) O_3, MeOH–CH_2Cl_2, −78°C.

Scheme 2. A proposed ketone transposition sequence from enone **6** to enone **9**.



Scheme 3. Proposed mechanism for α-acetoxylation of enone **6**.

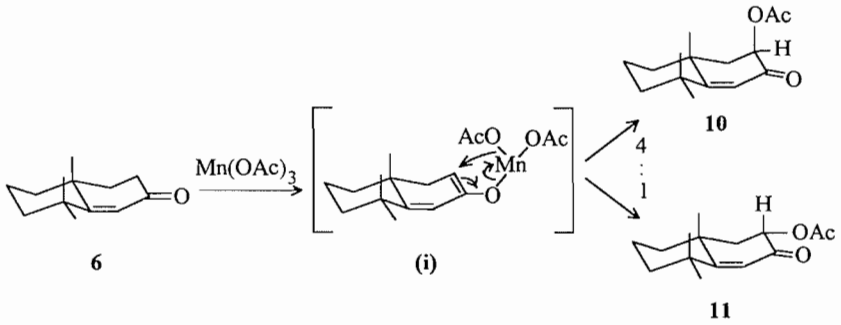
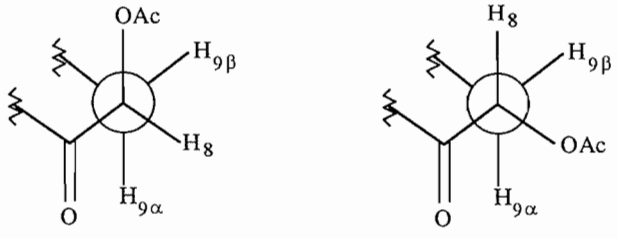


Fig. 1. The spatial relationship of the C8 and C9 protons in isomers **10/11**.

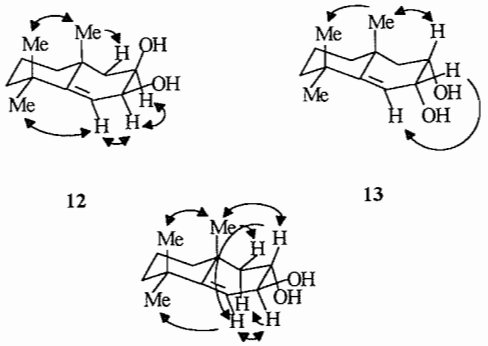


isomer displayed a triplet at δ 5.25 ppm (J = 4 Hz), which is in accordance with an equatorial position at C8 since it resides at an equal distance from the C9-αH and C9-βH (Fig. 1). On the other hand, the minor isomer, with its acetoxyl group in the α orientation, displayed a doublet of doublets at δ 5.60 ppm (J = 12, 4 Hz) for the axial C8 proton, being anti-periplanar to the C9-αH, and displaying therefore a large coupling constant (J = 12 Hz) when coupled with this hydrogen, and a small coupling constant (J = 4 Hz) when coupled with C9-βH, which corresponds to an angle of 60°.

The mixture of isomers **10/11** was reduced with LAH, yielding a mixture of four isomeric diols **12/13/14/15** in a ratio of 50:1:3:18, as observed after isolation of the pure diols. The diols **12–15** were separated by column chromatography for characterization purposes. Assignment of the different configurations for diols **12–14** was done by ^{1}H NMR and NOE difference experiments (Fig. 2). It was expected that the two major isomers should possess the hydroxyl group at position C7 in the β orientation, since the reducing agent was expected to approach the carbonyl function predominantly from the less hindered side (α face). The remaining diol **15** was then assigned as the 7α,8β isomer.

The following dehydration step was experimentally rather "delicate." A selective dehydration of the hydroxyl at position C7 was required in order to furnish the desired ketone **9**. The expected different reactivity of the two hydroxyl groups was a key factor for the success of the sequence. Discrimination of

Fig. 2. A summary of proton interactions as determined from NOE difference experiments with alcohols **12**, **13**, and **14**.



12 **13**

14

the hydroxyl groups under acidic conditions was indeed achieved and the hydroxyl at C7 underwent selective dehydration and conversion to the desired product **9** (Scheme 4). The elimination of the hydroxyl group at C8 would simply regenerate the initial enone **6** but this was not observed. The final step, in which the migration of the double bond occurs, was expected to take place easily under acidic conditions, fortunately towards the desired *trans*-decalone system.

By using 1.2 equivalents of *p*-toluenesulfonic acid and 0.1 M concentration of diols **12–15** in anhydrous THF, 64% of the *trans*-enone **9**, 25% of the nonconjugated enone (**16**), and less than 2% of the *cis*-enone (**17**) were isolated. These results suggested that the transformation of **12–15** to the mixture of **9**, **16**, **17** is kinetically controlled since published studies (ref. 19, footnote 9) have determined that the proportions at thermodynamic equilibrium are **9** (26%), **16** (6%), and **17** (69%). In a separate experiment, when enone **16** was submitted to the same conditions, a 65% yield of the *trans*-decalone (**9**), and 31% of the nonconjugated enone (**16**) was obtained, while no *cis*-decalone was isolated.

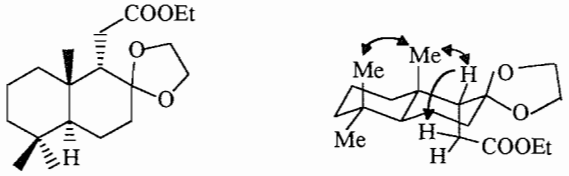
The overall yield in the three steps for the conversion, **12–15** to **9**, was 64% when the isolated nonconjugated enone (**16**) was recycled. A notable advantage of this novel sequence is that these three operations can be done without isolation of the intermediates, so that an effective route to **9** was now available. For preparative purposes, the sequence, **6** → **10/11** → **12–15** → **9**, can be conducted *without* isolation of the pure components in the various stages and in an overall yield of 64%.

Compound **9** displayed a peak at *m/z* 192 in the mass spectrum, corresponding to the molecular ion. Its ^{1}H and ^{13}C NMR spectra agreed with the published data (20), although an authentic sample was unavailable for direct comparison. Similarly, the data for the *cis*-decalone (**17**) and the nonconjugated enone (**16**) were also in agreement with the published data (20).

Enone **9** as well as **16** have been prepared as racemic intermediates, by a completely different route, by Snowden et al. (19) in their synthesis of (±)-Polywood® (**18**) and its unsaturated analogs. On this basis, a formal synthesis of (−)-Polywood® (**18**) and its chiral unsaturated analogs has been completed starting from thujone (**1**) (Scheme 5).

With the desired enone **9** on hand, introduction of a two-carbon unit at C9 was considered. Generation of the enolate by reacting **9** with lithium diisopropylamide at −78°C and subsequent reaction with ethyl iodoacetate afforded the desired intermediate **19** in 73% yield. The α orientation of the side chain in **19** was established from an analysis of the NMR data (see Experimental). It should be noted that a minor by-product (8% yield) was isolated and, on the basis of spectroscopic data (see Experimental), was assigned the structure **27**.

Fig. 3. A summary of proton interactions as determined from a NOE difference experiment with ketal **21**.



21

Catalytic hydrogenation of the double bond in **19** was achieved in quantitative yield by using catalytic amounts of 10% palladium on charcoal in ethanol at 40 psi of hydrogen (1 psi = 6.9 kPa). Under these conditions, the double bond in compound **19** was selectively hydrogenated in 20 min without reducing the carbonyl group.

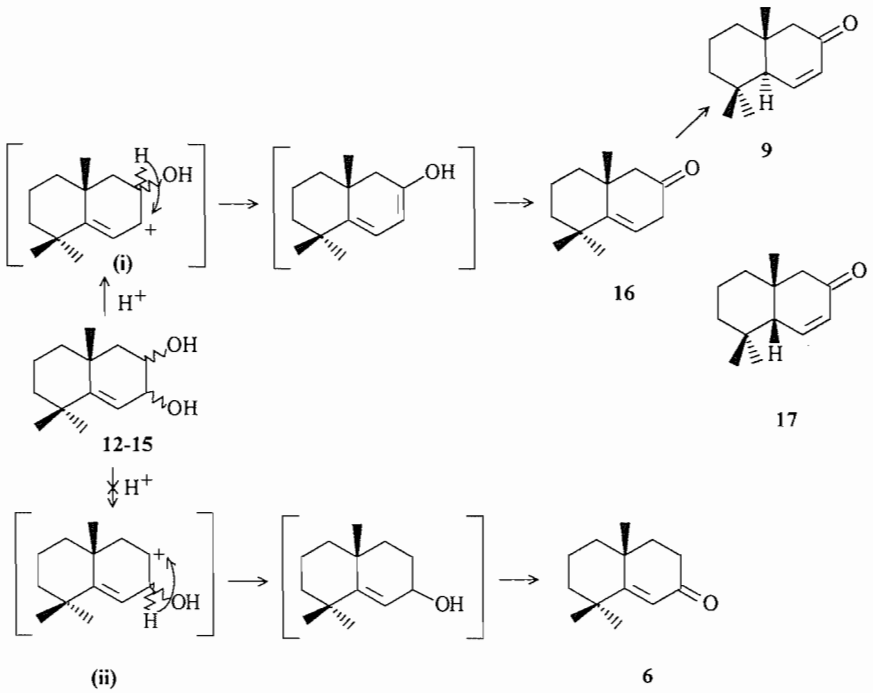
Elaboration of the ester side chain in **20** to the required primary alcohol **22** (Scheme 6) via classical LAH reduction required prior protection of the ketone function. Preliminary experiments under acid-catalyzed ketalization conditions suggested a facile epimerization of the α-oriented side chain in **19** to the thermodynamic β-oriented position (see **28**, Scheme 6). On this basis, a series of reactions, under carefully controlled conditions and utilizing triflic acid (20) and TMS-triflate (21, 22) as catalysts, were undertaken. With the former catalyst, ketal **21** could be obtained in reasonable yield (67%) when the ketone **20** (1.0 mmol in anhydrous THF) was reacted with triflic acid (0.2 mmol) and 1,2-bis(TMSO)–ethane (1.9 mmol) at 0°C (14 h). Similar results were obtained with TMS-triflate and further details are provided in the experimental section. Detailed NOE experiments (Fig. 3 and Experimental) established that no epimerization of the axially oriented side chain had occurred during the ketalization reaction. The isomeric ketal **28** was obtained as a minor product (8%).

Having found a suitable protection method for the ketone functionality, we turned our attention to the synthetic steps required to obtain diol **26**. Reduction of the ester in **21**, protection of the alcohol, deprotection of the ketone, Grignard reaction, and finally deprotection of the primary alcohol, were the synthetic steps envisaged in order to obtain diol **26**.

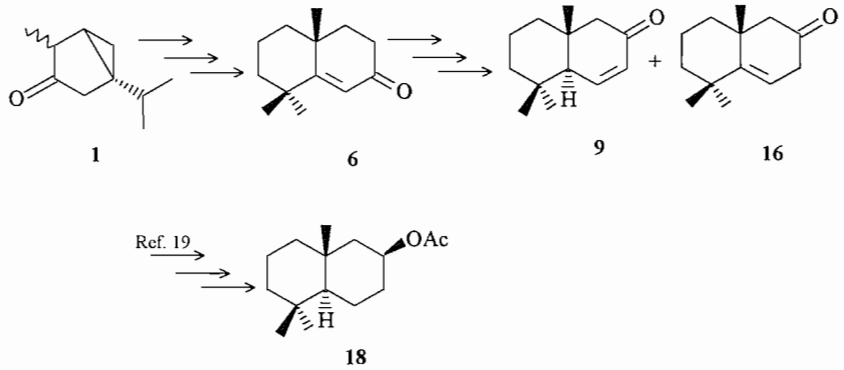
Ketal ester **21** was reduced with an excess of LAH in diethyl ether in 10 min at room temperature, affording the alcohol **22** in essentially quantitative yield.

Protection of the primary alcohol was required before further transformation could be done since removal of the ketal function under mild acidic conditions afforded only low recovery of the desired keto alcohol, indicating that decomposition took place to a considerable extent. In addition, attempted purification of the expected keto alcohol showed that this compound was unstable and a complex mixture of compounds was obtained. For this purpose, the benzyl group appeared ideal since it is expected to be stable under acidic conditions and could be subsequently removed by catalytic hydrogenolysis. Reaction of **22** with benzyl chloride in

Scheme 4. Proposed mechanism for the dehydration of diols **12–15**.



Scheme 5. Formal synthesis of (−)-Polywood® (**18**) from thujone (**1**).



ethanol heated at reflux for 12 h in the presence of sodium hydride, potassium carbonate, and catalytic amounts of sodium iodide furnished the desired product in 68% yield (87% based on starting material recovered). A method reported by Provelenghiou and co-workers (23), used in the protection of hydroxyl groups in carbohydrates and claimed to be simple, rapid, and quantitative, was also evaluated. Removal of the weakly acidic alcoholic proton in compound **22** was done with sodium hydride, followed by addition of excess of benzyl bromide and 0.1 equivalent of tetrabutylammonium iodide followed by reflux, afforded an essentially quantitative yield of **23** (R = $CH_2C_6H_5$).

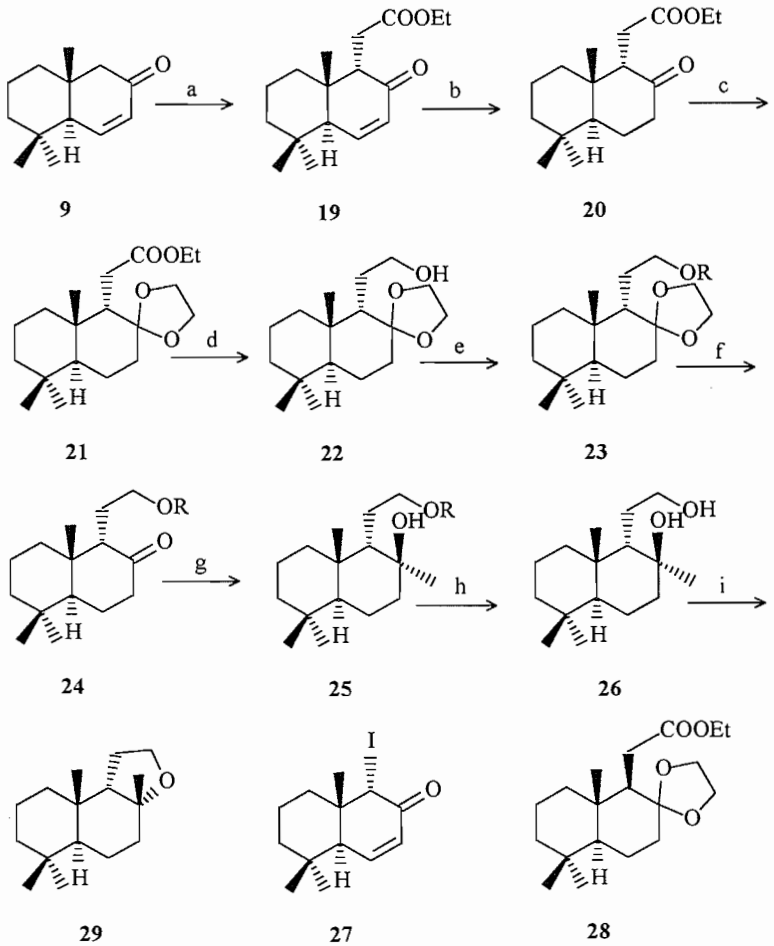
Regeneration of the carbonyl function to afford **24** (R = $CH_2C_6H_5$) was readily achieved (1 M HCl at room temperature). In summary, for preparative purposes, the three-step conversion, **21** → → **24**, could be achieved in a "one-pot" operation and in an overall yield of 87%.

With the ketone **24** (R = $CH_2C_6H_5$) available, the conversion to the tertiary alcohol **25** was now considered. Conventional Grignard reaction conditions (methylmagnesium iodide in refluxing ether) afforded **25** (R = $CH_2C_6H_5$) in low yield (20%). However, reaction of **24** (R = $CH_2C_6H_5$) with the methyl cerium(III) reagent, generated by reaction of methyllithium with anhydrous cerium(III) chloride (24–26), afforded **25** in essentially quantitative yield.

Removal of the benzyl group was achieved by catalytic hydrogenolysis (palladium in charcoal) to provide **26** in excellent yield (97%).

The final step in the synthetic route involved acid-catalyzed cyclization of **26** to (−)-*epi*-Ambrox® (**29**). Of the various approaches available from the literature (27–31), the method chosen involved *p*-toluenesulfonic acid as catalyst. When a nitromethane solution of **26** was treated with this catalyst at 80°C, the desired natural product **29** (32, 33) was obtained in 83% yield. For preparative purposes, (−)-*epi*-Ambrox® (**29**) has been prepared from the ketone **24** (R = $CH_2C_6H_5$) in 80%

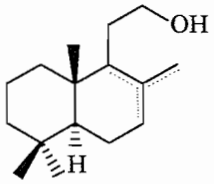
Scheme 6. Synthesis of (−)-*epi*-Ambrox® (**29**) from enone **9**.



(a) LDA; ICH_2CO_2Et; (b) H_2/Pd–C; (c) 1,2-bis(TMSO)ethane; TMS triflate; (d) LAH; (e) $PhCH_2Br$, *n*-Bu_4NI; (f) HCl, acetone; (g) MeLi, $CeCl_3$; (h) H_2/Pd–C; (i) *p*-TsOH, CH_3NO_2

overall yield without isolation of intermediates (see Method B, experimental section).

In addition to **29**, in the cyclization of **26**, a mixture of olefinic alcohols, tentatively assigned the general structure **30**, was also obtained (11%). This mixture could not be purified further by column chromatography and studies to clarify this mixture were not pursued.



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In conclusion, the above five-step synthetic route from enone **6** (previously prepared from thujone) to **29** allows synthesis of the latter in 33% overall yield.

A similar sequence to the one reported for (−)-*epi*-Ambrox® (**29**) has been followed for the synthesis of (−)-Ambrox® (**37**). In this case, the secondary product **31** from the ketalization reaction under protic conditions (and the main product when thermodynamic equilibration conditions were applied), was used to develop a parallel sequence towards (−)-Ambrox® (**37**) (Scheme 7). The starting material **31** contains the desired equatorial side chain required for Ambrox® (**37**). Reduction of ketal **31** with LAH afforded alcohol **32** in 92% yield.

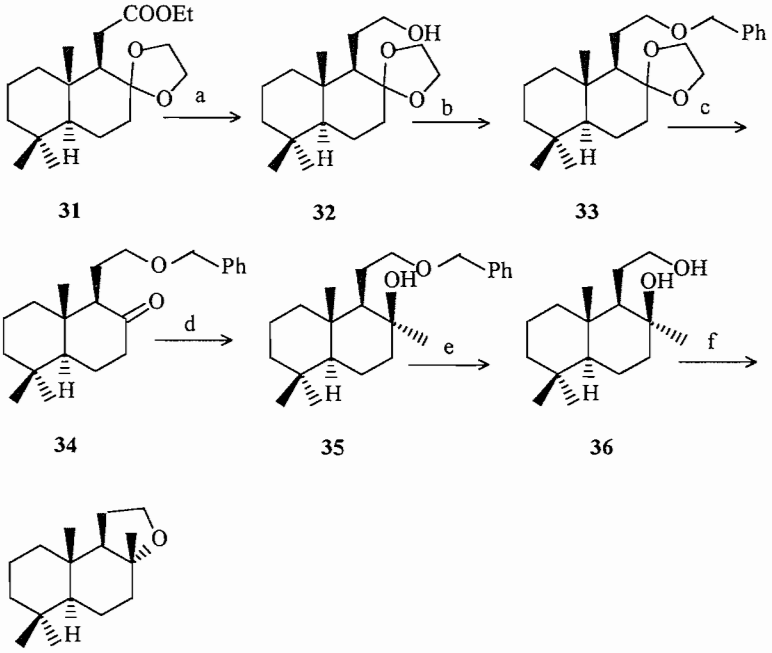
Benzylation of the hydroxyl group was performed as for compound **22**, yielding compound **33** in 92% yield.

Removal of the ketal group in **33** was performed as indicated for compound **23** although in this case longer reaction times were required when the same conditions were employed.

Ketone **34** was also obtained by isomerization of the axial side chain in compound **24** (R = $CH_2C_6H_5$) under equilibrating conditions (sodium methoxide in THF–MeOH, 22 h reflux). Under these conditions, an equilibrium mixture containing a 9:1 ration of **34**:**24** (R = $CH_2C_6H_5$), respectively, was observed.

Methylation of the carbonyl function in **34** was performed

Scheme 7. Synthesis of (−)-Ambrox® (**37**) from ketone **31**.



(a) $LiAlH_4$; (b) $PhCH_2Br$, *n*-Bu_4NI; (c) HCl; (d) MeLi, $CeCl_3$; (e) H_2, Pd–C; (f) *p*-TsOH, CH_3NO_2.

as for compound **24** (R = $CH_2C_6H_5$) using the organocerium reagent chemistry described earlier. Although in this case, having the side chain in an equatorial position may well facilitate the attack by a classical (and less reactive) Grignard reagent, as utilized by Buchi and Wuest (30), to achieve the desired stereochemistry at C8.

Hydrogenolysis of the benzyl group using palladium on charcoal, afforded diol **36**.

The cyclization of **36** was performed as for compound **26**. It was recognized that in this case the cyclization step, under acidic conditions, could generate the thermodynamically more stable *cis*-fused tetrahydrofuran ring, giving iso-Ambrox® (**38**) instead. It has been established that Ambrox® (**37**), with a *trans*-fused tetrahydrofuran ring, isomerizes to iso-Ambrox® (**38**) when treated with acid (34), demonstrating that the latter is the thermodynamically preferred isomer (35).

Equatorial approach to the tertiary carbocation at C8 should be preferred over the axial approach due to steric hindrance from the angular methyl group (30, 31). Therefore, Ambrox® (**37**) is preferentially produced through a lower energy transition state. However, iso-Ambrox® (**38**), resulting from the β-face attack, becomes the major product under prolonged reaction times under the same conditions. Investigation of the optimum conditions to effect such a cyclization by Buchi and Wuest (30) showed that treatment of diol **36** with a catalytic amount of *p*-toluenesulfonic acid in nitromethane at 80°C minimizes the formation of **38** in favour of Ambrox® (**37**).

In our case, under the same conditions, no formation of **38** was observed. The melting point and specific rotation $[\alpha]_D^{25}$ of the (−)-Ambrox® (**37**) obtained were measured to be 76–77°C and −24.1 (*c* = 1.00, $CHCl_3$), respectively. They agree well with the reported values (mp 77–77.5°C and −24.7 (*c* = 1.00, $CHCl_3$) (36). As in the previous study, a mixture of alcohols, tentatively assigned the general structure **30**, was also isolated (21% yield).

In summary, a novel route to (−)-Ambrox® (**37**) and (−)-*epi*-Ambrox® (**29**) has been developed from the thujone-derived enone **6**. Since a number of conversions can be achieved without isolation of intermediates, the overall yield from **6** to **29** is 33% while the synthetic route to **37** is 27%.

It should be noted that a very recent report by Tanimoto and Oritani (37) provides a completely different route to enantiomerically pure Ambrox from farnesyl acetate. The key reaction in this study involves a lipase-catalyzed kinetic resolution of (±)-drimane-8,11-diol. An extensive list of previous syntheses of Ambrox is also provided in this publication (37).

Experimental

General

Solvents used for chromatographic separations were glass-distilled prior to use. The term "petroleum ether" refers to a commercially available hydrocarbon mixture boiling in the 35–60°C range. All anhydrous solvents were prepared according to standard procedures. *n*-Butyllithium and methyllithium solutions were standardized by titration against diphenylacetic acid in anhydrous THF. Thujone was distilled from Western red cedar leaf oil generously donated by Intrinsic Research and Development Incorporated. All reactions were performed under a positive pressure of argon.

Reactions were monitored by analytical TLC and (or) gas chromatography. Analytical TLC was performed using Merck precoated silica gel 60 F_{254} aluminum-backed TLC plates. Visualization of the samples was realized with UV light and

(or) by spraying with a 10% solution of ammonium molybdate in 10% sulfuric acid followed by heating at 180°C until blue spots developed. Gas chromatography analyses were performed on a Hewlett–Packard 5890A gas chromatograph fitted with a fused silica capillary column coated with cyanopropylphenyl silicone gum (DB 1701) (J & W Scientific: 15 m × 0.262 mm) connected to a Hewlett–Packard 3388A integrator and flame ionization detector (carrier gas: helium; injection temperature: 250°C).

Ozone was generated in a Welsbach model T-23 laboratory ozonator.

Purification of all reaction products was carried out, unless otherwise stated, by flash chromatography using silica gel (Sigma, 10–40 μm), with nitrogen gas pressure to obtain a suitable flow.

Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus (the air bath temperature at which distillation occurred is given in parentheses).

All melting points were recorded on a Reichert melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 141 automatic polarimeter using quartz cells of 10 cm path length, in chloroform solution unless otherwise stated. The concentration (g/100 mL) is given in parentheses.

UV spectra were recorded on a Perkin–Elmer Lambda 4B UV/VIS spectrophotometer using quartz cells of 1 cm path length. IR spectra were recorded on a Perkin–Elmer 710B infrared spectrophotometer. Fourier transform IR spectra were recorded on either Perkin–Elmer 1710 or Bomen Michelson 100 Fourier transform infrared spectrophotometers.

^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz on a Bruker WH 400 spectrometer, unless otherwise noted. Chemical shifts were recorded in ppm relative to TMS (internal standard). ^{13}C NMR spectra were recorded on a Bruker AE-200 spectrometer and chemical shifts are reported in ppm relative to TMS.

Low-resolution mass spectra were recorded on Kratos MS 50 and MS 80 mass spectrometers. High-resolution mass spectra were recorded on a Kratos MS 50 mass spectrometer. Chemical ionization mass spectra were recorded on a Delsi–Nermag R10–10C mass spectrometer using ammonia as carrier gas.

Elemental analyses were carried out by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia, Vancouver.

All compounds are named in accordance with Chemical Abstracts Rules. The skeletal numbering system employed in the Discussion section, as well as proton and carbon designations to interpret the NMR spectra, follows the normal conventions of terpenoid and steroid literature. This allows an easier comparison between the compounds under discussion with related natural products.

4,4a,5,6,7,8-Hexahydro-3-acetyloxy-4aβ,8,8-trimethylnaphthalen-2(3*H*)-one (10/11)

To a solution of enone **6** (5.10 g, 26 mmol) in anhydrous benzene (280 mL), manganese triacetate dihydrate (20.40 g, 76 mmol) was added. The brown suspension was heated at reflux for 1 h with azeotropic removal of water. After cooling to room temperature, additional manganese triacetate dihydrate (20.40 g, 76 mmol) was added and the mixture was heated at reflux for 20 h. The reaction was then cooled to room temperature, diluted with ethyl acetate (500 mL), and washed with 1 M HCl (200 mL), saturated sodium bicarbonate solution (200 mL), and brine (200 mL). The organic fraction was dried, filtered, and concentrated in vacuo to yield 9.03 g of a yellow oil. Chromatographic purification of the oil using diethyl ether/hexanes 3:7 as eluent gave 5.71 g (86%) of a white solid. GC analysis (200°C) of this product showed a 4:1 mixture of isomers (**10/11**, R = Ac). Recrystallization from ethyl acetate gave colourless needles with the same isomeric ratio, mp 114–115°C; IR ($CHCl_3$) of the mixture ν_{max}: 3051, 2917, 1718, 1660, 1596 cm^{-1}; UV (methanol) λ_{max} (log ε): 240 (3.99); ^{1}H NMR of the mixture, signals corresponding to the major isomer, β acetate) δ: 1.18 (3H, s), 1.25 (3H, s), 1.40 (3H, s), 2.12 (3H, s), 5.25 (1H, t, J = 4 Hz, C8-H), 6.07 (1H, s, C6-H); (signals corresponding to the minor isomer, α acetate) δ: 1.17 (3H, s), 1.24 (3H, s), 1.39 (3H, s), 2.11 (3H, s), 5.60 (1H, t, J = 12, 4 Hz, C8-H), 5.98 (1H, s, C6-H); ^{13}C NMR (signals corresponding to the minor isomer) δ: 17.79, 20.92, 25.83, 29.28 (×2), 36.93, 38.01, 40.22, 40.83, 46.74, 71.00, 121.99, 170.31, 177.68, 194.85; MS *m/z*: 250 (M$^+$, 2.9), 208 (4.1), 193 (1.6), 164 (100); HRMS calcd. for $C_{15}H_{22}O_3$: 250.1570; found: 250.1568. Anal. calcd. for $C_{15}H_{22}O_3$: C 7.98, H 8.85; found: C 72.19, H 8.82.

2,3,4,4a,5,6,7,8-Octahydro-2β,3β-dihydroxy-4aβ,8,8-trimethylnaphthalene (12), 2,3,4,4a,5,6,7,8-octahydro-2α,3α-dihydroxy-4aβ,8,8-trimethylnaphthalene (13), 2,3,4,4a,5,6,7,8-octahydro-2α,3β-dihydroxy-4aβ,8,8-trimethylnaphthalene (15), and 2,3,4,4a,5,6,7,8-octahydro-2β,3α-dihydroxy-4aβ,8,8-trimethylnaphthalene (14)

To a solution of **10/11** (1.44 g, 5.76 mmol) (4:1 isomeric mixture) in anhydrous THF (80 mL) was added lithium aluminum hydride (LAH) (726 mg, 19.1 mmol). After stirring at room temperature for 10 min, the reaction was quenched by adding 1 M HCl (100 mL) slowly to the suspension and then extracted with diethyl ether (400 mL). The combined organic layers were washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, to yield 1.45 g of the crude products **12–15**. Chromatographic purification using EtOAc/petroleum ether (3:2) as eluent afforded 7β,8β diol **12** (770.8 mg, 63.7%) as well as 7α,8α diol **13** (15.4 mg, 1.3%). Further elution afforded 7α,8β diol **15** (46.2 mg, 3.8%) and 7β,8α diol **14** (277.5 mg, 23%).

*7β,8β-Diol **12***: mp 103–104°C (EtOAc); $[\alpha]_D^{25}$ +41.8 (c = 1.00); IR (KBr) ν_{max}: 3349, 3012, 2927, 1627 cm^{-1}; ^{1}H NMR δ: 1.09 (3H, s, C4-αCH_3), 1.16 (3H, s, C4-βCH_3), 1.35 (3H, s, C10-CH_3), 1.10–1.60 (5H, m), 1.51 (1H, dd, J = 14, 3 Hz, C9-H), 1.85 (2H, dd, J = 13, 8 Hz), 2.08 (2H, br s, O-H), 3.93 (1H, ddd, J = 7, 4, 3 Hz, C8-H), 4.21 (1H, dd, J = 4, 4 Hz, C7-H), 5.45 (1H, d, J = 4 Hz, C6-H); ^{13}C NMR δ: 18.59, 28.28, 29.22, 32.67, 35.51, 36.57, 42.09, 42.16, 45.30, 67.08, 68.58, 118.85, 154.15; MS *m/z*: 210 (M$^+$, 21.2), 192 (33.6), 177 (21.1), 166 (17.5), 151 (36.1), 135 (100); HRMS calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1615. Anal. calcd. for $C_{13}H_{22}O_2$: C 74.25, H 10.53; found: C 74.36, H 10.60.

^{1}H NMR decoupling experiment: irradiation of the signal resonating at δ 3.93 ppm simplified the doublet of doublets resonating at δ 4.21 ppm to a doublet with a coupling constant

of 4 Hz, and the doublet of doublets resonating at δ 1.51 ppm to a doublet with coupling constant of 14 Hz. Irradiation of the signal resonating at δ 4.21 ppm collapsed the doublet resonating at δ 5.45 ppm to a singlet, and the doublet of doublet of doublets resonating at δ 3.93 ppm was simplified to a doublet of doublets with coupling constants of 3 and 7 Hz.

^{1}H NMR NOE difference experiment: irradiation of the singlet resonating at δ 1.09 ppm led to enhancement of the signal resonating at δ 5.45 ppm; irradiation of the singlet resonating at δ 1.16 ppm led to enhancement of the signal resonating at δ 1.35 ppm; irradiation of the singlet resonating at δ 1.35 ppm led to enhancement of the signals resonating at δ 1.16 and 1.51 ppm; irradiation of the signal resonating at δ 3.93 ppm led to enhancement of the signal resonating at δ 4.21 ppm; irradiation of the doublet of doublets resonating at δ 4.21 ppm led to enhancement of the signals resonating at δ 3.93 and 5.45 ppm; irradiation of the doublet resonating at δ 5.45 ppm led to the enhancement of the signals resonating at δ 1.09 and 4.21 ppm.

7α,8α-Diol ***13***: mp 139–140°C (EtOAc); IR (KBr) ν_{max}: 3456, 3295, 3002, 2921, 1631 cm^{-1}; ^{1}H NMR δ: 1.10 (3H, s, C4-βCH$_3$). 1.11 (3H, s, C4-αCH$_3$), 1.24 (3H, s, C10-CH$_3$), 1.10–1.90 (9H, m), 2.34 (1H, br s, O-H), 3.95 (1H, m, C8-H), 4.10 (1H, dd, *J* = 5, 5 Hz, C7-H), 5.66 (1H, d, *J* = 5 Hz, C6-H); ^{13}C NMR δ: 18.17, 27.08, 29.35, 32.19, 35.81, 37.69, 41.18, 41.49, 45.47, 66.40, 66.73, 118.86, 156.66; MS *m/z*: 210 (M$^+$, 13.1), 192 (39.8), 177 (7.2), 166 (100); HRMS calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1612. Anal. calcd. for $C_{13}H_{22}O_2$: C 74.25, H 10.53; found: C 74.10, H 10.63.

^{1}H NMR decoupling experiment: irradiation of the multiplet resonating at δ 3.95 ppm collapsed the doublet of doublets resonating at δ 4.10 ppm to a doublet of coupling constant value of 5 Hz; irradiation of the doublet of doublets resonating at δ 4.10 ppm collapsed the doublet resonating at δ 5.66 ppm to a singlet and altered the multiplet resonating at δ 3.95 ppm.

^{1}H NMR NOE difference experiment: irradiation of the singlet at δ 1.24 ppm led to enhancement of the signals resonating at δ 1.10 and 3.95 ppm; irradiation of the signal resonating at δ 3.95 ppm led to enhancement of the singlet resonating at δ 1.24 ppm; irradiation of the signal resonating at δ 4.10 ppm led to enhancement of the doublet resonating at δ 5.66 ppm.

7α,8β-Diol ***15***: mp 73–74°C (EtOAC); IR (KBr) ν_{max}: 3337, 3011, 2926, 1638 cm^{-1}; ^{1}H NMR δ: 1.10 (3H, s), 1.16 (3H, s), 1.22 (3H, s), 1.10–1.60 (6H, m), 1.67 (1H, dd, *J* = 13, 4 Hz, C9-H), 1.80 (1H, m), 2.17 (2H, br s, O-H), 3.51 (1H, ddd, *J* = 11, 7, 4 Hz, C8-H), 4.00 (1H, dd, *J* = 7, 2 Hz, C7-H), 5.35 (1H, d, *J* = 2 Hz, C6-H); ^{13}C NMR δ: 19.35, 28.12, 29.86, 32.92, 36.75, 38.23, 41.04, 41.71, 46.18, 71.49, 74.24, 121.18, 152.07; MS *m/z*: 210 (M$^+$, 45.7), 192 (7.4), 177 (5.5), 166 (100); HRMS calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1614. Anal. calcd. for $C_{13}H_{22}O_2$: C 74.25, H 10.53; found: C 74.36, H 10.57.

^{1}H NMR decoupling experiment: irradiation of the signal resonating at δ 3.51 ppm collapsed the doublet of doublets resonating at δ 4.00 ppm to a doublet of coupling constant value of 2 Hz; irradiation of the doublet resonating at δ 4.00 ppm simplified the doublet of doublet of doublets resonating at δ 3.51 ppm to a doublet of doublets with coupling constant values of 4 and 11 Hz, and the doublet resonating at δ 5.35 ppm collapsed to a singlet.

7β,8α-Diol ***14***: mp 92–93°C (EtOAc); $[\alpha]_D^{25}$ −28.80° (*c* = 1.00); IR (KBr) ν_{max}: 3329, 3005, 2925, 1640 cm^{-1}; ^{1}H NMR δ: 1.08 (3H, s, C4-αCH$_3$), 1.11 (3H, s, C4-βCH$_3$), 1.28 (3H, s, C10-CH$_3$), 1.20–1.70 (7H, m), 1.80 (1H, m, C2-βH), 3.75 (2H, br s, O-H), 3.85 (1H, ddd, *J* = 12, 8, 4 Hz, C8-H), 4.08 (1H, dd, *J* = 8, 2.5 Hz, C7-H), 5.35 (1H, d, *J* = 2.5 Hz, C6-H); ^{13}C NMR δ: 18.35, 27.80, 29.03, 32.36, 35.54, 37.37, 41.62, 41.94, 48.95, 70.67, 75.58, 120.44, 152.45; MS *m/z*: 210 (M$^+$, 8.3), 192 (52.0), 177 (23.0), 135 (100); HRMS calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1625. Anal. calcd. for $C_{13}H_{22}O_2$: C 74.25, H 10.53; found: C 74.10, H 10.47.

^{1}H NMR decoupling experiment: irradiation of the signal at δ 3.85 ppm collapsed the doublet of doublets at δ 4.08 ppm to a doublet with a coupling constant value of 2.5 Hz and simplified the multiplet resonating at δ 1.50 ppm. Irradiation of the doublet of doublets resonating at δ 4.08 ppm collapsed the signal resonating at δ 5.35 ppm to a singlet, and simplified the signal at δ 3.85 ppm to a doublet of doublets with coupling constant values of 4 and 12 Hz.

^{1}H NMR NOE difference experiment: irradiation of the singlet resonating at δ 1.28 ppm led to enhancement of the signals resonating at δ 1.11, 1.50, 1.80, and 3.85 ppm; irradiation of the signal resonating at δ 1.80 ppm led to enhancement of the singlets resonating at δ 1.11 and 1.28 ppm; irradiation of the signal resonating at δ 3.85 ppm led to enhancement of the signals resonating at δ 1.28 and 5.35 ppm; irradiation of the doublet of doublets resonating at δ 4.08 ppm led to enhancement of the signals resonating at δ 1.50 and 5.35 ppm; irradiation of the doublet resonating at δ 5.35 ppm. led to enhancement of the signals resonating at δ 1.08 and 4.08 ppm.

4aα,5,6,7,8,8a-Hexahydro-5,5,8aβ-trimethylnaphthalen-2(1*H*)-one (9), 3,5,6,7,8,8a-hexahydro-5,5,8aβ-trimethylnaphthalen-2(1*H*)-one (16), and 4aβ,5,6,7,8,8a-hexahydro-5,5,8aβ-trimethylnaphthalen-2(1*H*)-one (17)

Method A

To a solution of isomeric diols **12–15** (1.35 g, 6.4 mmol) in glacial acetic acid (80 mL), concentrated sulfuric acid (395 μL) was added. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and diluted with water (300 mL). The aqueous layer was extracted with diethyl ether (400 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (200 mL), water (200 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue, using EtOAc/petroleum ether 5:95 as eluent, gave ketone **16** (60.9 mg, 5%) as a colourless oil, enone **17** (50.5 mg, 4%) as a light yellow oil, and enone **9** (72.5 mg, 6%) as a colourless oil that solidified upon standing. The spectroscopic data are in agreement with published values (19).

Method B

A mixture of 7β,8β-diol **12** (1.09 g, 5.2 mmol) and *p*-toluenesulfonic acid (1.19 g, 6.2 mmol) in anhydrous THF (50 mL) was heated at reflux for 24 h. After cooling to room temperature, the solvent was removed in vacuo and the residue was

chromatographed on silica gel using EtOAc/cyclohexane 1:9 as eluent, affording ketone **16** (250.5 mg, 25%) as a colourless oil. Further elution afforded enone **17** (18.0 mg, 2%) as a light yellow oil and enone **9** (643.0 mg, 64%) as a colourless oil that solidified on standing.

Method C

To a solution of 7β,8α-diol **14** (25.0 mg, 0.12 mmol) in anhydrous THF (5 mL), *p*-toluenesulfonic acid (27.0 mg, 0.14 mmol) was added. The mixture was heated at reflux for 24 h. After cooling the reaction to room temperature, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using EtOAc/cyclohexane 1:9 as eluent, affording ketone **16** (3.0 mg, 13%) and enone **9** (15 mg, 66%).

Method D

To a solution of enone **6** (2.30 g, 12.0 mmol) in anhydrous benzene (130 mL) was added manganese triacetate dihydrate (9.00 g, 33.5 mmol). The brown suspension was heated at reflux for 1 h with azeotropic removal of water. After cooling to room temperature, additional manganese triacetate dihydrate (9.00 g, 33.5 mmol) was added and the mixture was heated at reflux for a further 20 h. The reaction was cooled to room temperature, diluted with ethyl acetate (200 mL), and sequentially washed with 1 M HCl (75 mL), saturated sodium bicarbonate solution (75 mL), and brine (75 mL). The organic layer was dried, filtered, and concentrated in vacuo. The residue was dissolved in anhydrous THF (160 mL) and LAH (1.60 g, 42 mmol) was added. After stirring for 10 min at room temperature, the suspension was slowly poured into 1 M HCl (200 mL) and extracted with diethyl ether (600 mL). The combined organic layers were washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield a crude mixture of isomeric diols **12–15** (3.12 g) as a white solid. This solid was dissolved in anhydrous THF (115 mL). *p*-Toluenesulfonic acid (2.70 g, 14.2 mmol) was added and the mixture was heated at reflux for 24 h. After cooling to room temperature, the reaction was diluted with diethyl ether (500 mL), washed with saturated sodium bicarbonate solution (200 mL) and with water (200 mL), then dried, filtered, and concentrated in vacuo to yield 2.35 g of residue. Chromatographic purification of the crude using EtOAc/cyclohexane 1:9 as eluent gave ketone **16** (342 mg, 15%), enone **17** (40.5 mg, 2%), and enone **9** (1.12 g, 49%).

Method E

A solution of ketone **16** (230.7 mg, 1.2 mmol) and *p*-toluenesulfonic acid (286.8 mg, 1.5 mmol) in anhydrous THF (18 mL) was heated at reflux for 24 h. After cooling the reaction mixture to room temperature, the solution was concentrated in vacuo, and the residue was chromatographed on silica gel using EtOAc/cyclohexane 1:9 as eluent, yielding unreacted ketone **16** (72.0 mg, 31%), enone **17** (3.0 mg, 1%), and enone **9** (149.3 mg, 65%).

4aα,5,6,7,8,8a-Hexahydro-5,5,8aβ-trimethyl-2,oxo-lα-naphthalene acetic acid ethyl ester (19), and 4aα,5,6,7,8,8a-hexahydro-1α-iodo-5,5,8aβ-trimethylnaphthalen-2(1*H*)-one (27)

A solution of diisopropylamine (1.47 mL, 10.5 mmol) in anhydrous THF (12 mL) was cooled to −78°C and *n*-butyllithium (7.33 mL, 9.17 mmol) was added. The solution was allowed to warm up to −15°C for 30 min, then cooled to −78°C, and a solution of enone **9** (1.26 g, 6.56 mmol) in anhydrous THF (50 mL) was added dropwise. The reaction was warmed to 0°C for 30 min, then cooled to −78°C, and freshly distilled ethyl iodoacetate (2.32 mL, 19.65 mmol) was added. The reaction mixture was stirred at −78°C for 1 h and then warmed to 0°C for another hour, poured into a saturated ammonium chloride solution (200 mL), and extracted with diethyl ether (400 mL). The organic extracts were washed with water (200 mL), dried, filtered, and concentrated in vacuo to yield 2.12 g of residue as a yellow oil. Chromatographic purification of the residue, using EtOAc/hexanes 1:9 as eluent, gave unreacted starting material **9** (230 mg, 18%), enone **27** (185 mg, 9%) as a white solid, and enone **19** (1.33 g, 73%) as a yellowish oil.

Enone 27: mp 109–110°C (EtOAc); $[\alpha]_D^{25}$ −164.6 (c = 1.00); IR (KBr) ν_{max}: 3006, 2927, 1675, 1610 cm^{-1}; UV (methanol) ν_{max} (log ε): 245 (3.6); ^{1}H NMR δ: 0.95 (3H, s, C4-βCH_3), 1.11 (3H, s, C4-αCH_3), 1.16 (3H, s, C10-CH_3), 1.19–1.70 (6H, m), 2.16 (1H, dd, J = 3, 2 Hz, C5-H), 4.26 (1H, d, J = 1.4 Hz, C9-H), 6.12 (1H, ddd, J = 10, 3, 1.4 Hz, C7-H), 6.89 (1H, dd, J = 10, 2 Hz, C6-H); ^{13}C NMR δ: 15.34, 18.54, 22.40, 32.22, 32.45, 39.14, 40.74, 41.68, 50.79, 51.59, 127.23, 149.94, 193.08; MS *m/z*: 318 (M^+, 1.1), 191 (66.7), 147 (39.9), 135 (37.3), 121 (100); HRMS calcd. for $C_{13}H_{19}OI$: 318.0479; found: 318.0481. Anal. calcd. for $C_{13}H_{19}OI$: C 49.07, H 6.01, I 39.88; found: C 49.00, H 6.00, I 39.73.

^{1}H NMR NOE difference experiment: irradiation of the singlet resonating at δ 0.95 ppm led to enhancement of the signals resonating at δ 1.16 and 6.89 ppm; irradiation of the singlet resonating at δ 1.11 ppm led to enhancement of the signals resonating at δ 2.16 and 6.89 ppm; irradiation of the singlet resonating at δ 1.16 ppm led to enhancement of the signals resonating at δ 0.95 and 4.26 ppm; irradiation of the signal resonating at δ 2.16 ppm led to enhancement of the signals resonating at δ 1.11 and 6.89 ppm; irradiation of the doublet resonating at δ 4.26 ppm led to enhancement of the signal resonating at δ 1.16 ppm; irradiation of the signal resonating at δ 6.89 ppm led to enhancement of the signals resonating at δ 0.95, 1.11, 2.16, and 6.12 ppm.

Enone 19: $[\alpha]_D^{25}$ −126.80 (c = 1.00); IR (neat) ν_{max}: 3051, 2936, 1737, 1679, 1612 cm^{-1}; UV (methanol) ν_{max} (log ε): 236 (3.6); ^{1}H NMR δ: 0.92 (3H, s, C4-βCH_3), 1.06 (3H, s, C4-αCH_3), 1.08 (3H, s, C10-CH_3), 1.25 (3H, t, J = 8 Hz, CH_3-CH_2), 1.28–1.80 (6H, m), 2.14 (1H, dd, J = 3, 2 Hz, C5-H), 2.22 (1H, dd, J = 15, 8 Hz, C11-H_A), 2.50 (1H, dd, J = 8, 8 Hz, C9-H), 2.64 (1H, dd, J = 15, 8 Hz, C11-H_B), 4.15 (2H, q, J = 8 Hz, CH_3-CH_2), 6.00 (1H, ddd, J = 10, 3, 1 Hz, C7-H), 6.85 (1H, dd, J = 10, 2 Hz, C6-H); ^{13}C NMR δ: 14.13, 18.16, 21.38, 22.80, 31.81, 32.62, 32.69, 35.16, 40.87, 41.16, 48.40, 57.61, 60.87, 128.62, 149.25, 171.94, 201.33; MS *m/z*: 278 (M^+, 36.5), 263 (31.9), 232 (79.2), 217 (100); HRMS calcd. for $C_{17}H_{26}O_3$: 278.1883; found: 278.1884. Anal. calcd. for $C_{17}H_{26}O_3$: C 73.36, H 9.41; found: C 73.29, H 9.42.

^{1}H NMR NOE experiment: irradiation of the singlet resonating at δ 0.92 ppm led to enhancement of the signals resonating at δ 1.06, 1.08, and 6.85 ppm, irradiation of the singlet resonating at δ 1.06 ppm led to enhancement of the signals

resonating at δ 0.92, 2.14, and 6.85 ppm; irradiation of the singlet resonating at δ 1.08 ppm led to enhancement of the signals resonating at δ 0.92 and 2.50 ppm; irradiation of the signal resonating at δ 2.14 ppm led to enhancement of the signals resonating at δ 1.06 and 2.64 ppm, irradiation of the signal resonating at δ 2.22 ppm led to enhancement of the signals resonating at δ 2.50 and 2.64 ppm; irradiation of the signal resonating at δ 2.50 ppm led to enhancement of the signals resonating at δ 1.08 and 2.22 ppm; irradiation of the signal resonating at δ 2.64 ppm led to enhancement of the signals resonating at δ 2.14 and 2.22 ppm.

3,4,4aα,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethyl-2-oxo-1α-naphthalene acetic acid ethyl ester (20)

A hydrogenation vessel containing a suspension of enone **19** (2.106 g, 7.6 mmol) and 10% palladium on charcoal (210 mg) in EtOAc (100 mL) was purged three times with hydrogen at a pressure of 15 psi. The vessel was then pressurized to 40 psi with hydrogen and shaken for 20 min at room temperature. A sample taken for analytical TLC (EtOAc/hexanes 1:4) indicated the reaction was complete. The mixture was filtered through Celite 545, and the flask and Celite were washed with EtOAc (175 mL). The solution was concentrated in vacuo to yield 2.50 g of crude product. Chromatographic purification using EtOAc/hexanes 1:4 as eluent gave keto ester **20** (2.11 g, 100 %) as a colourless oil. $[\alpha]_D^{25}$ −34.8 (c = 1.00); IR (neat) ν_{max}: 2943, 1732 cm^{-1}; ^1H NMR δ: 0.87 (3H, s), 0.98 (3H, s), 0.99 (3H, s), 1.24 (3H, t, J = 8 Hz, CH_3-CH_2), 1.10–1.70 (8H, m), 1.95 (1H, m), 2.30–2.75 (5H, m), 4.11 (2H, q, J = 8 Hz, CH_3-CH_2) ; ^{13}C NMR δ: 14.08, 18.52, 21.55, 22.01, 23.33, 33.30 (×2), 33.44, 36.37, 38.54, 40.08, 42.15, 44.94, 60.38, 60.86, 171.72, 213.04; MS *m/z*: 280 (M^+, 1.4), 262 (3.6), 247 (6.3), 232 (30.1), 109 (100); HRMS calcd. for $C_{17}H_{28}O_3$: 280.2038; found: 280.2044. Anal. calcd. for $C_{17}H_{28}O_3$: C 72.83, H 10.06; found: C 72.68, H 9.99.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-5,5,8aβ-trimethyl-2,2-ethylenediozy-1α-naphthalene acetic acid ethyl ester (21), and 1,2,3,4,4aα,5,6,7,8,8a-decahydro-5,5,8aβ-trimethyl-2,2-ethylenedioxy-1β-naphthalene acetic acid ethyl ester (28)

Method A

A solution of keto ester **20** (133.2 mg, 0.5 mmol), *p*-toluenesulfonic acid (3.8 mg, 2×10^{-2} mmol), and ethylene glycol (0.159 mL, 2.8 mmol) in anhydrous benzene (7 mL) was heated at reflux with azeotropic removal of water. The reaction was monitored by GC and showed 90% conversion after 6 h. The reaction mixture was then cooled to room temperature, diluted with benzene (20 mL), washed with saturated sodium bicarbonate solution (10 mL) and with water (10 mL), then dried, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography using EtOAc/hexanes 1:4 as eluent. The silica gel was treated with a mixture of EtOAc/hexanes/Et_3N in a ratio of 1: 4: 4×10^{-2}, prior to use. Purification yielded ketal **21** (71.4 mg, 46%) as a colourless oil that solidified upon standing, ketal **28** (46.3 mg, 29%) as a colourless oil, and starting keto ester **20** (13 mg, 10%).

A longer reflux (19 h) proved to increase the ratio of ketal **28** (61% by GC), lowering the ratio of ketal **21** to 11% (by GC).

*Ketal **21***: mp 42°C; $[\alpha]_D^{25}$ −7.7 (c = 1.00); IR ($CHCl_3$) ν_{max}: 2946, 1735 cm^{-1}; ^1H NMR δ: 0.82 (3H, s, C4-βCH$_3$), 0.87 (3H, s, C4-αCH$_3$), 0.90–1.18 (2H, m), 1.19 (3H, s, C10-CH$_3$), 1.27 (3H, t, J = 7 Hz, CH_3-CH_2), 1.30–1.40 (2H, m), 1.50–1.70 (7H, m), 2.08 (1H, ddd, J = 5, 5, 2 Hz, C9-H), 2.47 (2H, dd, J = 5, 3.6 Hz, C11-2H), 3.80 (2H, dt, J = 6.5, 3 Hz), 3.98 (2H, m), 4.14 (2H, dq, J = 7, 1 Hz, CH_3-CH_2); ^{13}C NMR δ: 14.20, 18.51, 20.13, 21.74, 22.23, 32.69, 33.03, 33.42, 33.59, 37.01, 38.08, 42.22, 46.59, 50.30, 60.25, 63.34, 64.46, 111.04, 174.21; MS *m/z*: 324 (M^+, 29), 309 (6.4), 279 (18.8), 99 (100); HRMS calcd. for $C_{19}H_{32}O_4$: 324.2302; found: 324.2293. Anal. calcd. for $C_{19}H_{32}O_4$: C 70.35, H 9.93; found: C 70.50, H 10.04.

^1H NMR NOE difference experiment: irradiation of the singlet resonating at δ 0.82 ppm led to enhancement of the signal resonating at δ 1.19 ppm; irradiation of the singlet resonating at δ 0.87 ppm affected the multiplet resonating at δ 1.60 ppm; irradiation of the singlet resonating at δ 1.19 ppm led to enhancement of the signals resonating at δ 0.82 and 2.08 ppm; irradiation of the signal resonating at δ 2.08 ppm led to enhancement of the signals resonating at δ 1.19 and 2.47 ppm.

*Ketal **28***: $[\alpha]_D^{25}$ +8.3 (c = 1.00); IR (neat) ν_{max}: 2946, 1736 cm^{-1}; ^1H NMR δ: 0.83 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.25 (3H, t, J = 7.5 Hz, CH_3-CH_2), 1.00–1.21 (2H, m), 1.30–1.50 (5H, m), 1.55–1.65 (3H, m), 1.91 (1H, dd, J = 3, 9 Hz), 2.15 (2H, rn), 2.29 (1H, dd, J = 17, 9 Hz), 3.73–3.88 (2H, m), 3.92–4.16 (4H, m); ^{13}C NMR δ: 14.25, 14.73, 18.56, 19.69, 21.68, 28.83, 33.24, 33.60, 35.76, 38.47, 39.26, 41.80, 53.99, 54.92, 60.07, 63.24, 65.00, 110.50, 174.69; MS *m/z*: 324 (M^+, 19.3), 309 (3.4), 279 (9.2), 99 (100); HRMS calcd. for $C_{19}H_{32}O_4$: 324.2302; found: 324.2308. Anal. calcd. for $C_{19}H_{32}O_4$: C 70.35, H 9.93; found: C 70.43, H 9.87.

Method B

To a solution of trimethylsilyl triflate (30 μL, 0.15 mmol) in anhydrous methylene chloride (1 mL) at −78°C was added 1,2-bis(trimethylsilyloxy)ethane (0.42 mL, 1.7 mmol). A solution of keto ester **20** (434.6 mg, 1.55 mmol) in anhydrous methylene chloride (5 mL) was added to the reaction and the mixture was warmed to 0°C and stirred for 2 h; the reaction was monitored by GC. (Strict anhydrous conditions were required; traces of moisture were found to lower the yield of ketal **21** to 44%, increasing the presence of ketal **28** up to 30%.) The reaction was quenched with dry pyridine (0.35 mL), poured into saturated sodium bicarbonate solution (10 mL), and extracted with diethyl ether (50 mL). The combined organic layers were washed with 10% copper sulfate solution (30 mL) and water, dried, filtered, and concentrated in vacuo. Bulb-to-bulb distillation of the crude product gave 482 mg of a colourless oil (bp 118°C at 9 Torr (1 Torr = 133.3 Pa)). GC analysis of the oil showed a 93:5:2 mixture of products, the minor compounds being ketal **28** and starting keto ester **20**, respectively, and the major one being ketal **21**. The mixture was not further purified.

Method C

A solution of triflic acid (17.4 μL, 0.2 mmol) in anhydrous THF (2.4 mL) was cooled to −78°C, and 1,2-bis(trimethylsilyloxy)ethane (0.48 mL, 1.9 mmol) was added to the solution with temperature maintained at −78°C. A solution of

keto ester **20** (276.1 mg, 1.0 mmol) in anhydrous THF (12.2 mL) was added and the reaction mixture was stirred at 0°C. After 14 h, GC analysis showed a mixture of **21**, **28**, and **20** in an 8:1:1 ratio. The reaction was quenched with dry pyridine (150 μL), poured into saturated sodium bicarbonate solution (10 mL), and extracted with diethyl ether (50 mL). The combined organic layers were washed with 10% copper sulfate solution (20 mL) and with water (20 mL), then dried, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel treated with EtOAc/hexanes/Et_3N in a 1:4:4 × 10^{-2} ratio prior to use, and eluted with EtOAc/hexanes 1:4, affording ketal **21** (214.4 mg, 67%), ketal **28** (27.1 mg, 8%), and starting keto ester **20** (27.0 mg, 10%).

1,2,3,4,4aα,5,6,7,8,8α-Decahydro-2,2-ethylenedioxy-1α-(2′-hydroxyethylen)-5,5,8aβ-trimethylnaphthalene (22)

To a solution of ketal **21** (621.9 mg, 1.9 mmol) in anhydrous diethyl ether (50 mL) was added LAH (218 mg, 5.7 mmol). The suspension was stirred at room temperature. After 10 min, analytical TLC (EtOAc/hexanes 1:1) showed reaction completion. Water (10 mL) was slowly added to the reaction mixture and stirred for 5 min, then 15% sodium hydroxide solution (10 mL) was added and stirred for 5 min more. The mixture was then filtered and the filtrate was washed with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (60 mL). The combined organic layers were washed with water (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel, treated with EtOAc/hexanes/Et_3N in a 1:1:2 × 10^{-2} ratio prior to use, and eluted with EtOAc/hexanes 1:1, affording hydroxy ketal **22** (537.8 mg, 100%) as a colourless oil. $[\alpha]_D^{25}$ −7.5 (c = 1.00); IR (neat) $-\nu_{max}$: 3300, 2947 cm^{-1}; ^1H NMR δ: 0.83 (3H, s), 0.88 (3H, s), 1.00–1.15 (2H, m), 1.17 (3H, s), 1.25 (1H, m), 1.35–1.71 (10H, m), 1.82 (1H, m, C11-H_A), 2.02 (1H, m, C11-H_B), 3.49 (1H, m, C12-H_A), 3.68 (1H, m, C12-H_B), 3.85 (2H, m), 3.98 (2H, m); ^{13}C NMR δ: 16.46, 20.13, 21.52, 22.71, 30.95, 32.88, 32.96, 33.36, 36.09, 38.90, 42.31, 46.29, 52.72, 63.09, 64.46, 64.63, 112.32; MS *m/z*: 282 ($M^{+\cdot}$ 2.4), 267 (03), 252 (0.2), 99 (100); HRMS calcd. for $C_{17}H_{30}O_3$: 282.2195; found: 282.2195. Anal. calcd. for $C_{17}H_{30}O_3$: C 72.31, H 10.70; found: C 72.41, H 10.75.

^1H NMR decoupling experiment: irradiation of the signal resonating at δ 3.49 ppm affected the multiplets resonating at δ 1.82, 2.02, and 3.68 ppm; irradiation of the signal resonating at δ 3.68 ppm affected the multiplets resonating at δ 1.82, 2.02, and 3.49 ppm.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-2,2-ethylenedioxy-1α-(2′-*O*-benzyl ethyl)-5,5,8aβ-trimethylnaphthalene (23)

Method A

Sodium hydride, 60% dispersion in paraffin oil (9.2 mg, 0.23 mmol), was weighed and then washed three times with anhydrous THF (9 mL), under argon atmosphere. Anhydrous THF (3 mL) was added. A solution of hydroxy ketal **22** (58.7 mg, 0.21 mmol) in anhydrous THF (10 mL) was added dropwise with good stirring. Sodium iodide (3.3 mg, 0.02 mmol) and potassium carbonate (55 mg, 0.40 mmol) were added to the suspension, then benzyl chloride (25.3 μL, 0.22 mmol) was added. The reaction mixture was heated at reflux for 12 h. After cooling the reaction to room temperature, water (5 mL) was added slowly. The aqueous layer was extracted with diethyl ether (15 mL). The combined organic layers were washed with water (5 mL), dried, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel treated with EtOAc/hexanes/Et_3N 1:9:1 × 10^{-2} ratio prior to use, and eluted with EtOAc/hexanes 1:9, affording hydroxybenzyl ketal **23** (52.8 mg, 68%) as a colourless oil and starting hydroxy ketal **22** (12.8 mg).

*Hydroxybenzyl ketal **23***: $[\alpha]_D^{25}$ +0.95 (c = 1.00); IR (neat) ν_{max}: 2946 cm^{-1}; ^1H NMR δ: 0.82 (3H, s), 0.87 (3H, s), 1.06 (3H, m), 1.15 (3H, s), 1.35–1.80 (11H, m), 3.44 (2H, m), 3.80 (2H, m), 3.92 (2H, m), 4.52 (2H, d, J = 3 Hz, CH_2-Ph), 7.25 (1H, m), 7.32 (4H, m); ^{13}C NMR δ: 16.46, 20.13, 21.53, 22.67, 27.94, 32.87, 33.23, 33.36, 36.38, 38.66, 42.21, 46.19, 51.11, 63.25, 64.36, 71.98, 72.59, 112.15, 127.37, 127.59 (×2), 128.26 (×2), 138.75; MS *m/z*: 372 (M^+, 25.7), 357 (2.1), 281 (42.1), 99 (100); HRMS calcd. for $C_{24}H_{36}O_3$: 372.2666; found: 372.2665. Anal. calcd. for $C_{24}H_{36}O_3$: C 77.39, H 9.73; found: C 77.32, H 9.67.

Method B

Sodium hydride, 80% dispersion in paraffin oil (169 mg, 5.63 mmol), was weighed, and then washed three times with anhydrous THF (15 mL), under argon atmosphere. Anhydrous THF (24 mL) was added. A solution of hydroxy ketal **22** (529.5 mg, 1.88 mmol) in anhydrous THF (35 mL) was added dropwise with good stirring. Benzyl bromide (0.67 mL, 5.63 mmol) and tetrabutylammonium iodide (67.6 mg, 0.18 mmol) were added to the suspension. The reaction mixture was refluxed for 22 h, and monitored by analytical TLC (EtOAc/hexanes 1:4). After reaction completion, the mixture was cooled to room temperature and water (10 mL) was added slowly. The aqueous layer was extracted with diethyl ether (30 mL). The combined organic layers were washed with water (30 mL), dried, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel treated with EtOAc/hexanes/Et_3N 1:9:1 × 10^{-2} ratio prior to use, and eluted with EtOAc/hexanes 1:9, affording hydroxybenzyl ketal **23** (684.7 mg, 98%) as a colourless oil.

3,4,4aα,5,6,7,8,8a-Octahydro-1α(2′-*O*-benzyl ethyl)-5,5,8aβ-trimethylnaphthalen-2(1*H*)-one (24)

Method A

To a solution of hydroxybenzyl ketal **23** (683 mg, 1.83 mmol) in acetone (20 mL), 1 M HCl (5.5 mL) was added. The reaction mixture was stirred at room temperature. After 1 h, analytical TLC (EtOAc/hexanes 1:4) showed reaction completion. Saturated sodium bicarbonate solution (20 mL) was added and the solution was extracted with diethyl ether (80 mL). The combined organic layers were washed with water (30 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the crude product using EtOAc/hexanes 1:4 as eluent gave hydroxybenzyl ketone **24** (584 mg, 97%) as a colourless oil. $[\alpha]_D^{25}$ −27.6 (c = 1.00); IR (neat) ν_{max}: 2947, 1708 cm^{-1}; ^1H NMR δ: 0.86 (3H, s), 0.94 (3H, s), 0.95 (3H, s), 1.05–1.25 (2H, m), 1.40–1.70 (6H, m), 1.80–1.95 (3H, m), 2.02 (1H, m), 2.27 (1H, m), 2.54 (1H, m), 3.30 (1H, m), 3.42 (1H, m), 4.42 (2H, s), 7.32 (5H, m). ^{13}C NMR δ: 18.61, 21.78, 22.07, 23.48, 27.73, 33.29, 33.46,

36.93, 38.50, 40.02, 42.34, 44.80, 62.22, 68.85, 73.26, 127.57, 127.78 (×2), 128.33 (×2), 138.20, 215.00; MS *m/z*: 328 (M^+, 1.6), 313 (2.1), 269 (8.3), 221 (11.4), 206 (10.7), 91 (100); HRMS calcd. for $C_{22}H_{32}O_2$: 328.2402; found: 328.2396. Anal. calcd. for $C_{22}H_{32}O_2$: C 80.45, H 9.81; found: C 80.40, H 9.79.

Method B

To a solution of ketal **21** (3.95 g, 12.2 mmol) in anhydrous diethyl ether (120 mL), LAH (1.39 g, 36.6 mmol) was added and the solution was stirred at room temperature for 10 min. Water (50 mL) was added slowly and stirred for 5 min, then 15% sodium hydroxide solution (30 mL) was added and stirred for 5 min more. The mixture was filtered and the filtrate was washed with diethyl ether (150 mL). The aqueous layer was extracted with diethyl ether (200 mL). The combined organic layers were washed with water (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield 3.60 g of crude hydroxy ketal **22**. This was dissolved in anhydrous THF (100 mL) and added to a solution of sodium hydride (80% dispersion in paraffin oil) (1.10 g, 36.6 mmol) in anhydrous THF (22 mL). Benzyl bromide (4.35 mL, 36.6 mmol) and tetrabutylammonium iodide (439 mg, 1.2 mmol) were added to the suspension. The reaction mixture was heated at reflux for 22 h. After cooling to room temperature, water (70 mL) was added slowly. The aqueous layer was extracted with diethyl ether (250 mL). The combined organic layers were washed with water (100 mL), dried, filtered, and concentrated in vacuo. The residue was dissolved in acetone (122 mL) and 1 M HCl (37 mL) was added. The reaction was stirred at room temperature for 1 h. Saturated sodium bicarbonate solution (130 mL) was added and the solution was extracted with diethyl ether (500 mL). The combined organic layers were washed with water (200 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue using EtOAc/hexanes 1:4 as eluent afforded hydroxybenzyl ketone **24** (3.50 g, 87% from **21** over three steps) as a colourless oil.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-1α-(2′-*O*-benzyl ethyl)-2α,5,5,8aβ-tetramethylnaphthalen-2β-ol (25)

Method A

To a solution of hydroxybenzyl ketone **24** (44.5 mg, 0.13 mmol) in anhydrous diethyl ether (10 mL) was added methylmagnesium iodide (70 μL, 0.21 mmol). The mixture was refluxed for 5 h, then cooled to room temperature and saturated ammonium chloride solution (6 mL) added. The aqueous layer was extracted with diethyl ether (30 mL). The combined organic layers were washed with water (20 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue, eluting with EtOAc/hexanes 1:6, afforded starting ketone **24** (32.0 mg, 72%) as well as alcohol **25** (6.9 mg, 15%) as a white solid; mp 85–86°C (EtOAc); $[\alpha]_D^{25}$ −12.1 (c = 1.00); IR (KBr) ν_{max}: 3397, 2946 cm^{-1}; ^1H NMR δ: 0.83 (3H, s), 0.86 (3H, s), 1.02 (2H, m), 1.14 (2H, m), 1.25 (3H, s), 1.27 (3H, s), 1.35–1.60 (9H, m), 1.70 (1H, m), 1.87 (1H, m, C11-H), 3.40 (2H, dd, J = 8, 8 Hz, C12-2H), 4.52 (2H, s, CH_2-Ph), 7.26 (1H, m), 7.36 (4H, m); ^{13}C NMR δ: 18.33, 18.76, 21.38, 24.65, 29.44, 31.15, 32.89, 33.30, 36.18, 36.97, 38.71, 42.20, 46.63, 55.38, 72.12, 72.96, 75.08, 127.54, 127.58 (×2), 128.37 (×2), 138.50; MS *m/z*: 344 (M^+, 0.5), 329 (0.7), 253 (2.3), 91 (100); HRMS calcd. for $C_{23}H_{36}O_2$: 344.2715; found: 344.2706. Anal. calcd. for $C_{23}H_{36}O_2$: C 80.19, H 10.52; found: C 80.00, H 10.45.

^1H NMR decoupling experiment: irradiation of the doublet of doublets resonating at δ 3.40 ppm affected the signals resonating at δ 1.40 and 1.86 ppm.

Method B

Cerium chloride heptahydrate (652.0 mg, 1.75 mmol) was dried at 140°C for 2 h under high vacuum, then cooled to room temperature. Anhydrous THF (11 mL) was added and the suspension was stirred for 1 h at room temperature, then cooled to −78°C; methyllithium (1.25 mol, 1.75 mmol) was added and stirred for 1 h (at −78°C). Hydroxybenzyl ketone **24** (441.4 mg, 1.34 mmol) in anhydrous THF (14 mL) was added to the suspension. After the addition was completed, the syringe was rinsed into the reaction with anhydrous THF (2 mL). Analytical TLC (EtOAc/hexanes 1:6) showed reaction completion after 10 min. The reaction was quenched with saturated ammonium chloride solution (20 mL) at −78°C. The mixture was allowed to warm to room temperature, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. Chromatographic purification of the crude product, eluting with EtOAc/hexanes 1:6, gave alcohol **25** (458.5 mg, 100%) as a white solid.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-1α-(2′-hydroxyethyl)-2α,5,5,8aβ-tetramethylnaphthalen-2β-ol (26)

A suspension of alcohol **25** (114.4 mg, 0.33 mmol) and 10% palladium on charcoal (117.2 mg) in absolute EtOH (20 mL), was purged three times with hydrogen at a pressure of 15 psi in a hydrogenation vessel. The pressure was increased to 20 psi of hydrogen and the vessel was shaken for 10 min at room temperature. A sample taken for analytical TLC (EtOAc/hexanes 1:1) showed reaction completion. The suspension was filtered through Celite 545. The flask and Celite were washed with EtOH (60 mL). Concentration in vacuo afforded diol **26** (95.5 mg) as a white solid; mp 145.5–146°C (EtOAc); $[\alpha]_D^{25}$ −22.7 (c = 1.00). IR (KBr) ν_{max}: 3315, 2947 cm^{-1}; ^1H NMR δ: 0.84 (3H, s), 0.85 (1H, m, C9-H), 0.88 (3H, s), 0.98–1.20 (4H, m), 1.27 (3H, s), 1.29 (3H, s), 1.30–1.75 (10H, m), 1.84 (1H, m, C11-H), 3.57 (2H, dd, J = 8, 8 Hz, C12-2H); ^{13}C NMR δ: 18.31, 18.72, 21.35, 24.65, 31.15, 32.48, 32.88, 33.28, 36.28, 36.97, 38.65, 42.22, 46.71, 55.15, 64.50, 75.03; MS *m/z*: 254 (M^+, 4.9), 239 (27.1), 236 (50.9), 221 (100); HRMS calcd. for $C_{16}H_{30}O_2$: 254.2246; found: 254.2242. Anal. calcd. for $C_{16}H_{30}O_2$: C 75.55, H 11.88; found: C 75.50, H 11.79.

^1H NMR decoupling experiment: irradiation of the signal resonating at δ 3.57 ppm simplified the multiplet resonating at δ 1.34 ppm to a doublet of doublets with coupling constant values of 3 and 13 Hz, and simplified the multiplet resonating at δ 1.84 ppm to a doublet of doublets with coupling constant values of 4 and 13 Hz.

1,2,3β,3a,4,5,5aα,6,7,8,9,9a-Dodecahydro-3aβ,6,6,9aβ-tetramethylnaphtho[2,1-*b*]furan, (−)-*epi*-Ambrox® (29)

Method A

p-Toluenesulfonic acid (33 mg, 0.17 mmol) was added to a suspension of diol **26** (337 mg, 1.33 mmol) in nitromethane

(30 mL). The reaction mixture was heated to 80°C (oil bath temperature) for 30 min; after cooling to room temperature, it was diluted with diethyl ether (50 mL) and washed with saturated sodium bicarbonate solution (25 mL). The organic layer was dried, filtered, and concentrated in vacuo. Chromatographic purification of the crude product, eluting with EtOAc/hexanes 1:4 mixture, yielded (−)-*epi*-Ambrox® (**29**) (261 mg, 83%) as a colourless oil that solidified upon standing. The spectroscopic and other data were in agreement with the published data (36). The primary alcohol **30** was also obtained (33.8 mg, 11%).

Method B

Cerium chloride heptahydrate (1.45 g, 3.90 mmol) was dried at 140°C for 2 h under high vacuum, then cooled to room temperature. Anhydrous THF (16 mL) was added and the suspension was stirred for 1 h at room temperature, then cooled to −78°C. Methyllithium (2.9 mL, 3.90 mmol) was added and stirred for 1 h at −78°C. Hydroxybenzyl ketone **24** (640 mg, 1.95 mmol) in anhydrous THF (20 mL) was added dropwise to the suspension. After 10 min, analytical TLC (EtOAc/hexanes 1:6) showed reaction completion. Saturated ammonium chloride solution (30 mL) was added. The mixture was allowed to warm to room temperature, and the aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was dissolved in absolute ethanol (20 mL) in a hydrogenation vessel. 10% Palladium on charcoal (670 mg) was added and the vessel was purged 3 times with hydrogen at 15 psi, then shaken for 10 min at hydrogen pressure of 20 psi, at room temperature. The suspension was filtered through Celite 545 using a water aspirator. The flask and Celite were washed with ethanol (60 mL). Concentration in vacuo yielded 565 mg of an oil. Nitromethane (44 mL) was added to the crude product, then *p*-toluenesulfonic acid (49 mg, 0.26 mmol) was added, and the mixture was heated to 80°C (oil bath temperature) for 30 min. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (100 mL). The organic layer was washed with saturated sodium bicarbonate solution (50 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue, eluting with EtOAc/hexanes: 1:4, yielded (−)-*epi*-Ambrox® (**29**) (371 mg, 80% from **24**, three steps) as a colourless oil that solidified in vacuo, and 50 mg (11%) mixture of primary alcohols (**30**).

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-2,2-ethylenedioxy-1β-(2′-hydroxyethylen)-5,5,8aβ-trimethylnaphthalene (32)

To a solution of ketal **31** (428 mg, 1.32 mmol) in anhydrous diethyl ether (40 mL), LAH (150 mg, 3.95 mmol) was added. The suspension was stirred at room temperature. After 10 min, analytical TLC (EtOAc/hexanes 1:1) showed reaction completion. Water (5 mL) was added and stirrred for 5 min, then 15% sodium hydroxide solution (5 mL) was added and stirred for 5 min more. The mixture was filtered and the filtrate was washed with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The remaining oil was chromatographed on silica gel treated with EtOAc/hexanes/Et_3N in a 1:1:2 × 10^{-2} ratio, prior to use, and eluted with EtOAc/hexanes 1:1 to yield hydroxy ketal **32** (342.7 mg, 92%) as a white solid, mp 69–70°C (EtOAc); $[\alpha]_D^{25}$ +9.3 (c = 1.00, EtOH); IR (KBr) ν_{max}: 3228, 2916 cm^{-1}; ^1H NMR (acetone-d_6) δ: 0.84 (3H, s), 0.90 (6H, s), 0.90–1.00 (4H, m), 1.15–1.65 (8H, m), 1.73 (1H, m), 1.94 (1H, ddd, J = 12, 4, 4 Hz), 2.82 (1H, br s, O-H), 3.50 (2H, m), 3.80 (1H, dd, J = 8, 8 Hz), 3.90 (1H, m), 4.00 (2H, m); ^{13}C NMR (acetone-d_6) δ: 15.02, 19.17, 20.56, 22.04, 28.04, 33.81, 33.91, 36.60, 39.74, 39.82, 42.73, 55.02, 55.98, 63.94, 64.40, 65.73, 111.68; MS *m/z*: 282 (M^+, 0.1), 264 (0.5), 249 (1.1), 220 (15.6), 205 (100); HRMS calcd. for $C_{17}H_{30}O_3$: 282.2195; found: 282.2189. Anal. calcd. for $C_{17}H_{30}O_3$: C 72.31, H 10.70; found: C 72.52, H 10.85.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-2,2-ethylenedioxy-1β(2′-*O*-benzyl ethyl)-5,5,8aβ-trimethylnaphthalene (33)

Sodium hydride, 80% dispersion in paraffin oil (108.8 mg, 3.62 mmol) was weighed and washed three times with anhydrous THF (15 mL), under argon atmosphere. Anhydrous THF (15 mL) was added. A solution of hydroxy ketal **32** (340 mg, 1.20 mmol) in anhydrous THF (23 mL) was added dropwise with good stirring. Benzyl bromide (0.43 mL, 3.62 mmol) and tetrabutylammonium iodide (43.5 mg, 0.12 mmol) were added to the suspension. The reaction mixture was heated at reflux. After 22 h, TLC (EtOAc/hexanes 1:4) showed reaction completion. The reaction was cooled to room temperature and water (7 mL) was added slowly. The aqueous layer was extracted with diethyl ether (25 mL). The combined organic layers were washed with water (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel treated with EtOAc/hexanes/Et_3N 1:9:1 × 10^{-2}, prior to use, and eluted with EtOAc/hexanes 1:9, affording hydroxy benzyl ketal **33** (412.2 mg, 92%) as a white solid, mp 85–86°C (EtOAc); $[\alpha]_D^{25}$ +22.9 (c = 1.00); IR (KBr) ν_{max}: 2910 cm^{-1}; ^1H NMR δ: 0.82 (3H, s), 0.88 (3H, s), 0.90 (3H, s), 0.90–0.96 (2H, m), 1.15 (1H, ddd, J = 13, 13, 5 Hz), 1.25–1.80 (10H, m), 1.90 (1H, ddd, J = 10, 3, 3 Hz), 3.40 (1H, m, C12-H_A), 3.60 (1H, m, C12-H_B), 3.75 (1H, dd, J = 4, 4 Hz), 3.86 (1H, ddd, J = 7, 7, 5 Hz), 3.96 (1H, ddd, J = 7, 7, 7 Hz), 4.03 (1H, m), 4.50 (2H, d, J = 3 Hz, CH_2-Ph), 7.27 (1H, m), 7.34 (4H, m); ^{13}C NMR δ: 14.43, 18.50, 19.80, 21.68, 24.01, 33.22, 33.58, 36.09, 39.02, 39.17, 41.98, 53.84, 55.23, 63.28, 65.09, 72.39, 72.62, 111.35, 127.31, 127.54 (×2), 128.24 (×2), 138.90; MS *m/z*: 372 (M^+, 1.2), 357 (0.3), 281 (5.3), 205 (13.9), 99 (100); HRMS calcd. for $C_{24}H_{36}O_3$: 372.2664; found: 372.2656. Anal. calcd. for $C_{24}H_{36}O_3$: C 77.39, H 9.73; found: C 77.47, H 9.68.

3,4,4aα,5,6,7,8,8a-Octahydro-1β(2′-*O*-benzyl ethyl)-5,5,8aβ-trimethyl-1-naphthalene (34)

Method A

To a solution of hydroxybenzyl ketal **33** (411 mg, 1.1 mmol) in acetone (40 mL) was added 1 M HCl (3.3 mL). The reaction mixture was stirred at room temperature for 4 h. Saturated sodium bicarbonate solution (20 mL) was added slowly, and the solution was extracted with diethyl ether (200 mL). The combined organic layers were washed with water (100 mL), dried, and concentrated in vacuo. Chromatographic purification of the residue, eluting with EtOAc/hexanes 1:4, afforded hydroxybenzyl ketone **34** (346.7 mg, 96%) as a colourless oil. $[\alpha]_D^{25}$ −19.6 (c = 1.00); IR (neat) ν_{max}: 2947, 1709 cm^{-1}; ^1H NMR δ: 0.73 (3H, s), 0.86 (3H, s), 0.97 (3H, s), 1.15–1.30

(3H, m), 1.40–1.90 (6H, m), 2.04 (2H, m), 2.28 (2H, m), 2.41 (1H, ddd, J = 12, 5, 2 Hz), 3.29 (1H, ddd, J = 10, 9, 6 Hz, C12-H_A), 3.53 (1H, m, C12-H_B), 4.42 (1H, d, J = 12 Hz, CH_A-Ph), 4.49 (1H, d, J = 12 Hz, CH_B-Ph), 7.32 (5H, m); ^{13}C NMR δ: 14.67, 18.96, 21.63, 22.00, 23.93, 33.46, 33.65, 39.11, 41.88, 42.30, 42.41, 54.13, 60.06, 69.51, 72.60, 127.39, 127.54 (×2), 128.27 (×2), 138.68, 212.03; MS *m/z*: 328 (M^+, 2.7), 313 (2.5), 269 (10.3), 237 (62.6), 221 (8.9), 179 (88.9), 91 (100); HRMS calcd. for $C_{22}H_{32}O_2$: 328.2402; found: 328.2398. Anal. calcd. for $C_{22}H_{32}O_2$: C 80.45, H 9.81; found: C 80.54, H 9.81.

Method B

To a solution of hydroxybenzyl ketone **24** (546.0 mg, 1.66 mmol) in THF/MeOH 1:1 (20 mL) was added sodium methoxide (270.0 mg, 5.0 mmol) and the solution was heated at reflux for 22 h. After cooling to room temperature, saturated ammonium chloride solution (15 mL) was added and the mixture was extracted with diethyl ether (150 mL). The combined organic layers were washed with water (75 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue, eluting with EtOAc/hexanes 1:4, afforded hydroxybenzyl ketone **34** (487.6 mg, 89%) as a colourless oil and starting ketone **24** (52.3 mg, 10%).

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-1β-(2′-*O*-benzyl ethyl)-2α,5,5,8aβ-tetramethylnaphthalen-2β-ol (35)

Cerium chloride heptahydrate (720.0 mg, 1.93 mmol) was dried at 140°C under high vacuum for a period of 2 h, then cooled to room temperature. Anhydrous THF (12 mL) was added, and the suspension was stirred at room temperature for 1 h, then cooled to −78°C, and methyllithium (1.38 mL, 1.93 mmol) was added. The mixture was stirred at −78°C for 1 h. A solution of hydroxybenzyl ketone **34** (487.6 mg, 1.49 mmol) in anhydrous THF (15 mL) was added dropwise to the suspension, with maintenance of the temperature. After 10 min, a sample taken for analytical TLC (EtOAc/hexanes 1:4) showed reaction completion. Saturated ammonium chloride solution (15 mL) was added to the reaction mixture, and the temperature was allowed to rise to 25°C. The aqueous layer was extracted with EtOAc (80 mL). The combined organic layers were washed with water (40 mL), dried, filtered, and concentrated in vacuo. Chromatographic purification of the residue with EtOAc/hexanes 1:4 afforded hydroxybenzyl alcohol **35** (502.8 mg, 98%) as a white solid, mp 88.5–89°C (EtOAc/hexane); $[\alpha]_D^{25}$ +10.8 (c = 1.00); IR (KBr) ν_{max}: 3479, 2910 cm^{-1}; ^{1}H NMR δ: 0.83 (3H, s), 0.86 (3H, s), 0.70–0.90 (2H, m), 0.97 (3H, s), 1.10 (3H, s), 1.20–1.80 (13H, m), 3.44 (2H, m), 4.50 (2H, s), 7.27 (1H, m), 7.33 (4H, m); ^{13}C NMR δ: 15.07, 18.13, 18.30, 21.64, 25.28, 30.68, 33.25, 33.42, 38.63, 39.22, 41.98, 42.18, 54.91, 55.89, 72.42, 72.73, 72.89, 127.43, 127.48 (×2), 128.31 (×2), 138.63; CI MS *m/z*: 345 (M^+, +1), 326 (0.2), 311 (0.2), 267 (0.2), 235 (10.3), 218 (34.2), 91 (100). Anal. calcd. for $C_{23}H_{36}O_2$: C 80.19, H 10.52; found: C 80.40, H 10.58.

1,2,3,4,4aα,5,6,7,8,8a-Decahydro-1β-(2′-hydroxyethyl)-2α,5,5,8aβ-tetramethylnaphthalen-2β-ol (36)

A suspension of hydroxybenzyl alcohol **35** (502.8 mg, 1.46 mmol) and 10% palladium on charcoal (500.6 mg) in absolute ethanol (15 mL) was purged three times with hydrogen at 15 psi. The hydrogen pressure was then increased to 20 psi and the vessel was shaken for 10 min. A sample taken for analytical TLC (EtOAc/hexanes 1:1) showed reaction completion. The suspension was then filtered through Celite 545. The vessel and the Celite were washed with ethanol (50 mL). Concentration in vacuo and chromatographic purification of the residue, using diethyl ether/hexanes 5:1 as eluent, afforded diol **36** (370.0 gm, 100%) as a white solid, mp 168–170°C (EtOAc); $[\alpha]_D^{25}$ +15.7 (c = 1.00, ethanol); IR (KBr) $\nu_{max:}$ 3358, 3322, 2925 cm^{-1}; ^{1}H NMR δ: 0.83 (3H, s), 0.87 (3H, s), 0.80–0.90 (2H, m), 0.98 (3H, s), 1.14 (3H, s), 1.30–1.80 (14H, m), 3.56–3.68 (2H, m, C12-2H); ^{13}C NMR δ: 15.13, 18.13, 18.30, 21.64, 28.66, 30.68, 33.27, 33.42, 38.52, 39.33, 41.96, 42.25, 54.65, 55.88, 64.94, 72.91; MS *m/z*: 254 (M^+, 1.2), 236 (6.7), 221 (11.2), 43 (100); HRMS calcd. for $C_{16}H_{30}O_2$: 254.2247; found: 254.2254. Anal. calcd. for $C_{16}H_{30}O_2$: C 75.55, H 11.88; found: C 75.58, H 11.80.

1,2,3β,3a,4,5,5aα,6,7,8,9,9a-Dodecahydro-3aβ,6,6,9aβ-tetramethylnaphtho[2,1-*b*]furan, (−)-Ambrox® (37)

To a suspension of diol **36** (370 mg, 1.46 mmol) in nitromethane (29 mL) was added *p*-toluenesulfonic acid (11.6 mg, 6×10^{-2} mmol). The reaction mixture was heated to 80°C (oil bath temperature) for 30 min with good stirring. It was then cooled to room temperature and diluted with diethyl ether (60 mL). The organic layer was washed with saturated sodium bicarbonate solution (40 mL), dried, and concentrated in vacuo. Chromatographic purification of the residue, eluting with EtOAc/hexanes 1:4, gave pure (−)-Ambrox® (**37**) (261.4 mg, 76%). The spectroscopic and other data were in agreement with the published data (36).

Acknowledgements

We would like to express our gratitude to the Natural Sciences and Engineering Research Council of Canada for financial support, and to Intrinsic Research and Development Inc. for generous samples of Western red cedar leaf oil.

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