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Diastereoselective Synthesis of (±)-Ambrox by Titanium(III)-Catalyzed Radical Tandem Cyclization

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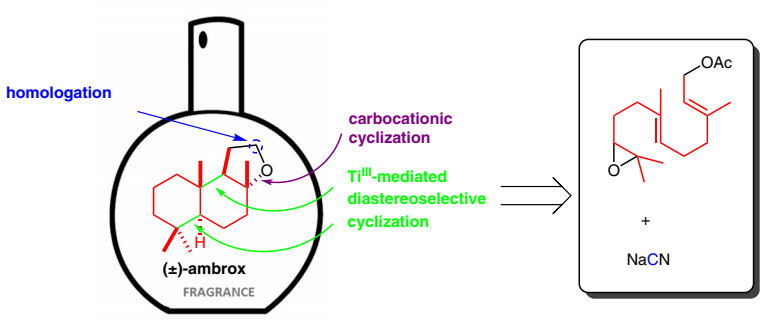
Dedicated to Prof. Emilio Diaz Ojeda



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Abstract A synthesis of (±)-ambrox, a compound with delicious ambergris-type scent, is presented. The key step is a highly diastereoselective titanocene(III)-catalyzed radical tandem cyclization of a farnesol derivative.

Key words ambrox, natural products, titanocene, radical chemistry, diastereoselective synthesis

Ambrox (**1**) is one of the natural components of ambergris (Figure 1) and, additionally, one of the commercially most important products for providing ambergris-type odor in fine perfumery.[1] Ambergris is a solid, waxy substance produced by photooxidation of ambrein, a substance accumulated in the gut of sperm whales (*Physeter macrocephalus L.*), which has been used in the past as a valuable constituent of fine fragrances due to its exceptional fixative and scent properties.[2] Nevertheless, ambergris itself is no longer used almost anywhere, because natural sources do not meet the increasing demand for perfume ingredients with ambergris-type odor. As a consequence, synthetic ambrox constitutes the most important commercial substitute with the desirable ambergris-type scent. Ambrox (**1**) is considered to be one of the most expensive fragrance ingredients, with a market price well above $500/kg for the enantiomerically pure product and an annual worldwide production of several tens of tons.[3]

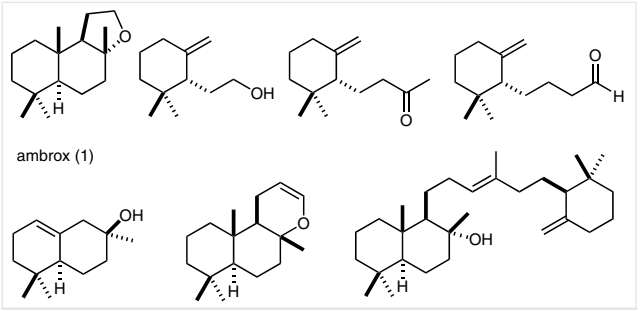


Figure 1 Naturally occurring terpene derivatives isolated from ambergris

Since the first synthesis of this compound was described more than sixty years ago,[4] a considerable number of different synthetic procedures have been reported. These procedures include both semisynthetic methods via oxidative degradation of naturally occurring products, such as sclareol, manool, ambrein, and communic acids,[5] and biomimetic cyclizations of precursors, such as homofarnesic acid, (*E*)-β-farnesene, homofarnesol, farnesylacetic acid and analogues.[6] Nevertheless, many of these procedures are expensive and laborious and/or provide yields that are nor-

mally susceptible of being improved. Therefore, novel procedures for the synthesis of ambrox are needed for a sustainable production of this valuable product.

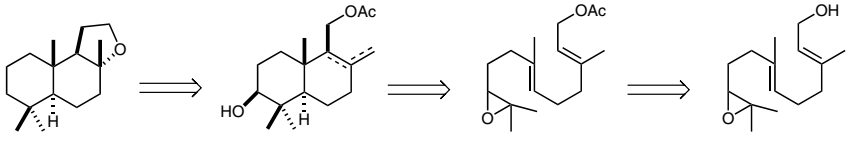
Titanium is one of the most abundant metals on Earth (the second among transition metals), and most of the titanium compounds are degraded in nature to TiO_2, which is not toxic.[7] In the last years Cp_2TiCl has emerged as a formidable tool in organic synthesis.[8] In fact, this single-electron transfer (SET) reagent has reported to be capable of promoting and/or catalyzing very important transformations in organic chemistry, such as radical-opening reactions, radical cascade cyclizations, coupling reactions, THF-ring-formation reactions, H-atom transfer, Barbier-type reactions, deoxygenation of alcohols, umpolung reactions, and polymerization reactions.

The synthesis of scarce natural products constitutes one of the most demanding tests to prove the utility of new methods or reagents in organic synthesis. As part of our contributions to the synthesis of natural compounds,[9] we were interested in the development of a new concise synthesis of ambrox (**1**). In the present report we describe a novel, concise, safe, and environmental friendly diastereoselective synthesis of (±)-ambrox, the key step of which is a radical tandem cyclization catalyzed by Cp_2TiCl.

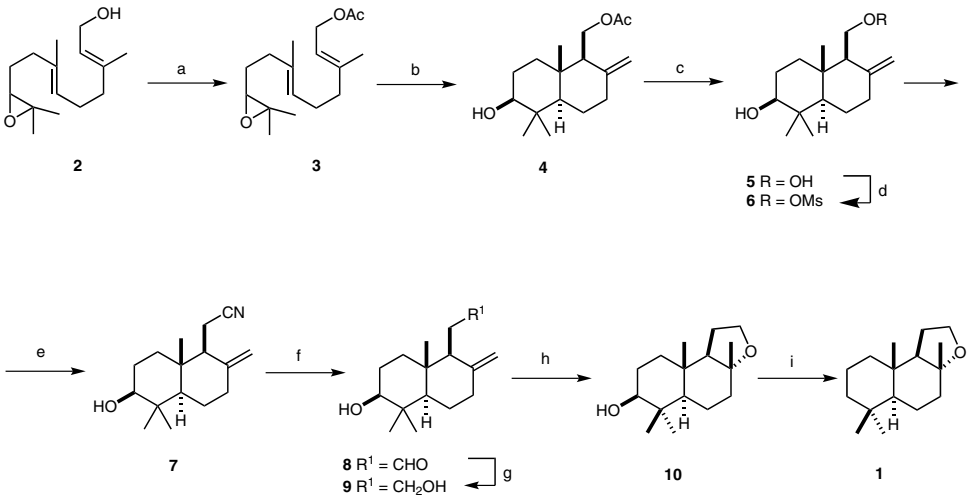
Compared to conventional cationic cyclizations,[10] radical cyclization of epoxypolyisoprenes is a complementary method because the generation of radicals proceeds under milder conditions. Therefore, many functional groups are tolerated that are not compatible with the cationic conditions. Here we present a synthetic strategy for the preparation of ambrox by exploiting the advantages of the titanocene(III)-catalyzed radical tandem cyclizations, such as the high diastereoselectivity,[11a,9b] the readily availability of the starting materials and catalysts, and the regioselective formation of an exocyclic olefin during the termination of the process.[11,9b,f] This last point is of paramount importance for the completion of the synthesis of ambrox as discussed later. Scheme 1 shows the retrosynthetic analysis of (±)-ambrox (**1**) from epoxyfarnesol (**2**).

The key step is the titanium(III)-catalyzed cyclization of epoxide **3** to the decalin derivative **4**, which is the crucial intermediate for the preparation of ambrox (**1**). On the basis of our experience, this cyclization will proceed with high regio- and stereoselectivity.[11a] This retrosynthetic analysis also addresses the important issues of the regio- and stereoselective formation of the tetrahydrofuran ring. The desired stereochemistry of ambrox (**1**) may also be obtained from the tetrasubstituted endocyclic double bond (4-*endo*).[12] According to the Markovnikov rule, only the tertiary cation would be formed under protic treatment of the exocyclic double bond in **4**. In contrast, in the case of the endocyclic olefins which are more commonly obtained from cationic cyclizations or through other approaches, this selectivity is often difficult to achieve and, usually, mixtures of isomeric tetrahydrofurans are obtained.

Our synthesis of **1** (Scheme 2) started with the selective epoxidation of farnesyl acetate following a previously described method[13] which yields the epoxyfarnesol **2**. Epoxyfarnesol acetate (**3**) was obtained quantitatively from **2** by acetylation.[14] The cyclization of compound **3** catalyzed by a catalytic quantity of Cp_2TiCl (0.1 equiv), using the couple TMSCl/2,4,6-collidine developed in our laboratory as a titanocene-regenerating agent,[9a] afforded the *trans*-fused decalin **4** bearing a crucial exocyclic double bond on C-8.[15] Although the bicyclic compound **4** was obtained in a moderate 40% yield, starting material **3** was recovered in a 40% yield, and the cyclization process underwent a rigid stereochemical control imposed by the geometry of the stereogenic center of epoxide **3**. Bicyclic compound **4** was obtained previously with similar yield when Cp_2TiCl (0.2 equiv) was used.[11a] Therefore, the yield can be regarded as satisfactory considering that the main compound has four stereocenters with a single relative configuration. Previously, theoretical and experimental evidences indicated that this radical tandem cyclization proceeds through a nonconcerted fashion via discrete carbon-centered radicals. Considering the nonconcerted nature of this radical tandem cyclization, the stereoselectivity observed can be explained in terms of Beckwith–Houk rules describes elsewhere.[16] This cyclization reaction proceed with high stereoselectivity and only one of the many possible stereoisomers was isolated. Similar results were previously reported.[9b] With enantiomerically pure epoxyfarnesol **3** that was described by Spinella et al.[17] **1** could be prepared enantiomerically pure. The termination step of this tandem cyclization is a β-elimination leading to an olefin. The exocyclic location of the double bond on C-8 in compound **4** is compulsory in order to complete the proposed synthesis of ambrox (**1**). Saponification of the acetate **4** gave isodrimenediol (**5**),[18] a microbial metabolite previously synthesized by Breslow et al.[19] and

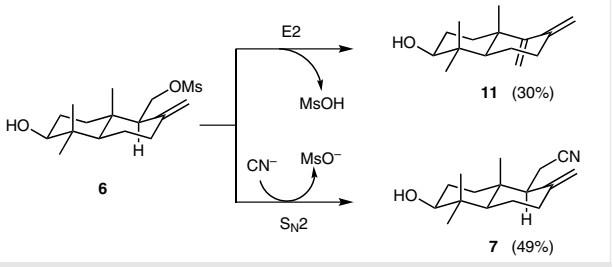


Scheme 1 Retrosynthetic analysis of (±)-ambrox (**1**)



Scheme 2 Synthesis of ambrox (**1**) from epoxyfarnesol (**2**). *Reagents and conditions*: (a) DMAP (1.25 equiv), Ac_2O (1.1 equiv), CH_2Cl_2, r.t., 1 h, quant.; (b) Cp_2TiCl (0.1 equiv), THF, r.t., 12 h, 40%; (c) K_2CO_3 (1.12 equiv), MeOH, r.t., 30 min, 95%; (d) DMAP (0.1 equiv), MsCl (1.05 equiv), pyridine, r.t., 2 h, 95%; (e) NaCN (5 equiv), DMSO, 100 °C, 12 h, 49%; (f) DIBAL-H (1.19 equiv), toluene, –78 °C, 30 min, 85%; (g) $NaBH_4$ (1.3 equiv), MeOH, 0 °C, 30 min, 95%; (h) PTSA (1.3 equiv), $MeNO_2$, r.t., 2 h, 60%; (i) (a) DMAP (3.0 equiv), $C_6F_5OC(S)Cl$ (2.0 equiv), CH_2Cl_2, 4 h; (b) AIBN (0.2 equiv), *n*-Bu_3SnH (2.5 equiv), benzene, reflux, 3 h, 74% (two steps).

isolated from *Polyporus arcularius*[20] and *Funalia trogii*.[21] Subsequently, mesylation of compound **5** with MsCl in Et_3N at –40 °C afforded a 95% yield of the compound **6**,[22] which was treated with NaCN in dimethyl sulfoxide (DMSO) to afford the nitrile compound **7** in a 49% yield[23] along with **11** (30%)[23] (Scheme 3). This result can be explained considering that under these experimental reaction conditions two competing processes can take place. On the first hand, the mesylate group can be substituted by the nitrile group through an S_N2 process to give the compound **7**, while on the second hand it can suffer elimination to give the diene **11** (Scheme 3). The C-1 elongation is crucial to the synthesis of the THF ring in ambrox (**1**), and the nitrile group was confirmed by a detailed analysis of its spectroscopic properties, specially the presence of a signal at δ = 120.0 ppm in its ^{13}C NMR spectrum.



Scheme 3 NaCN-mediated transformation of **6** to **7** and **11**

Reduction of **7** with diisobutylaluminum hydride (DIBAL-H) in toluene furnished the aldehyde **8** in a 85% yield,[24] which was further reduced with $NaBH_4$ to give diol **9** in 95% yield.[25] The conversion of the key intermediate **4** to ambrox (**1**) has been previously reported using similar conditions from the deoxy series and tributylsilylether derivative by Miyake et al.,[26] Kinoshita et al.,[27] Mori et al.,[28] and Heissler et al.[29]

The PTSA-mediated cyclization of **9** proved to be regio- and stereoselective, affording the THF derivative **10**, as only isolated product, in a 60% yield.[30] Finally, using the Barton–McCombie deoxygenation method,[31] the alcohol **8** could also be easily transformed in ambrox (**1**). In fact, conversion of the alcohol **10** into its trifluoromethoxythiocarbonyl derivative followed by radical reduction with Bu_3SnH, afforded ambrox (**1**) in a gratifying 74% yield.[32] Spectroscopic data for synthetic ambrox (**1**) were identical to those previously reported for the natural product.[5e]

In summary, we have developed a concise diastereoselective route to ambrox (**1**) using the titanium(III)-catalyzed radical cyclization of epoxypolyprene **3** as the key step. At the moment we are working on the synthesis of superambrox[33] that will be reported in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560594.

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(14) **Preparation of Acetate 3**
DMAP (153 mg, 1.25 mmol) and Ac_2O (0.1 mL, 1.1 mmol) were added to **2** (252 mg, 1.06 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was stirred at r.t. for 1 h. The mixture was then diluted with Et_2O and washed with 2 N HCl, a sat. solution of $NaHCO_3$, and brine. The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to yield 270 mg of the compound **3** (100%). ^1H NMR and ^{13}C NMR spectra of compound **3** were consistent with that of the original isolation literature.[34]
(15) **Cp_2TiCl-Catalyzed Cyclization of 3**
Strictly deoxygenated THF (15 mL) was added to a mixture of [Cp_2TiCl_2] (25 mg, 0.1 mmol) and Mn dust (440 mg, 8.0 mmol) under Ar, and the suspension was stirred at r.t. until it turned green (about 15 min). Then a solution of 2,4,6-collidine (0.9 mL, 7.0 mmol) and TMSCl (0.5 mL, 4.0 mmol) in THF (5 mL) was added, the mixture was stirred for 5 min, a solution of **3** (280 mg, 1 mmol) in THF (5 mL) was finally added, and the mixture was stirred at r.t. for 12 h. Then 2 N HCl was added, and the mixture was extracted with Et_2O. The combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was dissolved in THF, and 1 M solution of TBAF in THF (1.2 mmol) was added. The new mixture was stirred for 30 min, diluted with Et_2O, and washed with brine. The organic layer was dried with anhydrous Na_2SO_4 and the solvent removed. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to yield 112 mg of the cyclization compound **4** (40%), and 112 mg of starting material **3** was recovered (40%). Only the isomer **4** was isolated. ^1H NMR and ^{13}C NMR spectra of compound **4** were consistent with that of the original isolation literature.[11a]
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(18) **Saponification of 4**
Compound **4** (224 mg, 0.8 mmol) was dissolved in MeOH (2 mL), K_2CO_3 (124 mg, 0.9 mmol) was added, and the solution was stirred for 30 min. The mixture was then diluted with Et_2O and washed with 2 N HCl solution. The organic layer was dried (anhydrous Na_2SO_4), and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc, 85:15)

to yield 181 mg of compound **5** (95%). ^{1}H NMR and ^{13}C NMR spectra of compound isodrimenediol (**5**) were consistent with those of the original isolation literature (see ref. 20).

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(22) **Synthesis of Mesylate 6**

To a solution of isodrimenediol (**5**, 238 mg, 1.0 mmol) and DMAP (12 mg, 0.1 mmol) in pyridine (4 mL) was added MsCl (81 µL, 1.05 mmol), and the whole mixture was stirred for 2 h at r.t. The reaction mixture was diluted with sat. brine and extracted with Et_2O. The organic layer was washed with 2 N aq HCl, 7% aq $NaHCO_3$, dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to yield 300 mg of mesylate **6** (95%), isolated as a waxy mass.

Analytical Data for Mesylate 6

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.92 (s, 1 H), 4.62 (s, 1 H), 4.45 (dd, *J* = 10.0, 3.9 Hz, 1 H), 4.34 (dd, *J* = 9.8, 8.9 Hz, 1 H), 3.26 (dd, *J* = 11.7, 4.2 Hz, 1 H), 2.98 (s, 3 H), 2.43 (ddd, *J* = 13.2, 4.3, 2.4 Hz, 1 H), 2.11 (dd, *J* = 8.6, 3.2 Hz, 1 H), 2.02 (td, *J* = 13.0, 4.8 Hz, 1 H), 1.78–1.69 (m, 3 H), 1.66–1.54 (m, 2 H), 1.45–1.35 (m, 2 H), 1.13 (dd, *J* = 12.5, 2.8 Hz, 1 H), 1.00 (s, 3 H), 0.78 (s, 3 H), 0.76 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.1 (C), 108.0 (CH_2), 78.3 (CH), 66.4 (CH_2), 54.8 (CH), 54.2 (CH), 39.1 (C), 38.9 (C), 37.6 (CH_3), 37.2 (CH_2), 37.0 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 23.3 (CH_2), 15.4 (CH_3), 15.2 (CH_3).

(23) **Preparation of Nitrile 7**

To a solution of mesylate **6** (252 mg, 0.8 mmol) in DMSO (5 mL) was added NaCN (196 mg, 4 mmol), and the mixture of reaction was stirred for 12 h at 100 °C. The reaction mixture was diluted with sat. brine and extracted with Et_2O. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to yield 97 mg of the nitrile **7** (49%) and 53 mg of the diexo-olefin **11** (30%), both isolated as waxy mass.

Analytical Data for Nitrile 7

^{1}H NMR (401 MHz, $CDCl_3$): δ = 4.96 (s, 1 H), 4.62 (s, 1 H), 3.25 (dd, *J* = 11.6, 4.3 Hz, 1 H), 2.56–2.40 (m, 2 H), 2.34 (dd, *J* = 16.7, 10.6 Hz, 1 H), 2.17–2.00 (m, 2 H), 1.80–1.50 (m, 4 H), 1.45–1.28 (m, 2 H), 1.12 (dd, *J* = 12.5, 2.6 Hz, 1 H), 1.00 (s, 3 H), 0.77 (s, 3 H), 0.68 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.7 (C), 120.0 (C), 108.2 (CH_2), 78.2 (CH), 54.1 (CH), 52.9 (CH), 39.1 (C), 39.0 (C), 37.1 (CH_2), 37.0 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 23.3 (CH_2), 15.4 (CH_3), 14.0 (CH_2), 13.7 (CH_3).

Analytical Data for Diexo-olefin 11

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.81 (t, *J* = 2.1 Hz, 1 H), 4.77 (s, 1 H), 4.67 (s, 1 H), 4.53 (s, 1 H), 3.25 (dd, *J* = 10.3, 4.2 Hz, 1 H), 2.47 (br d, *J* = 12.6 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.82–1.49 (m, 6 H), 1.12 (dd, *J* = 12.5, 2.5 Hz, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H), 0.83 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.9 (C), 149.4 (C), 109.3 (CH_2), 103.5 (CH_2), 78.8 (CH), 51.7 (CH), 39.9 (C), 39.4 (C), 35.6 (CH_2), 35.3 (CH_2), 28.3 (CH_3), 27.7 (CH_2), 22.3 (CH_2), 20.8 (CH_3), 15.5 (CH_3).

(24) **Synthesis of Aldehyde 8**

To a solution of nitrile **7** (247 mg, 1.0 mmol) in toluene (3 mL) was added 1 M DIBAL in toluene (1.19 mL, 1.19 mmol) at –78 °C. The mixture of reaction was stirred for 30 min at the same temperature. After addition of acetone (0.75 mL), the reaction mixture was diluted with 2 M aq HCl and extracted with Et_2O. The organic layer was washed with sat. brine, dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to yield 212 mg of the aldehyde **8** (85%) as waxy mass.

Analytical Data for aldehyde 8

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.64 (dd, *J* = 3.1, 0.9 Hz, 1 H), 4.84 (s, 1 H), 4.41 (s, 1 H), 3.28 (dd, *J* = 11.6, 4.5 Hz, 1 H), 2.52 (ddd, *J* = 16.8, 10.8, 3.2 Hz, 1 H), 2.46–2.40 (m, 2 H), 2.35–2.30 (m, 1 H), 2.09 (td, *J* = 13.1, 5.0 Hz, 1 H), 1.81–1.51 (m, 5 H), 1.42 (qd, *J* = 13.0, 4.3 Hz, 1 H), 1.21 (dd, *J* = 12.5, 2.8 Hz, 1 H), 1.02 (s, 3 H), 0.80 (s, 3 H), 0.72 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 203.0 (CH), 147.9 (C), 108.4 (CH_2), 78.6 (CH), 54.3 (CH), 50.6 (CH), 39.8 (CH_2), 39.1 (C), 38.6 (C), 37.3 (2 × CH_2), 28.3 (CH_3), 27.7 (CH_2), 23.5 (CH_2), 15.4 (CH_3), 14.6 (CH_3).

(25) **Preparation of Alcohol 9**

To a solution of **8** (187 mg, 0.75 mmol) in MeOH (3.7 mL) was added $NaBH_4$ (37 mg, 0.98 mmol) at 0 °C. The mixture of reaction was stirred for 30 min at the same temperature. After addition of acetone (0.6 mL), the reaction mixture was condensed to give a residue, which was diluted with sat. brine and extracted with Et_2O. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. The crude of reaction was purified by flash chromatography (hexane–EtOAc, 85:15) to yield 179 mg of the alcohol **9** (95%) isolated as waxy mass.

Analytical Data for Alcohol 9

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.87 (br s, 1 H), 4.56 (br s, 1 H), 3.74 (ddd, *J* = 10.1, 7.3, 4.3 Hz, 1 H), 3.53 (dt, *J* = 10.1, 7.0 Hz, 1 H), 3.27 (dd, *J* = 11.8, 4.3 Hz, 1 H), 2.41 (ddd, *J* = 12.8, 4.3, 2.5 Hz, 1 H), 2.00 (td, *J* = 13.0, 5.1 Hz, 1 H), 1.82–1.56 (m, 7 H), 1.55–1.45 (m, 2 × OH), 1.40 (dd, *J* = 12.8, 4.2 Hz, 1 H), 1.21 (m, 1 H), 1.13 (dd, *J* = 12.5, 2.8 Hz, 1 H), 1.00 (s, 3 H), 0.78 (s, 3 H), 0.70 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.2 (C), 106.8 (CH_2), 78.8 (CH), 62.4 (CH_2), 54.6 (CH), 52.5 (CH), 39.1 (C), 39.1 (C), 38.1 (CH_2), 37.1 (CH_2), 28.3 (CH_3), 27.9 (CH_2), 27.2 (CH_2), 23.9 (CH_2), 15.41 (CH_3), 14.5 (CH_3).

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(30) **Synthesis of Tetrahydrofuran Derivative 10**

To a solution of **9** (100 mg, 0.39 mmol) in $MeNO_2$ (10 mL) was added PTSA (87 mg, 0.5 mmol). The mixture of reaction was stirred for 2 h at r.t. The reaction was quenched with aq $NaHCO_3$ (10%) and extracted with Et_2O. The organic layer was washed with sat. brine, dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc, 80:20) to yield **10** (60 mg, 60%) as a waxy mass. Only the isomer **10** was isolated. ^{1}H NMR and ^{13}C NMR spectra of compound **10** were consistent with that of the original isolation literature.[35]

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(32) **Barton–McCombie Deoxygenation of Alcohol 10**

DMAP (110 mg, 0.9 mmol) and *O*-pentafluorophenyl chlorothionoformate (160 mg, 0.6 mmol) were added to a solution of alcohol **10** (80 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at r.t. for 4 h. The reaction was quenched

with H_2O, the mixture extracted with EtOAc, the organic layer dried (anhydrous $MgSO_4$), and the solvent removed to give a residue (120 mg), which was dissolved in benzene (10 mL) and slowly added to a mixture of $HSnBu_3$ (220 mg, 0.76 mmol) and AIBN (10 mg) in benzene (10 mL). This mixture was refluxed for 3 h, the solvent was removed, and the residue was submitted to flash chromatography (hexane–EtOAc, 85:15) to yield **1** (50 mg, 74%) as a white solid. Its ^1H NMR and ^{13}C NMR data matched those previously reported for ambrox (see ref. 36).

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