Enantioselective Total Synthesis of (-)-9-Epi-Ambrox, a Potent Ambergris-Type Olfactory Agent

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Summary: Addition of the cerian reagent derived from 5-lithio-2,3-dihydrofuran and anhydrous CeCl₃ to bicyclic enone 5 (92% ee by lipase hydrolysis of its chloroacetate precursor) affords 6 selectively. Anionic oxy-Cope rearrangement of 6 in refluxing THF induces [3,3] sigmatropy and subsequent enolate ion equilibration. This tandem sequence of reactions allows for an efficient pathway to (-)-2.

Ambergris is produced as a metabolite of the blue sperm whale (Physeter macrocephalus L.) and occurs on concretions in the gut.¹ During several years of aging, the original major constituent (+)-ambrein² undergoes light- and air-induced oxidation to give odoriferous degradation products that combine a most fragrant woody scent with unique fixative properties. Release of the ambergris fragrance is related principally to the presence of Ambrox (1). The growing demand for ambergris-type odorants, coupled with the almost complete worldwide ban on whaling, has stimulated an intense search for substitutes. Indeed, several syntheses of 1 have recently been reported.³ In addition, Ohloff,⁴ Naf,⁵ and Winter⁶ and their co-workers have undertaken a detailed examination of structure–activity relationships among these tricyclic labdanoid ethers and related molecules. Of the distinct odors of varying quality and strength uncovered to the present, (-)-9-epi-Ambrox (2) has been found to possess the strongest scent and lowest threshold concentration (0.15 ppb) of all. The ability of 1 and 2 to trigger a strong sensory response and achieve good receptor affinity has been attributed to the presence of three axial methyl groups (the so-called "triaxial rule").⁷

The only documented synthesis of 2 has been realized by chemical transformations of (+)-scareolide (3), a lab dane diterpene derivative in its own right.⁸ We wish to delineate here a very different approach to this class of compounds, and particularly (-)-2, that extends the remarkable utility of the anionic oxy-Cope rearrangement⁹ in accessing polycyclic compounds.

In our approach the bicyclo[2.2.2]octene 5, holding functionality so positioned as to allow for the realization of high levels of x-facial selectivity during nucleophilic attack at its carbonyl group, was first elaborated (Scheme I). The known racemic alcohol 4⁰ was converted to its chloroacetate (96%) and subjected to hydrolysis with lipase P-30.¹⁰ By carrying out the enzymatic reaction to 60% completion and saponifying the unreacted ester, we were able to obtain (-)-4 of high optical purity (92% ee)¹¹ at an

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The equilibration efficiency level of 70%. Oxidation of this alcohol to \((-\)-5, \(\alpha\)\(^{25}D = -45^\circ\) (c. 1.31, CHCl\(_3\)) \(^{12}\) permitted determination of the absolute configuration by means of circular dichroism.\(^{13}\)

After 5 was condensed with the cerium reagent derived from 5-lithio-2,3-dihydrofuran \(^{14}\) and anhydrous CeCl\(_3\), 6 (65%, \(\alpha\)\(^{25}D = -93.9^\circ\) (c. 3.15, toluene)) and its epimer (9%) were separated chromatographically on activity II basic alumina. Heating the potassium salt of 6 with 18-crown-6 in anhydrous THF induced the operation of two key sequential reactions. The first is a [3,3] sigmatropic shift, relegated to a boat transition state geometry for structural reasons, which elaborates the global framework of interest. The thermal activation also induces the initially formed, electronically destabilized enolate anion 7 to experience equilibration completely in favor of 8.\(^{16}\) Quenching of the latter enolate with phenylethlylenenyl chloride followed by oxidative elimination of the \(\alpha\)-phenylethlyleno ketone so produced afforded 9 (54% overall), \(\alpha\)\(^{25}D = -95.1^\circ\) (c. 2.99, CHCl\(_3\)).

Introduction of the angular methyl group was easily accomplished since ketone 9 is capable only of unidirectional enolization (Scheme II). Conviction that the new CH\(_3\) substituent had indeed entered from the axial direction was substantiated by appropriate NOE studies at 300 MHz of the \(\alpha\)-alcohol derived from 10.\(^{16}\)

Advantage was taken of the rather folded topography of 10 to produce the \(\alpha\)-alcohol stereoselectively. The use of CeCl\(_3\)-doped sodium borohydride\(^{17}\) was well suited to this purpose, successfully furnishing this isomer in 78% purified yield. Although hydroxyl-directed hydrogenation has attained heightened levels of sophistication recently, recourse to [Rh(norbornadiene)(DIPHOS-4)]BF\(_4\) \(^{18}\) and Ir(cod)py(PCy)\(_2\)PF\(_3\) \(^{19}\) in the present instance resulted in reduction only of the dissubstituted double bond. Presumably, the high level of steric congestion in the vicinity of the allylic alcohol functionality impedes its reduction.\(^{20}\) Following these unsuccessful experiments, we turned to conventional 5% Pd/C as catalyst (30 mol %) and observed the smooth conversion of the \(\alpha\)-alcohol to 11 (78%) in ethyl acetate at atmospheric pressure during 48 h.

With 11 in hand, advantage was taken of the stability of \(\beta\)-alkoxy radicals toward fragmentation.\(^{21}\) Once the xanthate has been produced, reductive cleavage of the C-O bond was best achieved by heating this derivative with AIBN and \((\text{Me}_3\text{Si})_2\text{SiH}_2\) in benzene. The colorless oil 2 so obtained (89%) exhibited \(\alpha\)\(^{25}D = -6.0^\circ\) (c. 0.98, CHCl\(_3\)) \(^{22}\) and a \(^1\)H NMR spectrum identical with that kindly supplied by Dr. Ohloff.

In summary, a concise synthesis of \((-\)-9-epi-Ambrox (2) has been achieved. The convergency of the approach allows for the ready introduction of C rings of various size and degree of substitution.\(^{24}\) The efficiency and brevity of the scheme allow for the preparation of substantial quantities of these tricyclic ethers as desired.

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(12) All new compounds reported herein have been fully characterized by IR, high-field \(^1\)H and \(^{13}\)C NMR, and high-resolution mass spectrometry and/or combustion analysis.

(13) For material for \(83\%\) ee: \(\alpha\)\(^{25}D\) = +408\(^\circ\) (c. 0.22, CHCl\(_3\)); CD \(\gamma_{


(18) This phenomenon has been encountered previously. Paquette, L. A.; Ross, J. R.; Shi, Y.-J. J. Org. Chem. 1990, 55, 1589.


(20) This phenomenon has been encountered previously. Paquette, L. A.; Ross, J. R.; Shi, Y.-J. J. Org. Chem. 1990, 55, 1589.


(23) Lit. \(\alpha\)\(^{25}D\) = -6.1\(^\circ\) (c. 1.0, CHCl\(_3\)).