enantiomeric purity was lost during the transformation held at 80 °C. In order to prevent loss of enantiomeric purity, transformation of **5d** into **6d** was carried out at 40 °C (Table I).

In summary, quantitative transfer of stereogenicity from 4-(acyloxy)-2-butyn-1-ol derivatives **5** into dihydrofurans **6** is achieved by silver(I)-catalyzed rearrangement and cyclization, and the sequence is successfully applied to the synthesis of (−)-ascofuranone.

Acknowledgment. We are indebted to the analytical laboratory of Sagami Chemical Research Center for microanalysis and Dr. Koji Kimura, Department of Biochemistry, Tottori University School of Medicine, for recording mass spectra. We are also grateful for partial financial support by a Takeda Chemical Industries, Ltd. Award in Synthetic Organic Chemistry, Japan, and a Grant-in-Aid for Scientific Research (No. 62750801) from the Ministry of Education, Science, and Culture of Japan.

Supplementary Material Available: Detailed information on the obtainment of starting materials and physical and spectral data for compounds **3–6**, **8**, **10**, and **11** (7 pages). Ordering information is given on any current masthead page.

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

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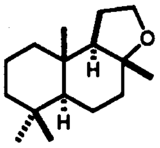
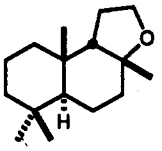
Received November 12, 1990

Summary: Addition of the cerium reagent derived from 5-lithio-2,3-dihydrofuran and anhydrous CeCl$_3$ 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**.

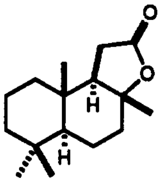
Ambergris is produced as a metabolite of the blue sperm whale (*Physeter macrocephalus* L.) and occurs as concretions in the gut.[1] During several years of aging, the original major constituent (+)-ambrein[2] undergoes light- and air-induced oxidation to give odoriferous degradation products that combine 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 an 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] Näf,[5] and Winter[6] and their co-workers have undertaken a detailed examination of structure–activity relationships within these tricyclic labdane 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"[1,4,7]).



1



2



3

The only documented synthesis of **2** has been realized by chemical transformations of (+)-sclareolide (**3**), a labdane diterpene derivative in its own right.[4c] 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 rearrangement[8] in accessing polycyclic compounds.

In our approach the bicyclo[2.2.2]octenone **5**, holding functionality so positioned as to allow for the realization of high levels of π-facial selectivity during nucleophilic attack at its carbonyl group, was first elaborated (Scheme I). The known racemic alcohol **4**[9] 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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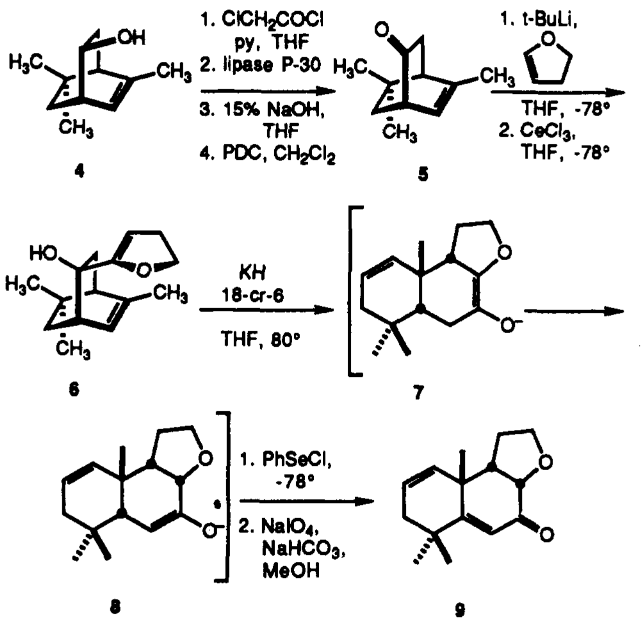
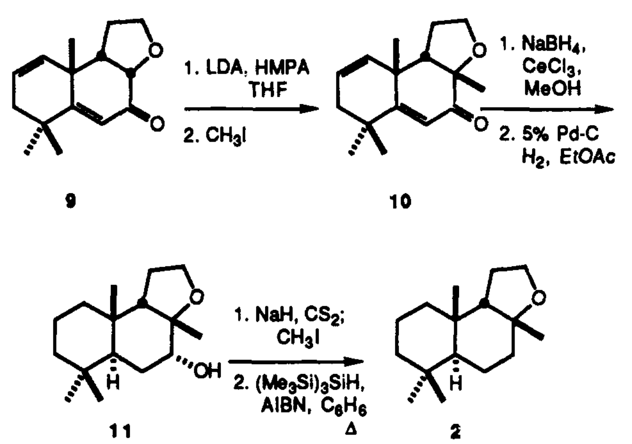
(11) 80 MHz ^{1}H NMR spectra were recorded on 20 mg samples of (+)-enriched alcohol in 1 mL of CDCl$_3$ at 25 °C to which 25 mol % Eu(dcm)$_3$ [McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038] had been added. The carbinol proton for the (+)- (δ 10.53; $\Delta\delta$ 6.65) and (−)-enantiomers (δ 9.90 ppm; $\Delta\delta$ 6.10) exhibited a sufficient "sense of nonequivalence" [Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150] such that integration of the signals allowed for % ee determination. By examining four samples of varying optical purity, it was possible to construct a plot of % ee vs $[\alpha]^{25}_{\mathrm{D}}$ whose slope was 1.12 (r = 0.99). Later % ee determinations were made by extrapolation or interpretation.

Scheme I



Scheme II



efficiency level of 70%. Oxidation of this alcohol to (−)-5, $[\alpha]^{25}{}_D$ −454° (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° (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.[15] Quenching of the latter enolate with phenylselenenyl chloride followed by oxidative elimination of the α-phenylseleno ketone so produced afforded 9 (54% overall), $[\alpha]^{25}{}_D$ −95.1° (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 α-alcohol derived from 10.[16]

Advantage was taken of the rather folded topography of 10 to produce the α-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)$_3$PF$_6$[19] in the present instance resulted in reduction only of the disubstituted 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 α-alcohol to 11 (78%) in ethyl acetate at atmospheric pressure during 48 h.

With 11 in hand, advantage was taken of the stability of β-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 (Me$_3$Si)$_3$SiH[22] in benzene. The colorless oily 2 so obtained (89%) exhibited $[\alpha]^{25}{}_D$ −6.0° (c 0.98, CHCl$_3$)[23] 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.

Acknowledgment. We thank the National Institutes of Health (GM 30827) for generous financial support of this research.

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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° (c 0.22, CHCl$_3$); CD $[\Psi]_{288}$ 2004°, $[\theta]_{max}$ +3291°. See: Crabbé, P. In *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965; p 232. The ketone derived from the lipase-hydrolyzed (+)-alcohol exhibited a large positive Cotton effect, indicating the (−)-alcohol to be of the desired absolute configuration.

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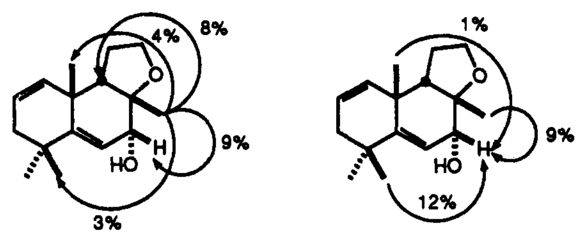
[16]



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[23] Lit.[4c] $[\alpha]^{25}{}_D$ −6.1° (c 1.0, CHCl$_3$).

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