Adaptation of Oxyanionic Sigmatropy to the Convergent Enantioselective Synthesis of Ambergris-Type Odorants

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(−)-(15,4R)-5,8,8-Trimethylbicyclo[2.2.2]oct-5-en-2-one has been prepared in high optical purity in order to adapt its β,γ-unsaturated ketone component to an anionic oxy-Cope strategy aimed at several labdane-like tricyclic ethers. Condensation reactions with the dichloro cerate derivatives of 2,3-dihydrofuran and dihydrofuran proceeded regioselectively from the less hindered p surface, thereby setting the stage for anionically accelerated [3,3] sigmatropic shift. The resulting enolate anions are electronically destabilized relative to their tautomers, which are consequently formed efficiently. These are captured by reaction with phenylselenenyl chloride. Once selenoxide elimination and reduction with NaBH₄-CeCl₃ had been accomplished, the stage was set for installation of trans A/B ring stereochemistry. Direct saturation of the original dienes leading to cis A/B isomers. The enantioselective syntheses were completed by conversion to the respective xanthates and reduction of these intermediates under free-radical conditions. The results indicate that a practical route to certain potent olfactory agents has been developed.

Ambrox (1), a labdane-like tricyclic ether initially synthesized in 1950 and discovered some time later in ambergris, has become a highly valued fragrance chemical. As a consequence of dwindling world supplies of ambergris (a metabolite of the blue sperm whale), an intensive search for synthetic substitutes has recently been mounted that includes de novo approaches to 1 itself. Several years ago, Ohloff and his co-workers made the surprising (to them) observation that 2, an isomer to become known as (−)-9-epi-Ambrox, exhibits a woody odor and tonality of a quality more persistent than that of any known analogue including 1. Its threshold concentration of 0.15 ppb is the lowest on record. At the inception of our work, (−)−2 had been prepared only by chemical modification of (+)-sclareolide (3) in unspecified yield.

In a related development of longer standing, the tricyclic ether 4 was isolated during the early structural elucidation work on (−)-ambrein. Although both 4 and its hydro-

α-metalated vinyl ether\(^\text{11,12}\) would set the stage for operation of the [3,3] sigmatropic event that serves to elaborate the complete tricyclic framework.

**Results and Discussion**

The first task in our exploration of the above plan centered on the electrophilic partner 11 in optically active condition and of the proper absolute configuration. Toward this objective, the racemic alcohol 9, which is readily available from 2,4,4-trimethylcyclohexene,\(^\text{13}\) was esterified with chloroacetyl chloride and subjected to controlled enzymatic hydrolysis with lipase P-30\(^\text{14}\) (Scheme I). When this process was allowed to proceed to approximately 60% completion and the unreacted ester was hydrolyzed, \((-\text{)}\)-9 of high optical purity was recovered with good overall efficiency (70%).\(^\text{15}\) Definition of the level of enantiomeric excess in the levorotatory alcohol as 92% was achieved by examination of the \(^1\text{H}\) NMR spectra (CDCl\(_3\), 25 °C) of samples of \((-\text{)}\)-enriched 9 of varying optical purity in the presence of 25 mol % Eu(dcm)\(_3\).\(^\text{16}\) The “sense of nonequivalence”\(^\text{17}\) of the carbinol proton for the \((+\text{)}\)-(δ 10.53; Δδ 6.65) and \((-\text{)}\)-enantiomers (δ 9.90, Δδ 6.10) under these circumstances permitted the construction of a plot of % ee versus [α]\(_D\)\(^\text{25}\) whose slope was 1.12 (r = 0.99). From this stage onward, additional ee determinations were readily made by extrapolation or interpolation.

When \((+\text{)}\)-9 of 83% ee was subjected to pyridinium dichromate oxidation, the dextrorotatory ketone 11 so produced exhibited [α]\(_D\)\(^\text{25}\) +408° (c 0.22, CHCl\(_3\)) and a large Cotton effect with the following circular dichroic characteristics: [ε]\(_{220}\) 204°, [ε]\(_{329}\) +3291°.\(^\text{18}\) Since our goals required the elaboration of (1S,2S)-9 and (1S)-11, effort was expended in maximizing the efficiency of production and stereochemical purity of \((+\text{)}\)-(−)-9, and (−)-11 as summarized in Scheme I.

The next stage was designed to gain rapid access to the global tricyclic frameworks of targets 2 and 7. Since 11 exhibits only low level diastereoselective discrimination toward vinyl lithium reagents, 5-lithio-2,3-dihydrofuran\(^\text{19}\) was first converted to its dichlorocarbonate by reaction with anhydrous CeCl\(_3\)\(^\text{18}\) prior to its 1,2-addition to the ketone. By performing the coupling reaction at −78 °C, the reasonable levels of facial selectivity were realized, favoring 12 over 13 (ca. 7:1, Scheme II). Although acid sensitive, 12 could be readily separated from its epimer 13 by chromatography on activity II basic alumina.

On heating the potassium salt of 12 to 80 °C in anhydrous THF and in the absence of air,\(^\text{20}\) anionic oxy-Cope rearrangement was triggered. For structural reasons, the transition state for this particular [3,3] sigmatropic shift must necessarily adopt a boatlike geometry. Whereas this

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feature has the important consequence of setting the three ring-fusion sites in an all-cis relationship, the resultant enolate anion 14 is seen to embrace electronic features that cause it to be unstable relative to 1,3,5-triprototropic shift.\(^{21}\) As a result, 14 isomerizes to 15 subsequent to the electronic reorganization and delivers the pivotal enolate intermediate 15. Trapping of this anion with phenylselenenyl chloride afforded 16, thereby providing access to 17 subsequent to selenoxide elimination.

At this juncture, all of the requisite carbon atoms have been properly assembled except for an angular methyl group adjacent to the other oxygen. This structural element could now be easily incorporated, since ketone 17 is capable only of unidirectional enolization to the desired site. Furthermore, the alkylation step proceeds with a high degree of \(\delta\)-diastereoselectivity\(^{22}\) as a direct consequence of the rather folded topography of the anion involved (Scheme III).

Reduction of enone 18 at room temperature with sodium borohydride in the presence of cerium trichloride\(^{23}\) resulted in exclusive formation of \(\alpha\)-isomer 19. As a consequence of NOE studies performed on this alcohol at 300 MHz (see A and B), the stereochemical configurations of the carbon atoms carrying the adjacent CH\(_3\) and OH groups could be firmly established.

In an effort to take advantage of hydroxyl-directed hydrogenation to set the desired trans \(A/B\) stereochemistry,

\(^{21}\) No information is available regarding whether the proton transfer occurs intra- or intermolecularly or via admixture of these two pathways.

\(^{22}\) No \(\alpha\)-methyl product was isolated.

28 was found to undergo extensive isomerization to 27 on basic aluminia.31 The requisite angular methylation of 27 was promoted by LDA in THF containing HMPA. These conditions were particularly effective in providing substantial levels of C-alkylation (77% of 29) relative to the O-alkylation option (4% of 30). Enol ether 30 was conveniently recycled via acid hydrolysis. Similar attempts to methylate 28 showed it to be more sluggish than 27.

As before, the task of establishing A/B stereochemistry required the adoption of two divergent protocols. Reduction of 29 under Luche conditions32 gave rise to 31. Decoupling, 2D, and NOE experiments performed on 31 confirmed the stereochemical configurations of the carbon atoms carrying the adjacent CH3 and OH groups (see C). The hydrogenation of 31 initially proved troublesome. Experiments conducted under 1 atm of H2 were found to give only cis ketone 34 over the course of a 48-h reaction period. Such 1,3-hydrogen transpositions are precedent- ed.26,32 The desired end result was realized when the hydrogenation of 31 was performed at 20 psi in the presence of a small amount of triethylamine33 (Scheme V). These conditions promoted conversion chiefly to 32 (62%), with coformation of 33 (8%) and 34 (18%). Further im-

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The synthesis of (+)-9-epiambroxide (6) was completed by reductive cleavage of the xanthate under free-radical conditions. The spectral data recorded for 6 are identical with those described by Kawanobe et al. for the racemic material.

The production of 8 proved equally direct (Scheme VI). It is noteworthy that borohydride reduction of the all-cis ketone 34 provided a small amount (3%) of β-alcohol 35 alongside 33. Hydride delivery from the convex surface of this conformationally folded ketone was expected to be heavily dominant. Tandem decoupling and NOE experiments performed on 33 confirmed that its central ring adopts chair conformation D so as to position both methyl groups and the hydroxyxyl substituent equatorially.

In conclusion, enantioselective syntheses of 2 and 6–8 have been achieved. As a result of the emphasis on convergency, the longest linear sequence from racemic 9 is 12 steps. If the racemic tricyclic ethers would suffice, the schemes are shortened to only eight laboratory manipulations. Accordingly, the strategy outlined herein allows for the ready de novo elaboration of agents having proven importance to the fragrance industry.

**Experimental Section**

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. 1H NMR were recorded at 300 MHz and 13C NMR spectra at 75 or 20 MHz as indicated. Mass spectra were recorded on a Kratos MS-30 instrument by Mr. Dick Weisemenger at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All MPLC separations were conducted on Merck Lobar columns (Lichroprep Si-60) with the help of a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in most cases dried prior to use.

**Exterification of (+)-9.** Chloroacetyl chloride (834 mg, 7.39 mmol) was added dropwise to a cold (0 °C), magnetically stirred solution of (+)-9 (302 mg, 1.24 mmol) in THF (5 mL) at room temperature. After 10 h, the reaction mixture was filtered and concentrated to a short pad of silica gel and concentrated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 2.45 g (75%) of (+)-11 as a colorless oil: IR (neat, cm⁻¹) 1720; 1H NMR (300 MHz, CDCl₃) δ 5.70 (dd, J = 4.8, 2.0 Hz, 1 H), 2.89 (m, 1 H), 2.29 (m, 1 H), 2.17 (m, 1 H), 1.94 (m, 1 H), 1.87 (d, J = 1.6 Hz, 3 H), 1.55 (m, 1 H), 1.44 (m, 1 H), 1.08 (s, 3 H), 0.96 (s, 3 H); 13C NMR (200 MHz, CDCl₃) δ 213.1, 147.6, 118.4, 49.9, 49.4, 38.7, 36.0, 33.4, 31.0, 28.3, 22.0; MS m/z (M⁺) calcd 164.1201, obsd 164.1203; [α]D = 84.5° (c 2.27, CHCl₃). The spectral properties of this alcohol is identical with those reported previously for the racemic alcohol.

Addition of 5-Lithio-2,3-dihydrofuran to (+)-11. To a cold (78 °C), magnetically stirred solution of 2.3-dihydrofuran (0.687 mL, 9.13 mmol) in anhydrous THF (6 mL) was added tert-butyl lithium (5.4 mL of 1.7 M in hexanes, 9.18 mmol). Following completion of the addition, the reaction mixture was brought to 0 °C for 30 min, returned to ~78 °C, and added via cannula to a cold (78 °C), stirred suspension of anhydrous CeCl₃ in THF (35 mL). The original CeCl₃/THF (3.4, 9.13 mmol) was dried by heating for 5 h at 140 °C (the fluid was evaporated at 25 °C for 1 h). The resulting suspension was stirred at 78 °C for 3 h, treated with (+)-11 (300 mg, 1.83 mmol), dissolved in THF (1 mL), and agitated for an additional 3 h at this temperature before being quenched with saturated aqueous NH₄Cl solution (40 mL). The products were extracted into ether, and the combined organic phases were dried and evaporated. Chromatography of the residue on activity II basic alumina (elution with ether) afforded 274 mg (65%) of 12 and 40 mg (9%) of 13.

For: faint yellow oil; IR (neat, cm⁻¹) 3520–3310, 1650; 1H NMR (300 MHz, CDCl₃) δ 6.59 (d, J = 6.5 Hz, 1 H), 4.44 (t, J = 2.4 Hz, 1 H), 3.39 (m, 2 H), 2.63 (m, 1 H), 2.19 (m, 2 H), 2.07 (m, 1 H), 1.67 (d, J = 1.4 Hz, 3 H), 1.64 (m, 1 H), 1.28 (s, 3 H), 1.20 (m, 1 H), 0.97 (m, 1 H), 0.89 (m, 1 H), 0.86 (s, 3 H) (OH not observed); 13C NMR (75 MHz, CDCl₃) δ 163.9, 143.5, 123.7, 93.9, 72.8, 70.0, 48.9, 41.9, 35.7, 35.3, 32.8, 32.1, 30.4, 28.2, 22.0; MS m/z (M⁺) calcd 234.1620, obsd 234.1620; [α]D = –89.3° (c 3.15, toluene). Anal. Calcd for C₁₃H₁₆O₆: C, 76.88; H, 9.46. Found: C, 76.72; H, 9.46.

For: faint yellow oil; IR (neat, cm⁻¹) 3610–3250, 1654; 1H NMR (300 MHz, CDCl₃) δ 5.70 (m, 1 H), 4.85 (t, J = 2.5 Hz, 1 H), 4.68 (t, J = 9.3 Hz, 2 H), 3.86 (m, 1 H), 3.63 (m, 1 H), 3.64 (m, 1 H), 3.81 (m, 1 H), 1.73 (d, J = 1.6 Hz, 3 H), 1.66 (br s, 1 H), 1.44 (td, J = 14.8, 1.9 Hz, 2 H), 1.03 (s, 3 H), 0.99 (m, 1 H), 0.79 (s, 3 H); 13C NMR (75 MHz, CDCl₃) δ 162.1, 144.4, 122.1, 96.1, 75.6, 70.1, 48.7, 42.2, 36.8, 36.2, 32.3, 31.6, 30.3, 29.9, 22.2; MS m/z (M⁺) calcd 234.1620,
obsd 234.1875; [α]D^28 = -91.6° (c 0.59, CHCl₃). Anal. Calc'd for C₁₈H₂₇Cl₂O₧: C, 69.6; H, 4.96. Found: C, 70.7; H, 5.0.

(+)-(3aS,5aS,9aR,9bS)-1,2,5,6,7,9a-Octahydro-2,4,6,8,9a-trimethyl-5-(phenylethynyl)naphtho[2,1-b]furan-4(3H)-one (16). To a magnetically stirred slurry of oil-free KH (106 mg, 2.67 mmol) in anhydrous THF (10 mL) was added (−)-12 (125 mg, 0.53 mmol) dissolved in the same solvent (10 mL). The mixture was stirred at 25 °C for 30 min, at which time color-6 was introduced. The contents were heated at 80 °C, cooled to −75 °C, treated with a solution of PhSeCl (511 mg, 2.67 mmol) in THF (10 mL), and allowed to warm slowly to 25 °C overnight. The mixture was recooled to −78 °C and then treated in turn with methanol (10 mL) and saturated aqueous NH₄Cl solution (10 mL). Following dilution with ether (40 mL), the mixture was washed with brine and the organic phase was dried and concentrated. The residue was purified by silica gel chromatography (elution with 50% ether in petroleum ether) to give 156 mg (65%) of 16 and 16 mg (5%) of an overoxidized byproduct considered to be II.

For 16: yellowish oil; IR (CHCl₃, cm⁻¹) 1710; ¹H NMR (300 MHz, CDCl₃) δ 7.49 (m, 2 H), 7.28 (m, 3 H), 5.60 (m, 1 H), 5.43 (dd, J = 10.6, 1.2 Hz, 1 H), 4.86 (d, J = 7.9 Hz, 1 H), 4.05 (td, J = 8.5, 4.0 Hz, 1 H), 3.81 (m, 1 H), 3.13 (m, 1 H), 2.96-2.08 (series of 2 H), 2.02-1.89 (series of 3 H), 1.62 (ddtt, J = 17.4, 5.4, 1.3 Hz, 1 H), 1.30 (s, 3 H), 1.14 (s, 3 H), 1.13 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 200.6, 134.2 (2C), 129.4 (2C), 128.8, 128.7, 121.7, 77.9, 72.6, 58.7, 50.2, 47.3, 38.8, 35.5, 34.6, 30.9, 28.7, 27.6, 27.3; MS m/z (M⁺ - SeCl₄) calcd 233.1541, obsd 233.1504; [α]D^{28} = -42.8° (c 0.18, CHCl₃). Anal. Calc'd for C₁₈H₁₅Cl₂Oₒ: C, 72.5; H, 8.12. Found: C, 72.8; H, 7.96.

(+)-(3aS,5aS,9aR,9bS)-1,2,5,6,7,9a-Octahydro-2,4,6,8,9a-tetramethyl-5-(phenylethynyl)naphtho[2,1-b]furan-4(3H)-one (17). To a magnetically stirred solution of LDA (from 12.4 mL 0.089 mmol of disopropylamine and 0.06 mL (0.089 mmol) of 1.55 M n-butyllithium in anhydrous THF (1 mL) was added 17 (10.3 mg, 0.044 mmol) dissolved in 1 mL of THF. The reaction mixture was warmed to 0 °C and stirred for 40 min before being recooled to −78 °C at which time 97 μL (0.56 mmol) of HMPA was introduced followed by methyl iodide (45 μL, 0.484 mmol, freshly filtered through basic alumina). After 30 min at this temperature, the mixture was warmed to 25 °C, stirred for 2 h, cooled to 0 °C, and quenched with saturated NH₄Cl solution. After dilution with ether (5 mL), the organic solution was washed with brine (2 × 5 mL) and the aqueous phases were back-extracted with ether. The combined ethereal solutions were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 25% ether in petroleum ether). There was obtained 6.5 mg (78%) of 18 as a yellowish solid, mp 92-94 °C (preparative GC): IR (CHCl₃, cm⁻¹) 1662; ¹H NMR (300 MHz, CDCl₃) δ 6.01 (d, J = 0.4 Hz, 1 H), 5.67 (m, 1 H), 5.43 (dt, J = 9.9, 0.8 Hz, 1 H), 3.86 (m, 2 H), 2.26 (dd, J = 8.3, 10.2 Hz, 1 H), 2.05 (m, 1 H), 1.99 (m, 2 H), 1.54 (m, 1 H), 1.49 (s, 3 H), 1.37 (s, 3 H), 1.21 (s, 3 H), 1.17 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 195.4, 173.2, 132.4, 121.4, 82.3, 65.6, 62.9, 40.7, 38.9, 38.1, 32.1, 31.8, 28.7, 28.5, 24.1; MS m/z (M⁺) calcd 246.1620, obsd 246.1645; [α]D^{28} = -70.3° (c 0.18, CHCl₃). Anal. Calc'd for C₁₉H₁₅Cl₂O₂: C, 72.5; H, 9.00. Found: C, 77.8; H, 9.01.

For 17: faintly yellow oil; IR (CHCl₃, cm⁻¹) 1685, 1608; ¹H NMR (300 MHz, CDCl₃) δ 6.01 (d, J = 0.7 Hz, 1 H), 5.72 (m, 1 H), 5.46 (dd, J = 10.8, 0.8 Hz, 1 H), 4.38 (d, J = 7.2 Hz, 1 H), 3.80 (m, 2 H), 2.62 (m, 2 H), 2.00 (dd, J = 4.8, 1.5 Hz, 2 H), 1.92 (m, 1 H), 1.48 (m, 1 H), 1.43 (s, 3 H), 1.25 (s, 3 H), 1.17 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 198.2, 174.0, 132.6, 124.0, 121.4, 78.1, 68.0, 51.9, 49.6, 39.1, 36.5, 30.9, 28.6 (2C), 28.5; MS m/z (M⁺) calcd 232.1448, obsd 232.1503; [α]D^{28} = -39.1° (c 0.29, CHCl₃). Calc'd for C₁₇H₁₅Cl₂O₂: C, 77.5; H, 8.68. Found: C, 77.55; H, 8.78.

For: yellowish solid, mp 130-134 °C (from preparative GC); IR (CHCl₃, cm⁻¹) 1683; ¹H NMR (300 MHz, CDCl₃) δ 6.13 (d, J = 0.8 Hz, 1 H), 5.76 (m, 1 H), 5.43 (m, 1 H), 4.24 (br s, 1 H), 3.98-3.81 (m, 2 H), 2.52 (dd, J = 11.4, 7.5 Hz, 1 H), 2.17-1.82 (m, 3 H), 1.45 (m, 1 H), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 194.1, 175.6, 132.1, 124.2, 118.8, 100.9, 67.3, 54.8, 40.7, 38.2, 36.3, 33.5, 31.3, 29.0, 28.2; MS m/z (M⁺) calcd 248.1412, obsd 248.1467; [α]D^{28} = -42.6° (c 0.18, CHCl₃). Anal. Calc'd for C₁₉H₁₅Cl₂O₂: C, 72.55; H, 8.12. Found: C, 72.98; H, 7.96.

(from preparative GC); IR (CHCl₃ cm⁻¹) 3700-3400; ¹H NMR (300 MHz, CDCl₃) δ 4.00 (t, J = 8.2 Hz, 2 H), 3.78 (m, 1 H), 3.60 (t, J = 2.3 Hz, 1 H), 2.74 (br s, 1 H), 2.15 (m, 1 H), 1.81 (m, 2 H), 1.70-1.38 (series of m, 7 H), 1.33 (s, 3 H), 1.26 (m, 2 H), 1.09 (s, 3 H), 0.92 (s, 3 H), 0.83 (s, 3 H); ¹³C NMR (62.5 MHz, CDCl₃) δ 81.9, 74.0, 67.5, 59.4, 42.3, 38.9, 33.2, 33.2, 32.4, 30.6, 28.0, 26.0, 22.7, 21.9, 18.5; MS m/z (M⁺) calculated 232.2096, observed 232.2212; [M]+ δ 15.09 (c 0.82, CHCl₃). Anal. Calcd for C₉H₈O₂C: 76.14; H: 11.18. Found: C: 76.26; H: 11.40.

Addition of 6-Lithiodihydropyran to (–)-11. To dihydroxypropane (74 mg, 0.69 mmol, freshly distilled, treated with tert-butyllithium and treated with anhydrous CeCl₃ was added (–)11 (464 mg, 2.88 mmol) as described above to give 23 (510 mg, 73%) and 24 (41 mg, 6%) after chromatography.

For 23: white solid, mp 63-67 °C; IR (CDCl₃ cm⁻¹) 3610-3200, 1683; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (dt, J = 6.5, 1.4 Hz, 1 H), 4.72 (t, J = 3.8 Hz, 1 H), 3.74 (td, J = 5.7, 1.5 Hz, 2 H), 2.70 (dt, J = 6.5, 3.2 Hz, 1 H), 2.65 (s, 1 H), 2.35 (dd, J = 12.4, 2.4 Hz, 1 H), 2.12 (dd, J = 15.4, 3.8 Hz, 1 H), 1.88-1.81 (m, 4 H), 1.77 (dd, J = 1.6 Hz, 3 H), 1.47 (m, 2 H), 1.40 (s, 3 H), 1.09 (dd, J = 12.4, 3.3 Hz, 1 H), 0.97 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 143.0, 124.0, 94.9, 75.6, 66.2, 49.2, 41.5, 37.9, 34.9, 32.9, 32.2, 28.3, 22.5, 21.2, 20.4; MS m/z (M⁺) calculated 248.1776, observed 248.1776; [M]+ δ 83.8° (c 0.19, CHCl₃). Anal. Calcd for C₉H₈O₂C: 77.38; H: 9.74. Found: C: 77.03; H: 9.76.

For 24: pale yellow oil; IR (neat cm⁻¹) 3965-3100, 1681; ¹H NMR (300 MHz, CDCl₃) δ 7.56 (dt, J = 6.5, 1.4 Hz, 1 H), 5.02 (t, J = 3.8 Hz, 1 H), 3.99 (m, 2 H), 2.75 (m, 1 H), 2.43 (dd, J = 14.6, 2.4 Hz, 1 H), 2.10 (s, 1 H), 2.07 (td, J = 6.3, 3.9 Hz, 2 H), 1.83 (s, J = 1.6 Hz, 3 H), 1.80 (m, 3 H), 1.28 (dd, J = 13.2, 1.8 Hz, 1 H), 1.15 (dd, J = 14.6, 3.3 Hz, 1 H), 0.98 (s, 3 H), 0.92 (m, 1 H), 0.79 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.3, 145.7, 121.4, 97.2, 75.6, 65.2, 45.5, 40.9, 36.3, 34.3, 32.5, 31.2, 28.6, 22.1, 21.5, 20.2; MS m/z (M⁺) calculated 248.1776, observed 248.1777; [M]+ δ 54.9° (c 0.84, CHCl₃). Anal. Calcd for C₉H₈O₂C: 77.38; H: 9.74. Found: C: 77.37; H: 9.78.

(4aS,6S,6aR,10aR,10bS)-2,3,6,6a,7,8,10a,10b-Octahydro-7,7,10a-trimethyl-naphthalen-1(2H)-one (24) and Its Stereoisomer 25. The anionic oxo-Cope rearrangement and in situ phenyleneselenylation of 23 (89 mg, 1.97 mmol) was performed in the described manner. The crude product was subjected to silica gel chromatography, elution first with petroleum ether and then 25% ethyl ether in petroleum ether, affording 291 mg (37%) of 24 and 338 mg (42%) of 26.

For 25: yellow oil; IR (CHCl₃ cm⁻¹) 1702; ¹H NMR (300 MHz, CDCl₃) δ 7.55 (m, 2 H), 7.29 (m, 3 H), 5.63 (m, 1 H), 5.44-5.37 (m, 2 H), 3.96 (td, J = 11.3, 3.9 Hz, 1 H), 3.88 (d, J = 1.0 Hz, 1 H); 3.68 (m, 1 H), 2.17 (s, 1 H), 2.13 (m, 1 H), 1.60-1.72 (m, 2 H), 1.53 (m, 1 H), 1.40-1.51 (series of m, 2 H); 1.41-1.25 (series of m, 2 H), 1.11 (s, 3 H), 0.85 (s, 3 H), 0.78 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 134.5, 126.6, 123.9, 128.2 (2 C), 131.4, 129.7, 129.2 (2 C), 128.8, 132.8, 72.8, 63.8, 58.2, 49.6, 47.6, 39.2, 34.7, 33.7, 30.6, 26.9, 24.2, 24.1; MS m/z (M⁺) calculated 404.1254, observed 404.1257; [M]+ δ 101.6° (c 4.0, CHCl₃). Anal. Calcd for C₉H₈O₂SeC: 65.50; H: 7.00. Found: C: 65.56; H: 7.10.

For 26: yellow solid, mp 91-96 °C; IR (CHCl₃ cm⁻¹) 1699; ¹H NMR (300 MHz, CDCl₃) δ 7.59 (m, 2 H), 7.29 (m, 3 H), 5.68 (m, 1 H), 5.47-5.37 (m, 2 H), 3.98 (td, J = 11.3, 3.9 Hz, 1 H), 3.88 (d, J = 1.0 Hz, 1 H); 3.68 (m, 1 H), 2.17 (s, 1 H), 2.13 (m, 1 H), 1.60-1.72 (m, 2 H), 1.53 (m, 1 H), 1.40-1.51 (series of m, 2 H); 1.41-1.25 (series of m, 2 H), 1.11 (s, 3 H), 0.85 (s, 3 H), 0.78 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 134.5, 126.6, 123.9, 128.2 (2 C), 131.4, 129.7, 129.2 (2 C), 128.8, 132.8, 72.8, 63.8, 58.2, 49.6, 47.6, 39.2, 34.7, 33.7, 30.6, 26.9, 24.2, 24.1; MS m/z (M⁺) calculated 404.1254, observed 404.1253; [M]+ δ 101.6° (c 3.8, CHCl₃). Anal. Calcd for C₉H₈O₂SeC: 65.50; H: 7.00. Found: C: 65.51; H: 7.27.
Acidic Hydrolysis of 30. A solution of 30 (26.5 mg, 0.102 mmol) in methanol (3 mL) was treated with a drop of concentrated hydrochloric acid and heated at 70 °C for 3 h. The cooled reaction mixture was evaporated, and the residue was chromatographed on silica gel. Elution with 50% ether in petroleum ether gave 13.2 mg (53%) of 27 and 9.8 mg (39%) of 28.

(4aS,laR,laS,10bS)-2,3,4,5,7,8,10a,10b-Hexahydro-4a,7,7,10a-tetramethyl-1H-naphtho[2,1-b]pyran-5(4H)-one (31). Enone 29 (20.6 mg, 0.079 mmol) was reduced as described earlier for 18 to give the corresponding tetrahydro compound (elution with 25% ether in petroleum ether) 16.6 mg (80%) of 31 and 2.5 mg (12%) of unreacted 29.

For 31: colorless oil that solidified on storage at −10 °C; mp 41.5–43.5 °C; IR (CHCl3 cm−1) 3580–3380; 1H NMR (300 MHz, CDCl3) δ 6.70 (1H, 0.51), 6.56 (1H, 0.51), 2.13 (s, 3H), 1.19 (s, 5H), 1.10 (s, 5H), 1.04 (t, 6H) (elution with 25% ether in petroleum ether) 16.6 mg (80%) of 31 and 2.5 mg (12%) of unreacted 29.

Acid-alkaline treatments of 31 (26.5 mg, 0.102 mmol) in methanol (3 mL) was treated with a drop of concentrated hydrochloric acid and heated at 70 °C for 3 h. The cooled reaction mixture was evaporated, and the residue was chromatographed on silica gel. Elution with 50% ether in petroleum ether gave 13.2 mg (53%) of 27 and 9.8 mg (39%) of 28.
Studies Directed at the Synthesis of Optically Active Pretazettine via Intramolecular Nitrone/Alkene Cycloaddition Reactions

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A protocol for the synthesis of optically active pretazettine which focuses on both the control of relative stereochemistry between the angular aryl and C6a hydroxyl groups and absolute stereochemistry has been developed and executed. The synthesis of the 1,3-dithiane ketal of (Z)-ethyl 3-(1,3-benzodioxol-5-yl)-5,7-dioxy-2-heptanone is described. Treatment of this alkenyl aldehyde with N-(methylbenzyl)hydroxylamine afforded a nitrone, which underwent intramolecular 1,3-dipolar cycloaddition to afford the two diastereomeric isoxazolidine cycloadducts in a 1:6 ratio. The sense of chirality transfer was determined by a single-crystal X-ray analysis of the major isomer.

Introduction

Pretazettine (1), a member of the crinine class of Amaryllidaceae alkaloids, was first characterized in the early 1960s.1,2 Interest in pretazettine stems from its promising antitumor3 and antiviral4 activity. Any synthetic work directed at pretazettine must take into account the complex relationships which exist among pretazettine (1), haemanthidine (2), and tazettine (3), which have been elegantly detailed by Wildman,5 as well as 6a-epipretazettine (4).6 In particular, Wildman showed that haemanthidine methodide is converted to pretazettine under mildly acidic conditions (pH 4) and that pretazettine is further converted to tazettine under basic conditions. This tendency to rearrange to tazettine constitutes one of the more interesting yet frustrating features of pretazettine architecture.

The first successful synthesis in the pretazettine area was that of Hendrickson in 1970,7 who prepared racemic haemanthidine and, therefore, pretazettine. All other syntheses of pretazettine have also involved the intermediary of haemanthidine.8-10 Without exception, attempts

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1H NMR (300 MHz, CDCl3) δ 5.44 (dd, J = 11.8, 4.2 Hz, 1 H), 3.80 (m, 2 H), 2.57 (s, 3 H), 2.02-1.93 (series of m, 7 H), 1.51 (m, 2 H), 1.40-1.23 (m, 2 H), 1.31 (s, 3 H), 1.28-1.19 (m, 2 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.09 (m, 1 H), 0.90 (s, 3 H); 13C NMR (62.5 MHz, CDCl3) δ 177.4, 90.8, 74.4, 59.7, 51.9, 47.2, 40.1, 34.7, 34.2, 33.7, 31.0, 30.6, 28.2, 21.8, 21.0, 19.4, 18.9, 18.2; MS m/z (M+) calcd 356.1844, obsd 356.1797; [α]D25 −15.5° (c 0.3, CHCl3). A 17.9 mg (0.050 mmol) mixture of this xanthate was reduced in the manner described previously to give 8 (11.3 mg, 90%) as a colorless oil; IR (CHCl3, cm−1) 1441, 1379, 1348, 1102, 905; 1H NMR (300 MHz, CDCl3) δ 3.94 (m, 1 H), 3.69 (dd, J = 11.7, 6.5 Hz, 1 H), 2.17-1.70 (series of m, 5 H), 1.66-1.42 (m, 5 H), 1.39-1.26 (m, 4 H), 1.24 (s, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 0.97 (d, J = 5.5 Hz, 1 H), 0.90 (s, 3 H), 0.89 (s, 1 H); 13C NMR (62.5 MHz, CDCl3) δ 177.2, 72.6, 60.2, 54.2, 47.1, 41.8, 39.9, 34.7, 34.4, 33.8, 31.0, 30.8, 28.7, 25.7, 22.3, 19.7, 16.8, 15.7; MS m/z (M+) calcd 250.2297, obsd 250.2250; [α]D25 −5.6° (c 0.8, CHCl3). Anal. Calcd for C17H23O: C, 81.51; H, 12.07. Found: C, 81.21; H, 12.00.

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Scheme I

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