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

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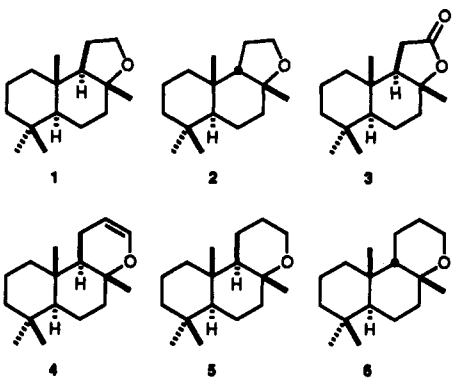
(-)-(1*S*,4*R*)-5,8,8-Trimethylbicyclo[2.2.2]oct-5-en-2-one has been prepared in high optical purity in order to adapt its β,γ-unsaturated ketone component to an anionic oxy-Cope strategy aimed at several labdane-like tricyclic ethers. Condensation reactions with the dichloro cerate derivatives of 2,3-dihydrofuran and dihydropyran proceeded regioselectively from the less hindered π 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 $NaBH_4$–$CeCl_3$ had been accomplished, the stage was set for installation of trans A/B ring stereochemistry. Direct saturation of the original dienones led instead to the 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.

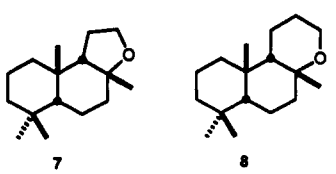
Ambrox (1), a labdane-like tricyclic ether initially synthesized in 1950[1] and discovered some time later in ambergris,[2] has become a highly valued fragrance chemical. As a consequence of dwindling world supplies of ambergris (a metabolite of the blue sperm whale), an intensive search for synthetic substitutes has recently been mounted[3] that includes de novo approaches to 1 itself.[4] 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.[5] Its threshold concentration of 0.15 ppb is the lowest on record. At the inception of our work,[6] (-)-2 had been prepared only by chemical modification of (+)-sclareolide (3) in unspecified yield.[5]

In a related development of longer standing, the tricyclic ether 4 was isolated during the early structural elucidation work on (-)-ambrein.[7] Although both 4 and its hydrogenation product 5 possess pleasant ambergris odors, little attention has since been paid to these compounds.[3a,j,4a,g,j] Weakly olfactory in their own right, the A/B cis-fused diastereomers of 1-3 have served as important reference compounds in support of the triaxial rule concept.[5b,8]




Despite the notable accomplishments recorded in the ambergris fragrance field,[8] there remained the challenge of designing a concise and efficient synthetic pathway that would, by virtue of its convergency, be capable of readily assembling either a furanoid or pyranoid end product.

As part of our interest in exploiting the substantial synthetic potential of the anionic oxy-Cope rearrangement,[9,10] we initiated an investigation directed toward the stereocontrolled enantioselective preparation of (-)-2, its homologue (+)-6, and their A/B cis-locked isomers 7 and 8. The linchpin intermediate of the strategy is the levorotatory [2.2.2]bicyclic enone 11, whose carbonyl group was envisioned to be structurally well disposed toward facially selective nucleophilic attack. Selection of the appropriate




(1) (a) Stoll, M.; Hinder, M. *Helv. Chim. Acta* **1950**, *33*, 1251. (b) Hinder, M.; Stoll, M. *Helv. Chim. Acta* **1953**, *36*, 1995.

(2) Mookherjee, B. D.; Patel, R. R. *7th Int. Congr. Essent. Oils*; Kyoto, 1977; paper 136.

(3) (a) Ohloff, G.; Vial, C.; Wolf, H. R.; Job, K.; Jégou, E.; Polonsky, J.; Lederer, E. *Helv. Chim. Acta* **1980**, *63*, 1932. (b) Bersuker, I. B.; Dimoglo, A. S.; Gorbachov, M. Y.; Koltsa, M. N.; Vlad, P. F. *Nouv. J. Chem.* **1984**, *9*, 211. (c) Ohloff, G.; Vial, C.; Demole, E.; Enggist, P.; Giersch, W.; Jégou, E.; Caruso, A. J.; Polonsky, J.; Lederer, E. *Helv. Chim. Acta* **1986**, *69*, 163. (d) Gautier, A.; Vial, C.; Morel, C.; Lander, M.; Näf, F. *Helv. Chim. Acta* **1987**, *70*, 2039. (e) Christenson, P. *Tetrahedron* **1988**, *44*, 1925. (f) Winter, B. *Helv. Chim. Acta* **1989**, *72*, 1278. (g) Vial, C.; Thommen, W.; Näf, F. *Helv. Chim. Acta* **1989**, *72*, 1390. (h) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Zaragozá, R. J. *J. Org. Chem.* **1989**, *54*, 5123. (i) Winter, B. *Prog. Clin. Biol. Res.* **1989**, *291*, 401. (j) Snowden, R. L.; Linder, S. M.; Wüst, M. *Helv. Chim. Acta* **1989**, *72*, 892. (k) Winter, B. *Pure Appl. Chem.* **1990**, *62*, 1377. (l) Snowden, R. L.; Brauchli, R.; Wüst, M. *Helv. Chim. Acta* **1990**, *73*, 640. (m) Martres, P.; Perefetti, P.; Zahra, J.-P.; Waegell, B. *Tetrahedron Lett.* **1991**, *32*, 765.

(4) (a) Vlad, P. F.; Ungur, N. D. *Synthesis* **1983**, 216. (b) dePascual Teresa, J.; Urones, J. G.; Pedrero, A. M.; Barcala, P. B. *Tetrahedron Lett.* **1985**, *26*, 5717. (c) Kawanobe, T.; Kogami, K.; Matsui, M. *Agric. Biol. Chem.* **1986**, *50*, 1475. (d) Decorzant, R.; Vial, C.; Näf, F.; Whitesides, G. M. *Tetrahedron* **1987**, *43*, 1871. (e) Koyama, H.; Kaku, Y.; Ohno, M. *Tetrahedron Lett.* **1987**, *28*, 2863. (f) González-Sierra, M.; Rúveda, E. A.; López, J. T.; Cortés, M. J. *Heterocycles* **1987**, *26*, 2801. (g) Coste-Manière, I. C.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett.* **1988**, *29*, 1017. (h) Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1989**, *72*, 996. (i) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, 361. (j) Vlad, P. F.; Ungur, N. D.; Perutsky, V. B. *Khim. Geterotsikl Soldin SSR* **1990**, *7*, 896.

(5) (a) Ohloff, G.; Giersch, W.; Pickenhagen, W.; Furrer, A.; Frei, B. *Helv. Chim. Acta* **1985**, *68*, 2022. (b) Escher, S.; Giersch, W.; Niclass, Y.; Bernadinelli, G.; Ohloff, G. *Helv. Chim. Acta* **1990**, *73*, 1935.

(6) Paquette, L. A.; Maleczka, R. E.; Jr. *J. Org. Chem.* **1991**, *56*, 912.

(7) (a) Ruzicka, L.; Seidel, C. F. *Helv. Chim. Acta* **1950**, *33*, 1285. (b) Collin-Asselineau, C.; Lederer, E.; Mercier, D.; Polonsky, J. *Bull. Soc. Chim. Fr.* **1950**, 720.

(8) (a) Ohloff, G. In *Olfaction and Taste*; van der Starre, H., Ed.; IRL Press: London-Washington, 1980. (b) Ohloff, G. In *Gustation and Olfaction*; Ohloff, G., Thomas, A. F., Eds.; Academic Press: London-New York, 1971. (c) Ohloff, G. In *Fragrance Chemistry*; Thiemer, E. T., Ed.; Academic Press: New York, 1982.

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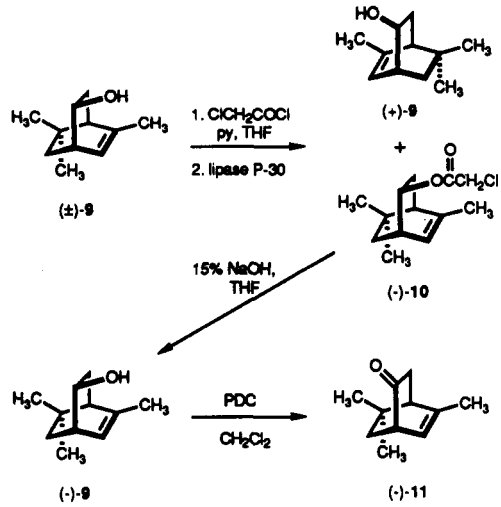
**Scheme I**

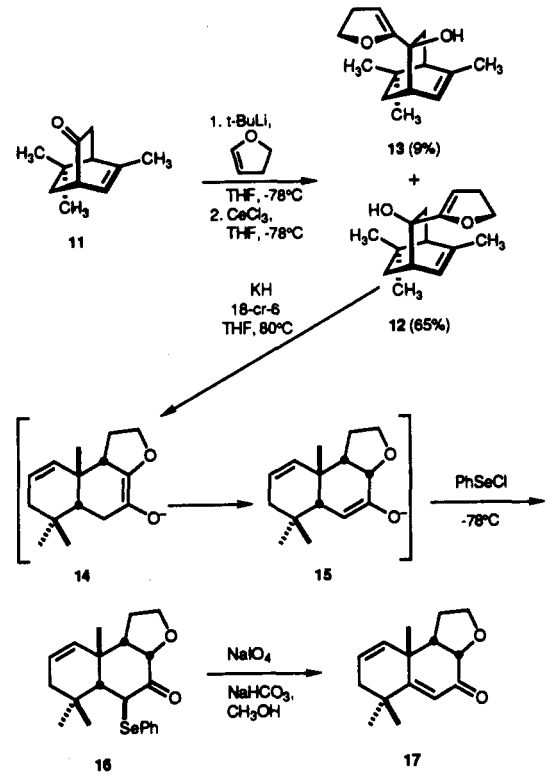



$\alpha$-metalated vinyl ether[11,12] would set the stage for operation of the [3,3] sigmatropic event that serves to elaborate the complete tricyclic framework.

## Results and Discussion

The first task in our exploration of the above plan centered on preparation of 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-trimethylcyclohexenone,[13] was esterified with chloroacetyl chloride and subjected to controlled enzymatic hydrolysis with lipase P-30[14] (Scheme I). When this process was allowed to proceed to approximately 60% completion and the unreacted ester was hydrolyzed, (−)-**9** of high optical purity was recovered with good overall efficiency (70%).[15] Definition of the level of enantiomeric excess in the levorotatory alcohol as 92% was achieved by examination of the $^1$H NMR spectra ($CDCl_3$, 25 °C) of samples of (+)-enriched **9** of varying optical purity in the presence of 25 mol % Eu(dcm)$_3$.[16] The "sense of nonequivalence"[17] of the carbinol proton for the (+)-($\delta$ 10.53; $\Delta\delta$ 6.65) and (−)-enantiomers ($\delta$ 9.90, $\Delta\delta$ 6.10) under these circumstances permitted the construction of a plot of % ee versus $[\alpha]_D^{25}$ whose slope was 1.12 ($r$ = 0.99). From this stage onward, additional % ee determinations were readily made by extrapolation or interpolation.

**Scheme II**




When (+)-**9** of 83% ee was subjected to pyridinium dichromate oxidation, the dextrorotatory ketone **11** so produced exhibited $[\alpha]_D^{25}$ +408° ($c$ 0.22, $CHCl_3$) and a large Cotton effect with the following circular dichroic characteristics: $[\psi]_{288}$ 2004°, $[\theta]_{max}$ +3291°.[18] Since our goals required the elaboration of (1*S*,2*S*)-**9** and (1*S*)-**11**, effort was expended in maximizing the efficiency of production and stereochemical purity of (−)-**10**, (−)-**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 vinyllithium reagents, 5-lithio-2,3-dihydrofuran[11a] was first converted to its dichlorocerate by reaction with anhydrous $CeCl_3$[19] 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,[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

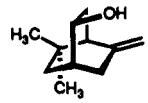
(11) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187. (b) Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959. (c) Kocienski, P.; Yeates, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1879. (d) Smith, A. B., III.; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (e) Cox, P.; Mahon, M. F.; Molloy, K. C.; Lister, S.; Gallagher, T. *Tetrahedron Lett.* **1988**, *29*, 1993.

(12) For optically active systems, see: (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Chem. Soc., Chem. Commun.* **1986**, 925. (b) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926. (c) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinaÿ, P. *Tetrahedron Lett.* **1986**, *27*, 6201. (d) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (e) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.

(13) Paquette, L. A.; Maleczka, R. E., Jr.; Qiu, F. *J. Org. Chem.* **1991**, *53*, 2455.

(14) For example: Schwartz, A.; Maden, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.

(15) A minor product isolated in 1.4% yield following the lipase hydrolysis exhibits spectral features suggestive that it possesses structure i.



i

We are unaware of any other double-bond migration having been observed under such reaction conditions.

(16) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

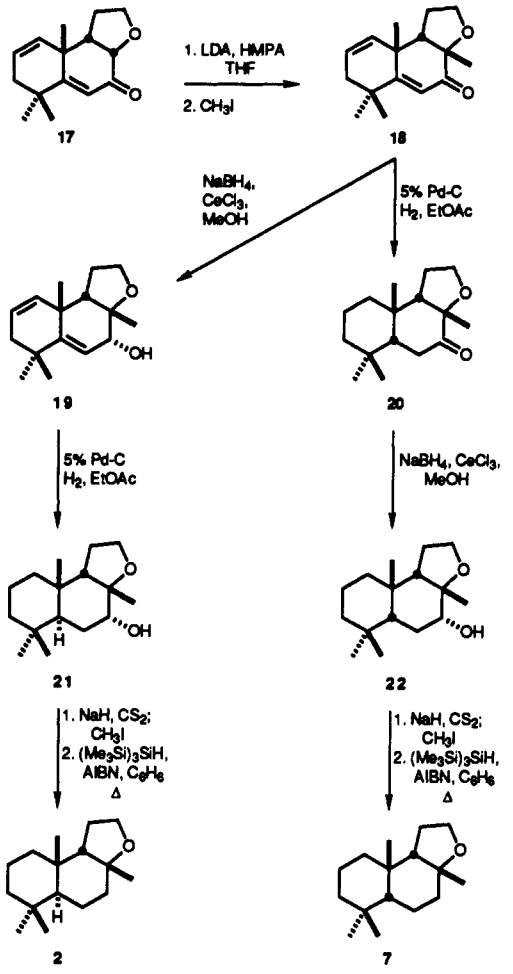
(17) Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150.

(18) Crabbé, P. In *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965; p 232.

(19) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organometal. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahdron Lett.* **1985**, *26*, 4763.

(20) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

**Scheme III**

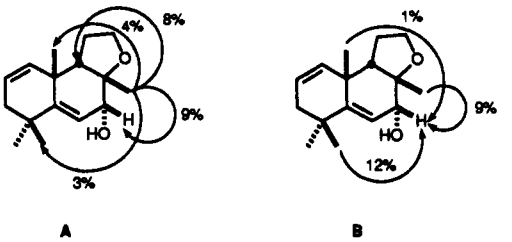



feature has the important consequence of setting the three ring-fusion sites in an all-cis relationship, the resultant enolate anion **14** is seen to embrace electronic features that cause it to be unstable relative to 1,3-prototropic shift.[12,21] As a result, **14** isomerizes to **15** subsequent 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 ether 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 β-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 α-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,




A B

several attempts were made to reduce **19** under $H_2$ in the presence of [Rh(norbornadiene)(DIPHOS-4)]$BF_4$[24] and Ir(cod)py$(PCy)_3PF_6$.[25] With both catalyst systems, reduction stopped after saturation of the disubstituted double bond. We assume that the high level of steric congestion in the vicinity of the allylic alcohol functionality impedes its reduction.[26] Consequently, recourse was made to 5% palladium on carbon. In the presence of 30 mol % of this more classical catalyst, **19** was smoothly transformed into **21** when stirred in ethyl acetate at atmospheric pressure for 48 h. The key stereochemical assignment was ultimately confirmed by the eventual conversion of **21** into **2**.

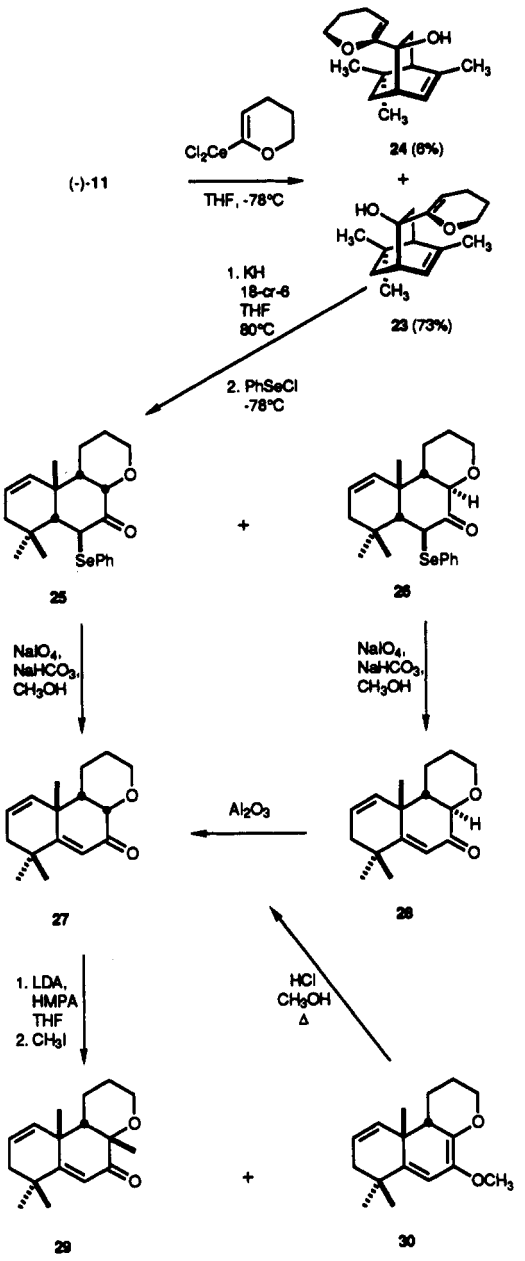
Quite remarkable is the totality of the stereochemical cross-over that operates when ketone **18** is reduced in a completely analogous manner. In this instance, only the all-cis tetrahydro derivative **20** was produced. α-Alcohol **22**, obtained cleanly by subsequent exposure of **20** to the action of sodium borohydride, was spectroscopically distinctive when compared to **21**.

With both **21** and **22** thus available, attention was next turned to reductive cleavage of their C–O bonds under free-radical conditions in order to preclude fragmentation.[27] To this end, the corresponding xanthates were prepared and heated with $(Me_3Si)_3SiH$[28] and AIBN in benzene. The colorless oily **2** so obtained, $[\alpha]_D^{25}$–6.0° (*c* 0.98, $CHCl_3$),[29] exhibited $^1H$ and $^{13}C$ NMR spectra identical with those kindly supplied by Dr. Ohloff. A characteristic feature of the 300-MHz $^1H$ spectrum of (–)-9-epi-Ambrox (**2**) is the set of four methyl singlets at δ 1.35, 1.07, 0.77, and 0.75 (in $CDCl_3$). The same alkyl groups in all-cis tricyclic ether **7**, which was produced analogously from **22**, appear at δ 1.11, 1.08, 1.07, and 0.92.

The synthesis of **6** and **8** was conceptually analogous. The addition of dihydropyranylcerium dichloride to (–)-**11** and subsequent anionic oxy-Cope rearrangement of **23** proceeded well. In contrast to the previously observed unilateral conversion of enolate **14** to **15**, the conformationally more flexible anion generated here was protonated from both possible directions to deliver **25** and **26** in approximately equal amounts after phenylselenenylation (Scheme IV). These epimers were separated chromatographically and individually subjected to oxidative elimination. With **27** and **28** in hand, stereochemical assignments could be advanced with confidence since **28** exhibits a strong axial–axial coupling ($J$ = 11.3 Hz) absent in **27** that is consistent with trans B/C geometry.[30] Usefully,

(21) No information is available regarding whether the proton transfer occurs intra- or intermolecularly or via admixture of these two pathways.
(22) No α-methyl product was isolated.
(23) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(24) (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (b) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.
(25) (a) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organometal. Chem.* **1979**, *168*, 183. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (c) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (d) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.
(26) This phenomenon has been encountered previously: Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589.
(27) Paquette, L. A.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5054 and relevant references cited therein.
(28) (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641. (b) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681.
(29) Lit.[5a] $[\alpha]_D^{25}$ –6.1° (*c* 1.0, $CHCl_3$).

**Scheme IV**

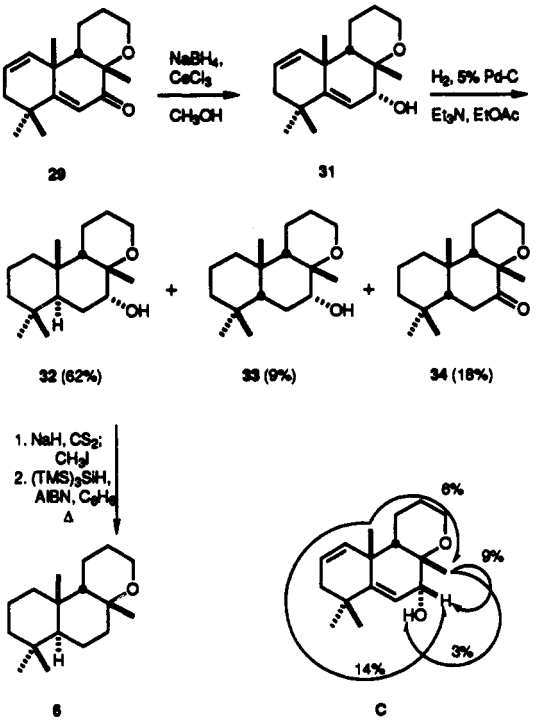



28 was found to undergo extensive isomerization to 27 on basic alumina.[31]

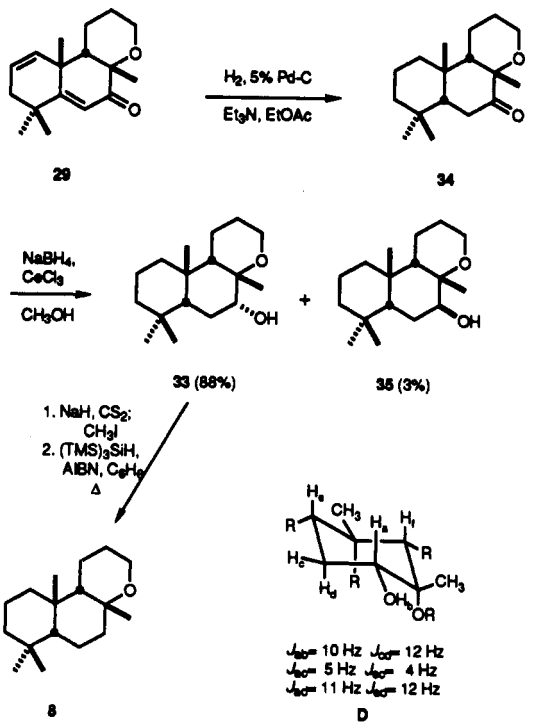
The requisite angular methylation of 27 was promoted by LDA in THF containing HMPA. These conditions were particularly effective in providing substantial levels of C-alkylation (77% of 29) relative to the O-alkylation option (4% of 30). Enol ether 30 was conveniently recycled via acid hydrolysis. Similar 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 conditions[23] gave rise to 31. Decoupling, 2D, and NOE experiments performed on 31 confirmed the stereochemical configurations of the carbon atoms carrying the adjacent $CH_3$ and OH groups (see C). The hydrogenation of 31 initially proved troublesome. Experiments conducted under 1 atm of $H_2$ were found to

**Scheme V**




**Scheme VI**




give only cis ketone 34 over the course of a 48-h reaction period. Such 1,3-hydrogen transpositions are precedented.[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 triethylamine[33] (Scheme V). These conditions promoted conversion chiefly to 32 (62%), with coformation of 33 (8%) and 34 (18%). Further im-

(30) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981; p 235.

(31) Corey, E.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5733.

(32) (a) Krause, M. *Coll. Czech. Chem. Commun.* **1972**, *37*, 460. (b) Sasson, Y.; Rempel, G. L. *Tetrahedron Lett.* **1974**, 4133. (c) Felföldi, K.; Bartók, M. *J. Organometal. Chem.* **1985**, *297*, C37. (d) Yanovshaya, L. A.; Shakhidaytov, K. *Russ. Chem. Rev.* **1970**, *39*, 859.

(33) Augustine, R. L.; Migliorni, D. C.; Foscante, R. E.; Sodano, C. S.; Sisbarro, M. J. *J. Org. Chem.* **1969**, *34*, 1075.

provement in this process was not sought.

The synthesis of (+)-9-epiambraoxide (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.[4c]

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 hydroxyl 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 $^{13}C$ NMR spectra at 75 or 20 MHz as indicated. Mass spectra were recorded on a Kratos MS-30 instrument by Mr. Dick Weisenberger 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.

**Esterification of (±)-9.** Chloroacetyl chloride (834 mg, 7.39 mmol) was added dropwise to a cold (0 °C), magnetically stirred solution of (±)-9[13] (409 mg, 2.46 mmol) and pyridine (2 mL) in anhydrous THF (4 mL). After 5 min, the mixture was diluted with ether and washed with 1 N HCl (2 × 5 mL) and saturated copper(II) sulfate solution (2 × 5 mL). The separated organic phase was dried and evaporated, and the residue was subjected to silica gel chromatography (elution with 5% ethyl acetate in petroleum ether). There was isolated 574 mg (96%) of the chloroacetate as a faintly yellow oil: IR (neat, $cm^{-1}$) 1746; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.62 (d, $J$ = 5.8 Hz, 1 H), 4.96 (dt, $J$ = 8.4, 3.3 Hz, 1 H), 3.98 (s, 2 H), 2.62 (m, 1 H), 2.38 (m, 1 H), 1.84 (d, $J$ = 1.6 Hz, 3 H), 1.78 (m, 1 H), 1.25 (dd, $J$ = 13.1, 2.2 Hz, 1 H), 1.13 (dd, $J$ = 13.1, 3.8 Hz, 1 H), 1.06 (m, 1 H), 1.01 (s, 3 H), 0.83 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 166.9, 144.8, 119.8, 75.4, 47.3, 41.0, 39.0, 35.9, 31.9, 31.0, 30.8, 29.0, 21.7; MS $m/z$ ($M^+$) calcd 242.1074, obsd 242.1073. Anal. Calcd for $C_{13}H_{19}ClO_2$: C, 64.32; H, 7.89. Found: C, 64.56; H, 8.02.

**(+)-(1*R*,2*R*,4*S*)-5,8,8-Trimethylbicyclo[2.2.2]oct-5-en-2-ol (9).** The pH of a rapidly stirred mixture of the chloroacetate ester (4.07 g, 16.76 mmol), water (50 mL), and phosphate buffer (pH 7.0, 10 mL) was brought to 7.0 by the addition of aqueous 1 N NaOH. Lipase P-30 (from *Pseudomonas fluorescens*, 250 mg) was introduced, and the pH was maintained at 7.0 as hydrolysis proceeded by controlled addition of 0.6 equiv of 0.1 N NaOH via a syringe pump interfaced with a pH controller. The reaction mixture was stirred for 5 days with an additional 250-mg portion of the lipase being added at the beginning of each day. When all of the NaOH had been consumed, the reaction mixture was extracted with ether (3 × 100 mL) and the combined ethereal phases were passed through Celite, dried, and concentrated. Product separation was achieved by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether). There was isolated 1.2 g (74%) of (−)-chloroacetate 10, $[\alpha]_D^{25}$ −62.1° (*c* 7.71, $CHCl_3$), subsequently shown to be 92% enantiomerically enriched, 1.07 g (64%) of (+)-9 as a white solid, $[\alpha]_D^{25}$ + 76.4° (*c* 3.12, $CHCl_3$), subsequently shown to be 85% enantiomerically enriched, and 40 mg (1.4%) of i (see ref 15), a white solid, mp 86–87.5 °C (from aqueous methanol), $[\alpha]_D^{25}$ −2.7° (*c* 2.35, $CHCl_3$). The spectra for (+)-9 were identical with those previously reported for the racemic alcohol.[13]

For i: IR ($CHCl_3$, $cm^{-1}$) 3640–3540, 3520–3320, 1645; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.71 (m, 2 H), 3.96 (m, 1 H), 2.64 (dt, $J$ = 17.3, 2.5 Hz, 1 H), 2.45 (td, $J$ = 13.5, 3.2 Hz, 1 H), 2.03 (br d, $J$ = 17.3 Hz, 1 H), 1.79 (q, $J$ = 3.1 Hz, 1 H), 1.74 (t, $J$ = 2.9 Hz, 1 H), 1.36–1.17 (m, 4 H), 0.96 (s, 3 H), 0.92 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 149.4, 106.9, 68.3, 48.0, 40.1, 35.5, 35.0, 31.5, 29.9, 29.6, 26.9; MS $m/z$ ($M^+ - H_2O$) calcd 148.1252, obsd 148.1198. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.34; H, 10.89.

**(−)-(1*S*,2*S*,4*R*)-5,8,8-Trimethylbicyclo[2.2.2]oct-5-en-2-ol (9).** A magnetically stirred solution of (−)-10 (302 mg, 1.24 mmol) in THF (5 mL) was treated with 15% NaOH solution (1 mL, 3.7 mmol), heated at reflux for 4 h, cooled, and diluted with ether (50 mL). The ether phase was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give (−)-9 (195 mg, 95%) as a white solid, mp 59–60 °C (from aqueous methanol); $[\alpha]_D^{25}$ −84.5° (*c* 2.27, $CHCl_3$). The spectral properties of this alcohol are identical with those reported previously for the racemic alcohol.[13]

**(−)-(1*S*,4*R*)-5,8,8-Trimethylbicyclo[2.2.2]oct-5-en-2-one (11).** A solution of (−)-9 (3.41 g, 21 mmol) in dichloromethane (25 mL) was added to a rapidly stirred mixture of pyridinium dichromate (11.66 g, 31 mmol) in the same solvent (75 mL) at room temperature. After 10 h, the reaction mixture was eluted through a short pad of silica gel and concentrated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 2.43 g (70%) of (−)-11 as a colorless oil: IR (neat, $cm^{-1}$) 1720; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (20 MHz, $CDCl_3$) 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; $[\alpha]_D^{25}$ −454° (*c* 1.31, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.24; H, 9.77.

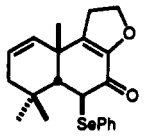
**Addition of 5-Lithio-2,3-dihydrofuran to (−)-11.** To a cold (−78 °C), magnetically stirred solution of 2,3-dihydrofuran (0.687 mL, 9.13 mmol) in anhydrous THF (6 mL) was added *tert*-butyllithium (5.4 mL of 1.7 M in hexanes, 9.18 mmol). Following completion of the addition, the reaction mixture was brought to 0 °C for 30 min, returned to −78 °C, and added via cannula to a cold (−78 °C), stirred suspension of anhydrous $CeCl_3$ in THF (35 mL). (The original $CeCl_3 \cdot 7H_2O$ (3.4 g, 9.13 mmol) was dried by heating at 130 °C (0.1 Torr) for 4 h and then stirred in the THF 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 $NH_4Cl$ 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 278 mg (65%) of 12 and 40 mg (9%) of 13.

For 12: faint yellow oil; IR (neat, $cm^{-1}$) 3520–3310, 1650; $^1H$ NMR (300 MHz, $C_6D_6$) δ 5.69 (d, $J$ = 6.5 Hz, 1 H), 4.44 (t, $J$ = 2.4 Hz, 1 H), 3.93 (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); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 163.9, 143.5, 123.7, 93.8, 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; $[\alpha]_D^{25}$ −93.9° (*c* 3.15, toluene). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.72; H, 9.46.

For 13: faint yellow oil; IR (neat, $cm^{-1}$) 3610–3250, 1654; $^1H$ NMR (300 MHz, $C_6D_6$) δ 5.70 (m, 1 H), 4.83 (t, $J$ = 2.5 Hz, 1 H), 4.04 (t, $J$ = 9.3 Hz, 2 H), 2.83 (m, 1 H), 2.40–2.09 (series of m, 4 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); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 162.1, 144.4, 122.1, 96.1, 73.6, 70.0, 48.7, 42.2, 36.8, 36.2, 32.8, 31.6, 30.3, 28.9, 22.2; MS $m/z$ ($M^+$) calcd 234.1620,

obsd 234.1673; $[\alpha]_D^{25}$ -91.6° (c 0.59, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.63; H, 9.50.

**(+)-(3a*S*,5*S*,5a*R*,9a*R*,9b*S*)-1,2,5,5a,6,7,9a,9b-Octahydro-6,6,9a-trimethyl-5-(phenylselenyl)naphtho[2,1-*b*]furan-4-(3a*H*)-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 18-crown-6 (705 mg, 2.67 mmol) in THF (10 mL) was introduced. The contents were heated at 80 °C for 3 h, cooled to -78 °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 $NH_4Cl$ 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 135 mg (65%) of **16** and 16 mg (8%) of an overoxidized byproduct considered to be ii.

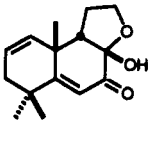



ii

For **16**: yellowish oil; IR ($CHCl_3$, $cm^{-1}$) 1710; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2 H), 7.28 (m, 3 H), 5.60 (m, 1 H), 5.43 (dt, *J* = 10.6, 1.2 Hz, 1 H), 4.96 (d, *J* = 7.9 Hz, 1 H), 4.05 (td, *J* = 8.6, 4.0 Hz, 1 H), 3.81 (d, *J* = 1.3 Hz, 1 H), 3.13 (m, 1 H), 2.26–2.08 (series of m, 2 H), 2.02–1.89 (series of m, 3 H), 1.62 (ddt, *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); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 206.0, 134.2 (2 C), 129.4 (2 C), 128.8, 128.7, 128.1, 127.7, 79.2, 67.4, 58.7, 50.2, 47.3, 38.8, 35.5, 34.6, 30.9, 28.7, 27.6, 27.3; MS *m/z* ($M^+ - SeC_6H_5$) calcd 233.1541, obsd 233.1504; $[\alpha]_D^{25}$ +21.8° (c 7.77, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.78; H, 6.73. Found: C, 64.35; H, 6.76.

For **ii**: yellowish oil; IR ($CHCl_3$, $cm^{-1}$) 1663; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 2 H), 7.35–7.24 (m, 3 H), 5.66 (ddd, *J* = 10.0, 6.2, 1.9 Hz, 1 H), 5.49 (dd, *J* = 10.1, 2.8 Hz, 1 H), 4.43 (t, *J* = 9.4 Hz, 2 H), 4.20 (s, 1 H), 2.87 (t, *J* = 9.6 Hz, 2 H), 2.43 (s, 1 H), 2.01 (d, *J* = 17.4 Hz, 1 H), 1.72 (dd, *J* = 17.3, 6.2 Hz, 1 H), 1.53 (s, 3 H), 1.02 (s, 3 H), 0.71 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 185.9, 146.0, 136.9, 135.3, 131.3, 131.5, 130.8, 129.2, 129.2, 128.7, 124.6, 69.2, 58.8, 47.8, 41.0, 37.5, 34.8, 30.8, 30.5, 29.5, 22.3; MS *m/z* ($M^+$) calcd 388.0942, obsd 388.0984.

**(-)-(3a*S*,9a*R*,9b*S*)-1,2,6,7,9a,9b-Hexahydro-6,6,9a-trimethylnaphtho[2,1-*b*]furan-4(3a*H*)-one (17).** A magnetically stirred solution of **16** (158.9 mg, 0.407 mmol) in methanol (10 mL) and water (2 mL) was treated with sodium bicarbonate (172 mg, 2.05 mmol) and sodium periodate (435 mg, 2.03 mmol). A precipitate formed immediately. After 15 min, the reaction mixture was diluted with ether (50 mL) and the separated organic phase was washed with brine, dried, and evaporated. The residue was subjected to silica gel chromatography (elution with 50% ether in petroleum ether) to give 84 mg (89%) of **17** and 5 mg (5%) of iii.




iii

For **17**: faintly yellow oil; IR ($CHCl_3$, $cm^{-1}$) 1665, 1608; $^1H$ NMR (300 MHz, $CDCl_3$) 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, 1 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 198.2, 174.0, 132.6, 124.0, 121.4, 78.1, 68.0, 51.9, 40.6, 39.1, 36.5, 30.9, 28.6 (2C), 28.5; MS *m/z* ($M^+$) calcd 232.1448, obsd 232.1506; $[\alpha]_D^{25}$ -95.1° (c 2.99, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.35; H, 8.78.

For **iii**: yellowish solid, mp 130–134 °C (from preparative GC); IR ($CHCl_3$, $cm^{-1}$) 1663; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) 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; $[\alpha]_D^{25}$ -42.6° (c 0.18, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.98; H, 7.95.

**(-)-(3a*S*,9a*R*,9b*S*)-1,2,6,7,9a,9b-Hexahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-4(3a*H*)-one (18).** To a cold (-78 °C), magnetically stirred solution of LDA (from 12.4 μL (0.089 mmol) of diisopropylamine and 0.06 mL (0.089 mmol) of 1.55 M *n*-butyllithium) in anhydous 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 $NH_4Cl$ 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 8.6 mg (78%) of **18** as a yellowish solid, mp 92–94 °C (from preparative GC): IR ($CHCl_3$, $cm^{-1}$) 1662; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 198.4, 173.2, 132.9, 123.4, 121.1, 82.3, 66.2, 56.9, 40.7, 38.9, 36.1, 32.1, 31.1, 28.7, 28.5, 24.1; MS *m/z* ($M^+$) calcd 246.1620, obsd 246.1643; $[\alpha]_D^{25}$ -70.3° (c 1.66, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.88; H, 9.01.

**(-)-(3a*S*,4*R*,9a*R*,9b*S*)-1,2,3a,4,6,7,9a,9b-Octahydro-3a,6,6,9a-tetramethylnaphtho-[2,1-*b*]furan-4-ol (19).** Enone **18** (62.1 mg, 0.252 mmol) was dissolved in a methanol solution 0.4 M in $CeCl_3$ (3 mL) and treated with sodium borohydride (19 mg, 0.5 mmol). The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NH_4Cl$ solution, and extracted with ether. The combined organic phases were dried and evaporated to leave a residue that was purified by silica gel chromatography (elution with 25% ether in petroleum ether). There was isolated 50.9 mg (81%) of **19** as a white solid, mp 85–86 °C (from petroleum ether/ether): IR ($CHCl_3$, $cm^{-1}$) 3680–3380; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 1 H), 5.59 (d, *J* = 1.1 Hz, 1 H), 5.35 (m, 1 H), 4.02 (dd, *J* = 10.0, 1.6 Hz, 1 H), 3.61 (m, 1 H), 3.08 (d, *J* = 10.0 Hz, 1 H), 1.97–1.82 (series of m, 4 H), 1.42 (s, 3 H), 1.26 (m, 1 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 3 H) (OH not observed); $^{13}C$ NMR (75 MHz, $CHCl_3$) δ 148.1, 134.4, 123.8, 123.6, 83.9, 71.4, 65.8, 56.6, 40.0, 38.9, 34.2, 33.7, 29.3, 28.5, 27.5, 24.6; MS *m/z* ($M^+$) calcd 248.1776, obsd 248.1804; $[\alpha]_D^{25}$ -122.8° (c 1.23, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.23; H, 9.80.

**(-)-(3a*S*,5a*R*,9a*S*,9b*S*)-Decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-4(3a*H*)-one (20).** A solution of **18** (40.2 mg, 0.163 mmol) in ethyl acetate (4 mL) containing 50 mg of 5% palladium on charcoal was stirred under a hydrogen atmosphere at ambient conditions for 12 h. The mixture was filtered through Celite and evaporated. Chromatography of the residue over silica gel (elution with 50% ether in petroleum ether) gave 35.6 mg (87%) of a clear oil comprised of a 5:1 mixture of **20** and its 5a-epimer: IR ($CHCl_3$, $cm^{-1}$) 1714; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.76 (td, *J* = 7.0, 2.2 Hz, 2 H), 2.46 (dd, *J* = 9.2, 2.9 Hz, 2 H), 2.21 (m, 1 H), 1.98 (m, 1 H), 1.85 (m, 2 H), 1.52–1.42 (series of m, 6 H), 1.40 (s, 3 H), 1.21 (s, 3 H), 1.16 (s, 3 H), 0.87 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 213.9, 84.2, 66.5, 60.2, 50.4, 38.6, 37.7, 34.6, 32.7, 31.3, 30.1, 29.4, 28.4, 26.5, 25.9, 18.6; MS *m/z* ($M^+$) calcd 250.1933, obsd 250.1956; $[\alpha]_D^{25}$ -17.3° (c 0.44, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.34; H, 10.42.

**(-)-(3a*S*,4*R*,5a*S*,9a*S*,9b*S*)-Decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-4-ol (21).** A solution of **19** (114.2 mg, 0.460 mmol) in ethyl acetate (5 mL) containing 300 mg of 5% palladium on charcoal was stirred under hydrogen at atmospheric pressure for 48 h. Workup in the predescribed manner afforded 90.6 mg (78%) of **21** as a white solid: mp 111.5–113.5

°C (from preparative GC); IR ($CHCl_3$, $cm^{-1}$) 3700–3040; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.00 (t, $J$ = 8.2 Hz, 1 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); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) δ 81.9, 74.0, 67.5, 59.4, 42.3, 38.9, 38.2, 35.4, 33.2, 32.4, 30.6, 28.0, 26.0, 22.7, 21.9, 18.5; MS $m/z$ ($M^+$) calcd 252.2089, obsd 252.2122; $[\alpha]_D^{25}$ −15.9° ($c$ 0.82, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.26; H, 11.40.

**(−)-9-Epiambrox (2).** To a cold (0 °C), magnetically stirred solution of **21** (66.7 mg, 0.264 mmol) in $CS_2$ (3 mL) was added sodium hydride (24.8 mg, 0.644 mmol) as a 60% dispersion in oil. The mixture was stirred for 20 min prior to the addition of methyl iodide (233 mg, 1.65 mmol), warmed to 25 °C for 16 h, and recooled to 0 °C prior to quenching with saturated aqueous $NH_4Cl$ solution (5 mL). The product was extracted into ether, and the combined ether extracts were dried and evaporated. The residue was purified by silica gel chromatography (elution with 25% ether in petroleum ether) to furnish 78.3 mg (87%) of yellow, oily xanthate: IR ($CHCl_3$, $cm^{-1}$) 1710; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1 H), 3.90 (td, $J$ = 8.6, 1.5 Hz, 1 H), 3.70 (qd, $J$ = 8.7, 2.6 Hz, 1 H), 2.52 (s, 3 H), 2.26–2.07 (m, 1 H), 1.96–1.71 (m, 1 H), 1.68–1.52 (m, 4 H), 1.35 (s, 3 H), 1.30–1.10 (series of m, 6 H), 1.07 (s, 3 H), 0.77 (s, 3 H), 0.75 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 215.3, 86.4, 80.3, 67.1, 59.0, 42.1, 40.1, 38.5, 35.5, 33.2, 32.4, 27.3, 24.7, 22.6, 21.6, 19.0, 18.4, 14.1; MS $m/z$ ($M^+ - SCH_3$) calcd 295.1732, obsd 295.1774; $[\alpha]_D^{25}$ −57.9° ($c$ 2.03, $CHCl_3$).

A solution of the xanthate (59.7 mg, 0.174 mmol) and AIBN (5 mg) in anhydrous benzene (5 mL) was heated to reflux and treated with tris(trimethylsilyl)silane (100 μL, 0.336 mmol). After 3 h of heating, during which time the color had changed from yellow to colorless, the reaction mixture was diluted with ether and washed with 10% KF solution. The organic layer was dried and evaporated to leave a residue that was chromatographed (silica gel, elution with petroleum ether, then 50% ether in petroleum ether). There was isolated 36.5 mg (89%) of **2** as a colorless oil; IR ($CHCl_3$, $cm^{-1}$) 2940, 2872, 1458, 1382, 1129, 1098, 1047, 900, 715, 650; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.85 (td, $J$ = 11.7, 3.3 Hz, 1 H), 3.76 (q, $J$ = 8.0 Hz, 1 H), 2.03 (m, 1 H), 1.90 (m, 1 H), 1.66–1.52 (m, 5 H), 1.43–1.38 (m, 2 H), 1.37 (s, 3 H), 1.29–1.14 (m, 5 H), 1.10 (s, 3 H), 0.89 (s, 3 H), 0.82 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 80.8, 64.1, 59.0, 46.7, 42.3, 38.7, 36.0, 35.8, 33.6, 32.9, 28.9, 27.7, 22.8, 21.8, 20.4, 18.5; MS $m/z$ ($M^+$) calcd 236.2140, obsd 236.2152; $[\alpha]_D^{25}$ −6.0° ($c$ 1.0, $CHCl_3$) [lit.[5] $[\alpha]_D^{25}$ −6.1° ($c$ 1.0, $CHCl_3$)].

**(−)-(3a*S*,4*R*,5a*R*,9a*S*,9b*S*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-4-ol (22).** A 25.0-mg (0.10 mmol) sample of **20** was dissolved in 0.4 M methanolic $CeCl_3$ solution (1 mL) and treated at 0 °C with sodium borohydride (10 mg, 0.26 mmol). After 30 min of stirring, alcohol **22** (19.6 mg, 78%) was obtained as described above: colorless solid, mp 96–97 °C (from preparative GC); IR ($CHCl_3$, $cm^{-1}$) 3620–3440; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.78 (td, $J$ = 7.6, 1.9 Hz, 2 H), 3.49 (m, 1 H), 2.14 (m, 2 H), 1.94 (m, 1 H), 1.75 (m, 2 H), 1.69–1.50 (series of m, 3 H), 1.56 (s, 3 H), 1.43–1.30 (series of m, 3 H), 1.26 (s, 3 H), 1.24–1.09 (series of m, 2 H), 1.06 (s, 3 H), 0.94 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 82.6, 75.1, 65.1, 56.9, 51.3, 36.6, 34.6, 33.9, 31.0, 30.9, 30.4, 29.2, 29.0, 27.6, 24.4, 18.3; MS $m/z$ ($M^+$) calcd 252.2089, obsd 252.2099; $[\alpha]_D^{25}$ −10.1° ($c$ 1.02, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.06; H, 11.09.

**(−)-(3a*R*,5a*R*,9a*S*,9b*S*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan (7).** An 8.6-mg (0.034 mmol) sample of **22** was transformed into its xanthate (8.5 mg, 73%) in the predescribed manner. This yellow oil exhibited the following spectral properties: $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.72 (dd, $J$ = 11.8, 8.9 Hz, 1 H), 3.88 (m, 2 H), 2.59 (s, 3 H), 2.00–1.86 (series of m, 2 H), 1.59–1.29 (series of m, 6 H), 1.26–1.09 (series of m, 4 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 0.92 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 217.0, 87.5, 82.0, 65.9, 57.5, 51.5, 37.5, 34.6, 34.3, 33.0, 30.3, 28.8, 26.8 (2C), 24.0, 23.1, 19.1, 19.0; MS $m/z$ ($M^+ - C_2H_3OS_2$) calcd 235.3062, obsd 235.2032; $[\alpha]_D^{25}$ −30.0° ($c$ 0.65, $CHCl_3$).

The above xanthate (23.2 mg, 0.068 mmol) was reduced according to the protocol detailed above to give 14.8 mg (92%) of **7** as a colorless oil: IR ($CHCl_3$, $cm^{-1}$) 2980, 2937, 2870, 1710, 1490, 1448, 1385, 1365, 1330, 1120, 1080, 1049, 1030, 905, 847, 796; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.72 (m, 2 H), 2.09 (m, 1 H), 1.91 (m, 2 H), 1.76–1.32 (series of m, 9 H), 1.22–1.12 (m, 2 H), 1.11 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 0.92 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 80.9, 65.0, 55.1, 52.3, 36.8, 35.4, 34.7, 34.2, 31.8, 31.1, 30.3, 28.4, 28.1, 27.3, 19.8, 18.8; MS $m/z$ ($M^+$) calcd 236.2140, obsd 236.2110; $[\alpha]_D^{25}$ −22.1° ($c$ 0.293, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.61; H, 12.10.

**Addition of 6-Lithiodihydropyran to (−)-11.** To dihydropyran (714 mg, 8.49 mmol, freshly distilled from $CaH_2$) metalated with *tert*-butyllithium and treated with anhydrous $CeCl_3$ was added (−)-**11** (464 mg, 2.83 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 ($CDCl_3$, $cm^{-1}$) 3610–3200, 1663; $^1H$ NMR (300 MHz, $C_6D_6$) δ 5.78 (dt, $J$ = 6.5, 1.4 Hz, 1 H), 4.62 (t, $J$ = 3.8 Hz, 1 H), 3.74 (td, $J$ = 5.5, 1.7 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 (d, $J$ = 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); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 158.6, 143.0, 124.0, 94.9, 75.6, 66.2, 49.2, 41.6, 35.7, 34.9, 32.9, 32.2, 28.3, 22.5, 22.1, 20.4; MS $m/z$ ($M^+$) calcd 248.1776, obsd 248.1760; $[\alpha]_D^{25}$ −83.8° ($c$ 1.09, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.03; H, 9.76.

For **24**: pale yellow oil; IR (neat, $cm^{-1}$) 3605–3160, 1661; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.74 (dt, $J$ = 6.4, 1.6 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 (d, $J$ = 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 155.3, 145.7, 121.4, 97.2, 76.5, 66.2, 48.5, 40.9, 36.3, 34.3, 32.5, 31.2, 28.6, 22.1, 22.0, 20.2; MS $m/z$ ($M^+$) calcd 248.1776, obsd 248.1773; $[\alpha]_D^{25}$ −54.8° ($c$ 0.84, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O$: C, 77.38; H, 9.74. Found: C, 77.37; H, 9.78.

**(4a*S*,6*S*,6a*R*,10a*R*,10b*S*)-2,3,6,6a,7,8,10a,10b-Octahydro-7,7,10a-trimethyl-6-(phenylselenyl)-1*H*-naphtho[2,1-*b*]pyran-5(4a*H*)-one (25) and Its Stereoisomer 26.** The anionic oxy-Cope rearrangement and in situ phenylselenenylation of **23** (489 mg, 1.97 mmol) was performed in the predescribed manner. The crude product was subjected to silica gel chromatography, elution first with petroleum ether and then 25% ether in petroleum ether, affording 291 mg (37%) of **25** and 336 mg (42%) of **26**.

For **25**: yellow oil; IR ($CHCl_3$, $cm^{-1}$) 1702; $^1H$ NMR (300 MHz, $CDCl_3$) 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), 1.86–1.72 (m, 2 H), 1.60–1.51 (m, 2 H), 1.49 (s, 3 H), 1.41–1.25 (series of m, 2 H), 1.11 (s, 3 H), 0.85 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 205.8, 135.2 (2 C), 134.1, 129.7, 129.2 (2 C), 128.8, 123.8, 72.8, 63.8, 58.2, 49.6, 47.6, 39.2, 39.1, 34.7, 33.7, 30.6, 26.9, 24.2, 24.1; MS $m/z$ ($M^+$) calcd 404.1254, obsd 404.1257; $[\alpha]_D^{25}$ +101.1° ($c$ 4.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{28}O_2Se$: C, 65.50; H, 7.00. Found: C, 65.85; H, 7.10.

For **26**: yellow solid, mp 91–96 °C; IR ($CHCl_3$, $cm^{-1}$) 1699; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2 H), 7.29 (m, 3 H), 5.68 (m, 1 H), 5.55 (d, $J$ = 10.3 Hz, 1 H), 4.10 (m, 1 H), 3.84 (s, 1 H), 3.40 (m, 1 H), 3.38 (dd, $J$ = 11.7, 1.0 Hz, 1 H), 2.26 (td, $J$ = 11.6, 3.6 Hz, 1 H), 2.13 (s, 1 H), 2.04 (m, 1 H), 1.79–1.67 (series of m, 3 H), 1.64–1.42 (series of m, 2 H), 1.26 (s, 3 H), 1.09 (s, 3 H), 1.01 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 202.4, 135.7 (2 C), 129.9, 129.2 (2 C), 128.9, 126.8, 78.4, 70.0, 56.4, 49.3, 44.9, 37.1, 35.6, 34.9, 30.7, 27.8, 27.3, 26.4, 23.6; MS $m/z$ ($M^+$) calcd 404.1254, obsd 404.1253; $[\alpha]_D^{25}$ −17.5° ($c$ 3.5, $CHCl_3$). Anal. Calcd for $C_{22}H_{28}O_2Se$: C: 65.50; H, 7.00. Found: C, 65.51; H, 7.27.

**(4a*S*,10a*R*,10b*S*)-2,3,7,8,10a,10b-Hexahydro-7,7,10a-trimethyl-1*H*-naphtho[2,1-*b*]pyran-5(4a*H*)-one (27).** Oxidative elimination of **25** (90.4 mg, 0.224 mmol) as before furnished 45.7 mg (83%) of **27** as a white solid, mp 70–74 °C: IR ($CHCl_3$, $cm^{-1}$) 1665, 1608; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 1 H), 5.74 (dt, $J$ = 9.8, 4.2 Hz, 1 H), 5.30 (d, $J$ = 10.0 Hz, 1 H), 4.67 (d, $J$ = 5.0 Hz, 1 H), 3.73 (m, 1 H), 3.36 (td, $J$ = 12.1, 2.7 Hz, 1 H), 2.11 (dt, $J$ = 12.6, 5.1 Hz, 1 H), 1.97 (m, 2 H), 1.74–1.50 (series of m, 3 H), 1.46 (s, 3 H), 1.21 (s, 3 H), 1.19–1.00 (m, 1 H), 1.15 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 198.2, 173.7, 132.4, 124.4, 122.3, 75.8, 63.1, 49.7, 42.9, 39.3, 36.4, 28.9, 28.1, 27.7, 25.5, 21.9; MS $m/z$ ($M^+$) calcd 246.1620, obsd 246.1629; $[\alpha]_D^{25}$ −3.6° ($c$ 0.5, $CHCl_3$). Anal.

Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.91; H, 9.16.

**(4a*R*,10a*R*,10b*S*)-2,3,7,8,10a,10b-Hexahydro-7,7,10a-trimethyl-1*H*-naphtho[2,1-*b*]pyran-5(4a*H*)-one (28).** Oxidative elimination of **26** (72.1 mg, 0.179 mmol) in the predescribed manner gave **28** (28.7 mg, 88%) as a white solid, mp 80–84 °C: IR ($CHCl_3$, $cm^{-1}$) 1681, 1604; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.90 (m, 1 H), 5.88 (s, 1 H), 5.79 (m, 1 H), 4.06 (dq, $J$ = 11.3, 2.0 Hz, 1 H), 3.64 (d, $J$ = 12.4 Hz, 1 H), 3.33 (m, 1 H), 2.23 (dq, $J$ = 17.2, 2.1 Hz, 1 H), 2.08–1.91 (series of m, 2 H), 1.72–1.50 (series of m, 4 H), 1.29 (s, 3 H), 1.27 (s, 3 H), 1.12 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 196.1, 172.8, 130.2, 128.1, 120.4, 77.9, 67.5, 45.6, 43.0, 42.2, 38.2, 32.5, 30.0, 27.3, 26.1, 24.9; MS $m/z$ ($M^+$) calcd 246.1620, obsd 246.1594; $[\alpha]_D^{25}$ +214.0° ($c$ 0.6, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.96; H, 9.08.

Epimerization of **28** to **27**. A solution of **28** (139 mg, 0.564 mmol) in ether was adsorbed onto a 3 × 5 cm column of basic alumina. After 3 h, the column was eluted with ether and the eluate was evaporated to give 116 mg (84%) of **27** and 8.3 mg (6%) of **28**.

**(4a*S*,10a*R*,10b*S*)-2,3,7,8,10a,10b-Hexahydro-4a,7,7,10-tetramethyl-1*H*-naphtho[2,1-*b*]pyran-5(4a*H*)-one (29).** Dienone **27** (121 mg, 0.491 mmol) was methylated in the same manner as **17**. Chromatography of the crude product on silica gel (elution with 10–50% ether in petroleum ether) afforded 98.4 mg (77%) of **29** and 5.1 mg (4%) of **30**.

For **29**: white solid, mp 84–86 °C; IR ($CHCl_3$, $cm^{-1}$) 1662, 1609; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.99 (s, 1 H), 5.64 (m, 1 H), 5.37 (d, $J$ = 10.0 Hz, 1 H), 3.74 (ddt, $J$ = 11.5, 4.6, 1.8 Hz, 1 H), 3.30 (td, $J$ = 12.1, 2.8 Hz, 1 H), 1.98 (m, 2 H), 1.90 (dt, $J$ = 14.0, 2.1 Hz, 1 H), 1.81 (dd, $J$ = 12.2, 4.2 Hz, 1 H), 1.61 (s, 3 H), 1.59–1.34 (series of m, 2 H), 1.52 (s, 3 H), 1.24 (s, 3 H), 1.18 (s, 3 H), 1.07 (dq, $J$ = 4.3, 0.9 Hz, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 200.9, 172.8, 134.4, 121.9, 121.8, 79.3, 63.6, 54.5, 43.6, 40.2, 36.7, 31.8, 29.4, 29.4, 28.3, 25.6, 24.7; MS $m/z$ ($M^+$) calcd 260.1776, obsd 260.1776; $[\alpha]_D^{25}$ +6.4° ($c$ 0.5, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.14; H, 9.37.

For **30**: pale yellow oil; IR ($CHCl_3$, $cm^{-1}$) 1668; $^1H$ NMR (300 MHz, $CDCl_3$ $\delta$ 5.71 (m, 1 H), 5.65 (d, $J$ = 0.8 Hz, 1 H), 5.30 (dd, $J$ = 9.9, 2.4 Hz, 1 H), 4.16 (dt, $J$ = 10.7, 3.2 Hz, 1 H), 3.73 (s, 3 H), 3.66 (td, $J$ = 10.9, 3.1 Hz, 1 H), 1.95–1.57 (series of m, 5 H), 1.41–1.24 (series of m, 2 H), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.14 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 145.4, 140.3, 136.5, 132.3, 124.4, 113.8, 72.5, 58.8, 49.5, 40.0, 39.7, 34.6, 29.0, 28.8, 26.8, 26.7, 25.5; MS $m/z$ ($M^+$) calcd 260.1776, obsd 260.1803; $[\alpha]_D^{25}$ −294.5° ($c$ 2.1, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.35; H, 9.33.

**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**.

**(4a*S*,5*R*,10a*R*,10b*S*)-2,3,4a,5,7,8,10a,10b-Octahydro-4a,7,7,10a-tetramethyl-1*H*-naphtho[2,1-*b*]pyran-5-ol (31).** Enone **29** (20.6 mg, 0.079 mmol) was reduced as described earlier for **18** to give after chromatography (silica gel, elution with 25% ether in petroleum ether) 16.6 mg (80%) of **31** and return 2.5 mg (12%) of unreacted **29**.

For **31**: colorless oil that solidified on storage at −10 °C; mp 41.5–43 °C: IR ($CHCl_3$, $cm^{-1}$) 3580–3380; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.70 (m, 1 H), 5.61 (d, $J$ = 0.8 Hz, 1 H), 5.29 (dd, $J$ = 10.0, 2.8 Hz, 1 H), 4.14 (dd, $J$ = 9.3, 1.8 Hz, 1 H), 3.78–3.58 (m, 2 H), 3.28 (d, $J$ = 9.4 Hz, 1 H), 1.90 (dt, $J$ = 16.4, 2.6 Hz, 1 H), 1.76 (dd, $J$ = 16.4, 6.1 Hz, 1 H), 1.71–1.59 (m, 3 H), 1.44 (s, 3 H), 1.37 (m, 1 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.08 (s, 3 H), 1.05 (m, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 148.4, 134.7, 123.6, 123.5, 76.3, 72.7, 58.7, 52.2, 40.8, 38.6, 34.4, 29.4, 28.7, 26.6, 26.4, 22.4, 22.0; MS $m/z$ ($M^+$) calcd 262.1933, obsd 262.1899; $[\alpha]_D^{25}$ −78.6° ($c$ 1.1, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.73; H, 9.89.

**(4a*S*,5*R*,6a*S*,10a*S*,10b*S*)-Dodecahydro-4a,7,7,10a-tetramethyl-1*H*-naphtho[2,1-*b*]pyran-5-ol (32).** A mixture of **31** (39 mg, 0.149 mmol) and 5% palladium on charcoal (250 mg) in ethyl acetate (20 mL) containing 1 drop of triethylamine was stirred under 20 psi of hydrogen for 16 h. The reaction mixture was filtered through Celite (subsequently washed with ethyl acetate), and the combined filtrates were evaporated. Chromatography of the residue on silica gel (elution with 10% ether in petroleum ether) gave **32** (24.5 mg, 62%), alcohol **33** (3.6 mg, 9%), and ketone **34** (7.1 mg, 18%).

For **32**: colorless oil; IR ($CHCl_3$, $cm^{-1}$) 3600–3460; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.73 (m, 1 H), 3.70 (m, 1 H), 3.65 (dq, $J$ = 11.4, 5.7 Hz, 1 H), 3.07 (br s, 1 H), 1.91 (m, 1 H), 1.80–1.38 (series of m, 8 H), 1.34 (s, 3 H), 1.28–1.10 (series of m, 5 H), 1.05 (d, $J$ = 0.5 Hz, 3 H), 0.90 (s, 3 H), 0.83 (s, 3 H); $^{13}C$ NMR (50 MHz, $C_6D_6$) $\delta$ 76.5, 74.8, 58.1, 52.8, 42.8, 40.2, 38.0, 36.8, 33.3, 33.1, 26.9, 26.8, 24.9, 24.5, 22.3, 19.3, 19.2; MS $m/z$ ($M^+$) calcd 266.2246, obsd 266.2273; $[\alpha]_D^{25}$ −6.2° ($c$ 0.4, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.82; H, 11.28.

For the spectral properties of **32** and **33**, see below.

**(+)-9-Epiambroxide (6).** Application of the xanthate preparation of **32** (12.6 mg, 0.047 mmol) afforded 15.1 mg (90%) of the ester as a clear oil after silica gel chromatography (elution with 5% ether in petroleum ether); IR ($CHCl_3$, $cm^{-1}$) 1442, 1382, 1207, 1150, 1110, 1062; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.86 (m, 1 H), 3.85 (m, 1 H), 3.67 (m, 1 H), 2.60 (s, 3 H), 1.97 (m, 1 H), 1.88–1.70 (series of m, 5 H), 1.65–1.41 (series of m, 4 H), 1.39 (s, 3 H), 1.32–1.15 (series of m, 4 H), 1.12 (s, 3 H), 0.84 (s, 3 H), 0.82 (s, 3 H); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 215.4, 88.8, 74.7, 62.8, 53.2, 42.7, 42.3, 37.4, 37.1, 33.2, 33.1, 28.0 (br), 25.9, 25.1, 24.9, 21.8, 21.5, 19.1, 18.9; MS $m/z$ ($M^+$) calcd 356.1844, obsd 356.1866; $[\alpha]_D^{25}$ −51.3° ($c$ 1.1, $CHCl_3$).

A sample of this material (11.5 mg, 0.032 mmol) was reduced in the predescribed manner to give 7.2 mg (90%) of **6** as a clear, colorless oil following chromatography (silica gel, elution with 5% ether in petroleum ether): IR ($CHCl_3$, $cm^{-1}$) 1460, 1388, 1204, 1090, 998, $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.58 (m, 2 H), 2.09 (td, $J$ = 12.2, 4.4 Hz, 1 H), 1.81 (m, 1 H), 1.70–1.41 (series of m, 8 H), 1.39 (s, 3 H), 1.37–1.18 (series of m, 4 H), 1.13 (m, 1 H), 1.12 (s, 3 H), 1.01 (m, 1 H), 0.87 (s, 3 H), 0.80 (s, 3 H); $^{13}C$ NMR (75 MHz, $C_6D_6$) $\delta$ 74.7, 59.7, 54.5, 46.8, 42.4, 38.0, 36.5, 33.2, 33.0, 31.8, 30.9, 26.7, 24.7, 21.8, 21.6, 20.8, 19.0; MS $m/z$ ($M^+$) calcd 250.2297, obsd 250.2301; $[\alpha]_D^{25}$ +2.5° ($c$ 0.3, $CCl_4$).

These data are entirely comparable to those reported by Kawanabe et al. for the racemic ether.[4c]

**(4a*S*,6a*R*,10a*S*,10b*S*)-Dodecahydro-4a,7,7,10-tetramethyl-1*H*-naphtho[2,1-*b*]pyran-5(4a*H*)-one (34).** Enone **29** (36.9 mg, 0.142 mmol) was hydrogenated in the manner described for **18**. After similar workup, 35.1 mg (94%) of **34** was recovered as a clear, colorless oil; IR ($CHCl_3$, $cm^{-1}$) 1712; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.71 (m, 1 H), 3.51 (m, 1 H), 2.48 (d, $J$ = 1.4 Hz, 1 H), 2.45 (s, 1 H), 1.95 (m, 1 H), 1.74–1.46 (series of m, 8 H), 1.47 (s, 3 H), 1.35–1.26 (m, 3 H), 1.31 (s, 3 H), 1.01 (s, 3 H), 0.88 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 213.7, 79.9, 62.0, 52.7, 48.2, 38.9, 38.0, 34.5, 33.7, 31.6, 31.4, 31.2, 30.2, 25.3, 25.1, 23.6, 18.3; MS $m/z$ ($M^+$) calcd 264.2089, obsd 264.2095; $[\alpha]_D^{25}$ +47.6° ($c$ 0.95, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 76.87; H, 10.69.

**Hydride Reduction of 34.** Reduction of **34** (42.9 mg, 0.162 mmol) with $NaBH_4$ and 0.4 M $CeCl_3$ in methanol as described above led after chromatography on silica gel to the isoilation of **33** (37.9 mg, 88%) and **35** (1.2 mg, 3%).

For **33**: colorless oil; IR ($CHCl_3$, $cm^{-1}$) 3590–3490; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.78–3.71 (m, 2 H), 3.24 (m, 1 H), 2.38 (d, $J$ = 10.3 Hz, 1 H), 1.96–1.69 (series of m, 6 H), 1.61–1.46 (m, 3 H), 1.39 (s, 3 H), 1.37–1.26 (m, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.01 (m, 1 H), 0.93 (s, 3 H), 0.88 (m, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 78.1, 74.5, 59.9, 51.5, 47.2, 39.8, 34.6, 34.1, 33.9, 30.7, 30.6, 29.1, 28.4, 22.6, 21.6, 19.4, 18.4; MS $m/z$ ($M^+$) calcd 266.2246, obsd 266.2238; $[\alpha]_D^{25}$ −6.2° ($c$ 1.6, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.56; H, 11.45.

For **35**: white solid, mp 77–78 °C; IR ($CHCl_3$, $cm^{-1}$) 3600–3450; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.88 (td, $J$ = 11.6, 4.4 Hz, 1 H), 3.68 (m, 1 H), 3.57 (m, 1 H), 2.16–1.73 (series of m, 5 H), 1.71–1.57 (m, 2 H), 1.37 (m, 1 H), 1.33 (s, 3 H), 1.32–1.24 (m, 7 H), 1.16 (s, 3 H), 1.12 (s, 3 H), 0.87 (s, 3 H); MS $m/z$ ($M^+$) calcd 266.2246, obsd 266.2233.

**(4a*R*,6a*R*,10a*S*,10b*S*)-Dodecahydro-4a,7,7,10a-tetramethyl-1*H*-naphtho[2,1-*b*]pyran (8).** The xanthate of **33** (18.2 mg, 0.068 mmol) was prepared as before and obtained as a pale yellow solid (20.1 mg, 83%), mp 113.5–114.5 °C, after chromatography: IR ($CHCl_3$, $cm^{-1}$) 1459, 1378, 1263, 1235, 1094, 1059;

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.44 (dd, $J$ = 11.8, 4.2 Hz, 1 H), 3.80 (m, 2 H), 2.57 (s, 3 H), 2.02-1.83 (series of m, 7 H), 1.51 (m, 2 H), 1.40-1.33 (m, 2 H), 1.31 (s, 3 H), 1.29-1.18 (m, 2 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.09 (m, 1 H), 0.90 (s, 3 H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 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, 24.1, 21.8, 21.0, 19.4, 18.9, 18.2; MS $m/z$ ($M^+$) calcd 356.1844, obsd 356.1797; $[\alpha]_D^{25}$ -15.5° ($c$ 0.3, $CHCl_3$).

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 ($CHCl_3$, cm$^{-1}$) 1441, 1379, 1348, 1102, 905; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.84 (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, $J$ = 5.6 Hz, 1 H), 0.90 (s, 3 H), 0.89 (m, 1 H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 72.3, 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, 19.6, 18.7; MS $m/z$ ($M^+$) calcd 250.2297, obsd 250.2250; $[\alpha]_D^{25}$ -5.6° ($c$ 0.8, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.07. Found: C, 81.21; H, 12.00.

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# Studies Directed at the Synthesis of Optically Active Pretazettine via Intramolecular Nitrone/Alkene Cycloaddition Reactions[1]

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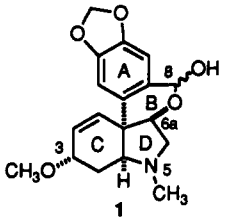
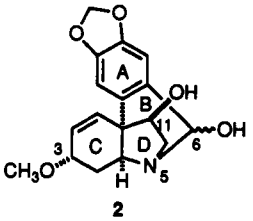
A protocol for the synthesis of optically active pretazettine which focuses on both the control of relative stereochemistry between the angular aryl and C6a hydroxyl groups and absolute stereochemistry has been developed and executed. The synthesis of the 1,3-dithiane ketal of (*Z*)-ethyl 3-(1,3-benzodioxol-5-yl)-5,7-dioxo-2-heptanoate is described. Treatment of this alkene aldehyde with *N*-($\alpha$-methylbenzyl)hydroxylamine afforded a nitrone, which underwent intramolecular 1,3-dipolar cycloaddition to afford the two diastereomeric isoxazolidine cycloadducts in a 16:1 ratio. The sense of chirality transfer was determined by a single-crystal X-ray analysis of the major isomer.

## Introduction

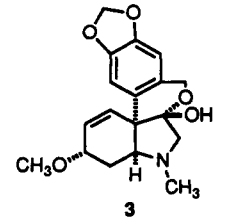
Pretazettine (1), a member of the crinine class of Amaryllidaceae alkaloids, was first characterized in the early 1960s.[2,3] Interest in pretazettine stems from its promising antitumor[4] and antiviral[5] activity. Any synthetic work directed at pretazettine must take into account the complex relationships which exist among pretazettine (1), haemanthidine (2), and tazettine (3), which have been elegantly detailed by Wildman,[3] as well as 6a-epipretazettine (4).[6] In particular, Wildman showed that haemanthidine methiodide 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.



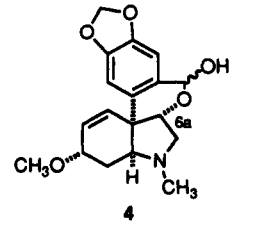

1




2



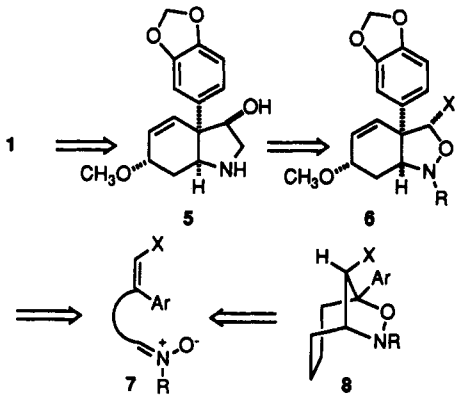

3




4

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 intermediacy of haemanthidine.[8-10] Without exception, attempts

**Scheme I**

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(1) (a) Taken in part from the Ph.D. dissertation of J.A., Duke University, 1984. (b) A portion of this work was presented at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 27-31, 1984; paper ORGN 171. (c) Partial support from the National Institutes of Health is gratefully acknowledged (GM 31634).

(2) For a recent review, see Amaryllidaceae alkaloids: Martin, S. F. The Amaryllidaceae Alkaloids. In The Alkaloids; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, pp 251-376.

(3) (a) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749. (b) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150 and references therein.

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