(dd, J = 2, 8 Hz, 1 H), 6.85 (br s, 2 H), 7.15 (m, 1 H), 7.23 (m, 5 H); mass spectrum, m/e 213 ($M^+/2$); UV (MeOH) λ_{max} 356 nm (ϵ 6900). Anal. ($C_{26}H_{26}N_4O_2$) C, H, N.

Isolation of 3d. The irradiation of a 100-mL methanolic or 10:1 pyridine–methanol solution for 3 or 4 h resulted in the complete disappearance of **1d**. In case of the 10:1 pyridine–methanol solution, the solvent was mostly evaporated in vacuo, and then methanol (10 mL) was added. White solids were precipitated upon cooling and then filtered to give **3d** (42 mg). The irradiated methanolic solution was condensed in vacuo to one-tenth of its volume to give **3d** (52 mg). This compound was recrystallized from a mixture of methanol and benzene: mp 273–276 °C; ^{1}H NMR ($CDCl_3$) δ 2.82–3.83 (m, 3 H), 7.02–7.80 (m, 10 H); IR (KBr) 1670 cm^{-1}. Anal. ($C_{30}H_{26}O_2$) C, H.

Isolation of 3g. After evaporation of the 100-mL methanolic or 10:1 pyridine–methanol solution (irradiated for 5 h) chloroform (30 mL) was added, and then the mixture was washed with diluted hydrochloric acid, saturated sodium bicarbonate, and brine. Evaporation of chloroform left a small amount of brownish oil, to which methanol (3 mL) was added, and then the mixture was cooled on an ice bath to give **3g** (5 mg) as a white solid: mp 254–255 °C (from methanol–benzene); ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 3.96–4.30 (m, 4 H), 6.70–7.20 (m, 10 H); IR (KBr) 1700 cm^{-1}. Anal. ($C_{32}H_{30}O_2$) C, H.

Registry No. **1a**, 87870-43-7; **1b**, 87870-44-8; **1c**, 837-66-1; **1d**, 614-47-1; **1e**, 30626-03-0; **1f**, 1896-62-4; **1g**, 38661-88-0; **1h**, 3815-30-3; **1i**, 67472-79-1; **1j**, 52148-89-7; **1k**, 36854-27-0; **1l**, 3461-34-5; **1m**, 1754-62-7; **1n**, 27519-25-1; **1o**, 79430-98-1; **1p**, 79430-99-2; **1q**, 6114-57-4; **1r**, 3531-24-6; **1s**, 1885-38-7; **1t**, 53940-12-8; **1u**, 87883-10-1; **2a**, 54636-71-4; **2b**, 54636-00-9; **2c**, 5409-60-9; **2i**, 75567-85-0; **2j**, 40912-11-6; **2** (R^1 = CO_2Me; R^2 = H; R^3 = H; X = CO_2Me), 106-65-0; **3d**, 7028-45-7; **3g**, 87870-45-9; **4d**, 87883-11-2; **4e**, 87870-46-0; **4f**, 87870-47-1; **4g**, 87870-48-2; **4h**, 87870-49-3; **5**, 67146-57-0; BNAH, 952-92-1; $Ru(bpy)_3^{2+}$, 15158-62-0.

Gossypium Cadinanes and Their Analogues: Synthesis of Lacinilene C, 2,7-Dihydroxycadalene, and Their Methyl Ethers

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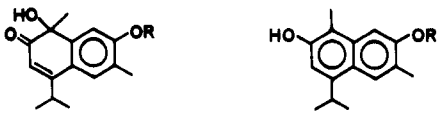
The total synthesis of lacinilene C methyl ether [1-hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2(1*H*)-naphthalenone] has been accomplished in ten steps with an overall, optimal yield of 38% by starting with *o*-methylanisole. Formation of the key α-aryl-α-ketol functionality, which is particularly sensitive to oxidation, was accomplished by stepwise oxidation reactions based on the use of *N*-methylmorpholine *N*-oxide/osmium tetraoxide acting on alkene and trimethylsilyl enol ether functionality. Other oxidations could be accomplished by using dichlorodicyanobenzoquinone to generate unsaturation adjacent to the α-ketol group or to form substituted naphthalenes. These reactions permitted adjustment of the oxidation level and oxygenation pattern of the key intermediate, 7-methoxy-α-calacorene (3,4-dihydro-4-isopropyl-7-methoxy-1,6-dimethylnaphthalene), to accomplish the synthesis of 2-hydroxy-7-methoxycadalene, 2,7-dihydroxycadalene, 7-methoxycadalene, and 7-hydroxycadalene, in addition to lacinilene C and its methyl ether.

Of the numerous *Gossypium* secondary metabolites, the cadinane sesquiterpenoids comprise the largest group characterized to date.[1] Various members of this group reportedly possess interesting physiological activities, including action as phytoalexins,[2] as natural insect control substances,[3] and as a fraction of cotton dust which causes "brown lung disease".[4] While these biological activities provide a justification for development of approaches to the synthesis of these cadinanes, the generally high degree of oxygenation or novel oxygenation patterns provides synthetic problems which are of theoretical and practical interest. In this report we describe the synthesis of four related *Gossypium* cadinanes: lacinilene C (**1**), 2,7-dihydroxycadalene (**3**), and their methyl ethers, **2** and **4**, respectively.[5,6] Brief descriptions of our initial synthesis of **2** and those by two other groups have been published.[7-9]



1 R=H **3** R=H

2 R=Me **4** R=Me

(1) McCormick, J. P. In "Cotton Dust: Controlling an Occupational Hazard"; Montalvo, J. G., Jr., Ed.; American Chemical Society: Washington, DC, 1982; Chapter 18.

(2) (a) Zaki, A. I.; Keen, N. T.; Erwin, D. C. *Phytopathology* **1972**, *62*, 1402. (b) Essenberg, M.; Doherty, M. d'A.; Hamilton, B. K.; Henning, V. T.; Cover, E. C.; McFaul, S. J.; Johnson, W. M. *Ibid.* **1982**, *72*, 1349.

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(6) (a) Stipanovic, R. D.; Wakelyn, P. J.; Bell, A. A. *Phytochemistry* **1975**, *14*, 1041. (b) Jeffs, P. W.; Lynn, D. G. *J. Org. Chem.* **1975**, *40*, 2958.

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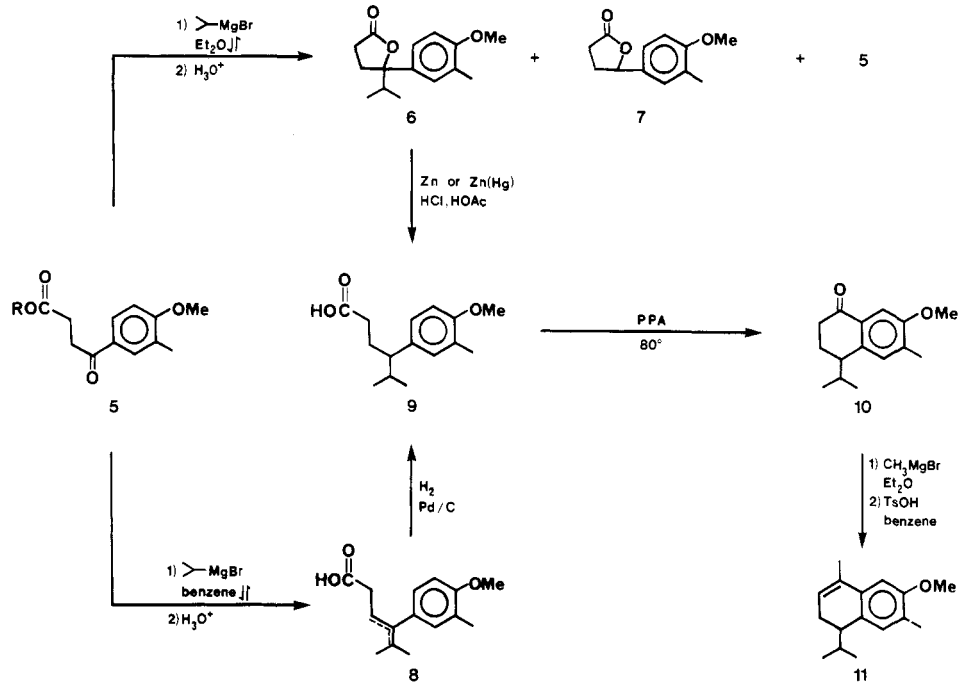
0022-3263/84/1949-0034$01.50/0

Scheme I



Results and Discussion

The approach followed for the synthesis of compounds **1–4** was designed to allow the preparation of a variety of cadinanes and to permit unambiguous confirmation of structures for which assignments were still open to question. The work can be divided into two stages: construction of 7-methoxy-α-calacorene (**11**),[10] a simple, representative cadinane, and the subsequent adjustment of the oxidation level and oxygenation pattern as required.

Synthesis of 7-Methoxy-α-calacorene (11). Skeletal assembly followed a synthetic route reminiscent of that used by other groups.[11] Acylation of *o*-methylanisole with succinic anhydride proceeded exclusively para to the methoxy group in nearly quantitative yield. The resulting keto acid possessed functionally differentiated carbonyl groups appropriate for the formation of the remaining three carbon–carbon bonds. Addition of Grignard reagents to the ketone of the derived keto ester **5** (R = Et) in ethereal solvent (Scheme I) was complicated by enolization, the major fate of **5**, and competing reduction, difficulties which led previous investigators to abandon this approach.[11] Evidently, the steric crowding developed during the addition to carbonyl makes the carbon–carbon bond-forming process energetically unfavorable compared to proton abstraction and energetically similar to hydride transfer. It was particularly important to suppress the reduction pathway, because the presence of the resulting unalkylated lactone, **7**, presented a tedious chromatographic separation problem.

A careful survey of the effects of changing the organometallic reagent, temperature, and solvent led to significant improvement of the addition reaction. The best results using THF as a solvent were obtained by inverse addition of isopropylmagnesium bromide at −15 °C to produce isolated yields of 25% of lactone **6**, 10% of lactone **7**, and 55% of keto acid **5** (R = H). Likewise, use of diethyl ether as the solvent at room temperature or lower temperatures also permitted competing reduction. It was therefore gratifying to observe that addition of isopropylmagnesium bromide, the preferred Grignard reagent, to the ketone in diethyl ether at reflux temperature completely eliminated the reduction pathway, affording a 78% yield of alkylated lactone **6**, based on recovered starting material (the absolute yield of **6** was 24%). The starting material and lactone **6** were readily separated by a procedure involving sequential saponification, acidification, and selective extraction of the keto acid, thereby circumventing chromatographic purification.

Although the use of diethyl ether as a solvent eliminated competing reduction, enolization continued to be a problem. A switch to benzene[11,12] in place of diethyl ether caused both a dramatic decrease in the competing enolization reaction and a change in the structure of the alkylated product: addition of isopropylmagnesium bromide in diethyl ether to keto ester **5** in refluxing benzene provided, after a mild acid workup and extractive removal of nonacidic material, a 64% yield (81% yield based on recovered keto ester) of unsaturated acids **8**, having a purity sufficient for use in subsequent steps without chromatographic purification. This mixture of 3- and 4-hexenoic acids apparently arises from initial lactone formation followed by elimination, conceivably promoted by alkoxymagnesium bromide.

The cadinane skeleton, embodied in 7-methoxy-α-calacorene (**11**), was obtained in excellent yield from either lactone **6** or the mixture of unsaturated acids **8** (Scheme I). Either route required initial reduction to carboxylic acid **9**. The lactone could be reduced quantitatively by zinc to the desired acid **9**. However, this reduction was found to be erratic, as was reduction using zinc amalgam. Fortunately, the unsaturated acids **8**, formed in greater yield than the lactone, could be reduced in high yield by catalytic hydrogenation with 10% palladium on carbon in absolute ethanol. The resulting aryl carboxylic acid **9** was cyclized in polyphosphoric acid[13] to afford tetralone **10** in

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(10) Herout, V.; Sykora, V. *Tetrahedron* **1958**, *4*, 246.
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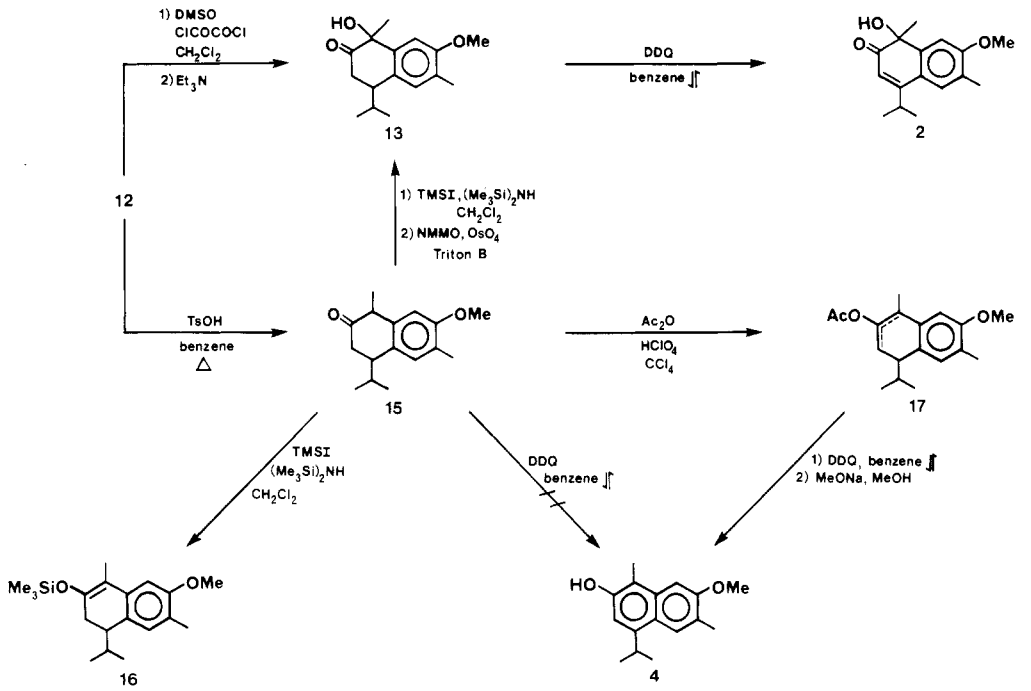
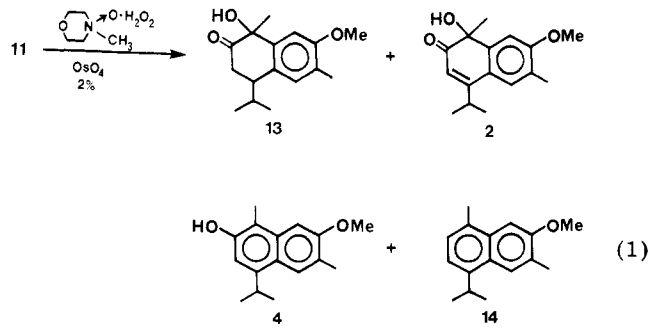
Scheme II



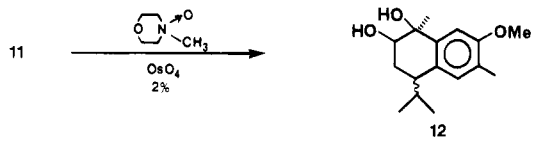
97% yield. Subsequent treatment with methylmagnesium bromide in diethyl ether, followed by acid-catalyzed dehydration of the alcohol, provided chromatographically pure 7-methoxy-α-calacorene in about 90% yield, based on tetralone **10**. This material, then, is accessible on a large scale in an optimal yield of 60%, based on *o*-methylanisole. The route requires chromatographic purification only after formation of 7-methoxy-α-calacorene (**11**) itself, making this simple cadinane an attractive intermediate for the preparation of a variety of other cadinanes by adjustment of oxidation level and oxygenation pattern.

Synthesis of Lacinilene C Methyl Ether (2). While several straightforward means for an increase in the oxidation level of dihydronaphthalene **11** to form lacinilene C methyl ether may be envisioned, this approach presents a challenge owing to the high sensitivity of the aryl-substituted α-ketol to oxidation. For example, attempts to employ the apparently well-suited method for formation of an α-ketol directly from an alkene by using *N*-methylmorpholine *N*-oxide–hydrogen peroxide with catalytic amounts of osmium tetraoxide[14] afforded a disappointing mixture of **2** (4%), expected ketol **13** (10%), naphthol **4** (17%), and naphthalene **14** (9%) (eq 1), together with a large amount of material, presumably more highly oxidized, which was not readily characterized.



(1)

In striking contrast, use of the Upjohn method[15] for diol formation employing catalytic osmium tetraoxide with *N*-methylmorpholine *N*-oxide as a stoichiometric oxidant provided much better results: a stereoisomeric mixture of diols **12** (eq 2) was obtained in 94% yield. Further



(2)

transformation of this material both by direct oxidation to α-ketol and by indirect means via β-tetralone **15** (Scheme II) were investigated. Because initial attempts to oxidize diols **12** to ketols **13** by using a variety of conditions and reagents revealed that the sensitivity of the desired α-ketol to overoxidation also plagued this approach, we sought a milder method.

β-Tetralone **15** could be obtained readily in high yield by acid-catalyzed dehydration of the diols **12**, as well as in about 80% yield from dihydronaphthalene **11** by hydroboration followed by oxidation. We therefore explored means for effective α-hydroxylation of this ketone. Existing literature methods,[16] though elegant, appeared to suffer from limitations which made them of questionable use in the case at hand, which required control of regiochemistry and use of mild oxidizing conditions. We reasoned that the application of the especially mild osmium tetraoxide/*N*-methylmorpholine *N*-oxide system, acting on an enol derivative as an electron-rich, activated alkene, could provide an effective approach to α-ketol generation. Other attractive aspects of enol derivatives are their ready accessibility from ketones under conditions which generally provide very high yields with excellent control of regiochemistry. Following initial exploration with model com-

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(15) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
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pounds,[17] this approach was applied to the transformation of tetralone **15** into α-ketol **13**. Thus, treatment of **15** with trimethylsilyl iodide/hexamethyldisilazane in methylene chloride[18] provided the corresponding trimethylsilyl enol ether **16** with complete regioselectivity. Treatment of this intermediate with osmium tetraoxide (2 mol %), *N*-methylmorpholine *N*-oxide, Triton B, water, and *tert*-butyl alcohol at 0 °C provided ketols **13** in 57% yield, based on tetralone.

While hydroxylation of β-tetralone **15** using the latter conditions gave an acceptable yield of the desired α-ketols, continued investigation of direct oxidation of diols **12** provided even better results. Of numerous methods examined, only the Swern modification of the Me_2SO oxidation utilizing oxalyl chloride was satisfactory.[19] Careful use of this method permitted oxidation of diols **12** to afford a 68% yield of crystalline α-ketols **13** (presumed to be a mixture of stereoisomers), after chromatography on silica gel.

The final increase in oxidation level, transforming α-ketols **13** to lacinilene C methyl ether (**2**), was accomplished by direct dehydrogenation. Treatment of the former with DDQ in refluxing benzene gave **2** in excess of 80% yield. Using unpurified α-ketols **13**, the two-step yield of **2** from diols **12** was 68%. This final product therefore was obtained from *o*-methylanisole in an overall (10-step) optimal yield of 38%. The synthetic material was identical (by melting point as well as spectral and chromatographic data) with the natural substance as characterized in two separate laboratories.[6] Owing to its racemic nature, the synthetic material might be expected to differ from the natural substance. However, there is some question regarding the optical purity of the compound as it is isolated from *Gossypium*,[20] and investigation of this point is currently underway in our laboratories.

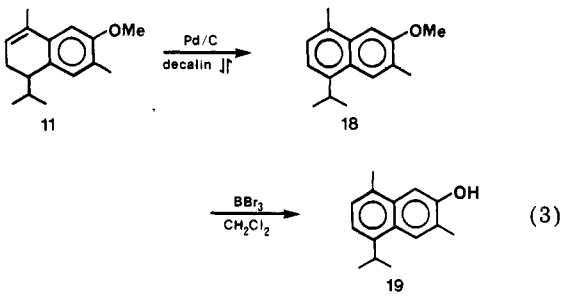
Synthesis of Other Cadinanes. 2-Hydroxy-7-methoxycadalene (**4**) is a natural *Gossypium* metabolite and may be the biosynthetic precursor to lacinilene C methyl ether.[5] Such a step would parallel autoxidation chemistry previously reported[21] for 1-alkyl-2-naphthols, as well as the last step in a reported synthesis of lacinilene C methyl ether.[8,9] Additionally, naphthol **4** may be involved in byssinosis.[5]

β-Tetralone **15** appeared to be an appropriate intermediate for direct conversion into this naphthol by DDQ, in the same manner used for transformation of β-tetralone **13** into lacinilene C methyl ether. Surprisingly, reflux of **15** together with DDQ in benzene left the former unchanged. In a successful alternative approach, **15** was treated with acetic anhydride and perchloric acid in carbon tetrachloride[22] to produce a mixture of enol acetates **17**, which were dehydrogenated effectively with DDQ, at room temperature. Following deacetylation, 2-hydroxy-7-methoxycadalene (**4**) was obtained in a 77% yield, based on tetralone **15**. Alternatively, tetralone **15** was converted directly into compound **4** in 41% yield by treatment with 10% palladium on carbon in refluxing decalin for 15 h. The synthetic naphthol, which was identical in all respects with the natural material,[5] was characterized by spectral means, as well as by melting point. Further characterization was carried out by preparation of the 3,5-dinitrobenzoate, the melting point and NMR spectrum of which were in agreement with those of the same derivative reported previously.[23]

2,7-Dihydroxycadalene (**3**) was readily prepared by demethylation of the monomethyl ether. Thus, treatment of naphthol **4** with boron tribromide in methylene chloride[24] provided a 69% yield of **3**. This product, which was identical with that previously isolated from *Gossypium*,[5] was also characterized by conversion to the bis(3,5-dinitrobenzoate).

Use of boron tribromide to accomplish demethylation of lacinilene C methyl ether provided **1** in 68% yield after chromatography, 38% after recrystallization. Alternatively, ethyl mercaptide in refluxing DMF[25] was used to convert the methyl ether into **1** in 30% yield, after purification on silica gel. The properties of the synthetic material were in accord with those of the natural substance.[6]

Finally, it is worth noting that this chemistry provides ready access to other cadinanes. For example, dehydrogenation of 7-methoxy-α-calacorene (**11**) with 10% palladium on carbon provided 7-methoxycadalene (**18**) in 57% yield (eq 3). Demethylation of this ether using boron



(3)

tribromide afforded an 85% yield of 7-hydroxycadalene (**19**), characterized by its melting point and spectral data which agreed with those previously published for this natural product.[26]

Experimental Section

Organic chemicals and reagents were obtained from Aldrich Chemical Co. and were used as received unless otherwise stated. Anhydrous ethereal solvents were prepared by reflux over sodium benzophenone ketyl, followed by distillation of the required amount directly into reaction flasks. The instruments used were as follows: ^1H NMR, Varian T-60 and 360L at 60 MHz (Me_4Si as an internal standard); IR, Perkin-Elmer 237B; UV, Carey 15; mass spectra, Du Pont 21-490 (EI); melting points (uncorrected), Thomas-Hoover capillary apparatus; GC, Varian-Aerograph 2440 with an FID detector. Silica gel chromatography utilized E. Merck PF_{254} or Merck silica gel 60 (230–400 mesh) for columns and E. Merck silica gel 60 F_{254} (0.2 mm on aluminum) for TLC, with visualization by UV or I_2 means, unless otherwise indicated. Elemental analyses were performed by Galbraith Laboratories.[27]

4-Hydroxy-4-(4-methoxy-3-methylphenyl)-5-methylhexanoic Acid Lactone (6). To a vigorously stirred solution of keto ester **5** (R = Et, 9.14 g, 36.5 mmol)[28] in 250 mL of Et_2O

(17) MCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.
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(27) Mention of firm names or trade products does not imply endorsement by the U.S. Department of Agriculture over other firms or similar products not mentioned.

at reflux was added 54 mmol of isopropylmagnesium bromide in 30 mL of Et_2O during a 25-min period. After an additional 1 h period of reflux, 400 mL of saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous portion was extracted with Et_2O (2 × 100 mL). The combined ethereal portions were washed (3 × 300 mL of saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to afford 8.66 g of a yellow-brown oil, 8.50 g of which was refluxed together with 8.0 g of KOH in 300 mL of 95% EtOH for 4 h. The EtOH was removed from this mixture under reduced pressure, 500 mL of H_2O was added, and the resulting mixture was extracted with Et_2O (4 × 50 mL). [Drying ($MgSO_4$) and concentration of this Et_2O extract afforded 0.60 g of unidentified material.] The aqueous portion was acidified to pH 1 with HCl and then heated on a steam bath for 2 h. After the mixture cooled, Et_2O was added, and the resulting mixture was extracted with saturated aqueous Na_2CO_3. The ethereal portion was washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated under reduced pressure to afford 2.74 g of lactone **6**. The aqueous Na_2CO_3 solution was acidified (concd HCl); the resulting precipitate was collected by filtration and dried to give 5.45 g (24.6 mmol) of keto acid **5** (R = H).

Chromatographic purification (50 g of silica gel; eluted with EtOAc/hexane, 4/1) of the crude lactone afforded 2.17 g (8.74 mmol, 24.4%, 78% when calculated on the basis of recovered keto acid) of purified lactone **6**: mp 41–42 °C; TLC R_f 0.43 (EtOAc/hexane, 3/7); UV max (95% EtOH) 274 nm (ϵ 1690), 227 (9080); IR (neat) 1775 (C=O) cm^{-1}; NMR (CCl_4) δ 0.83 and 0.88 (2 d, 6, J = 7 Hz, $C(CH_3)_2$), 2.17 (s, 3, $ArCH_3$); mass spectrum (70 eV), m/e (relative intensity) 248 (8.0), 204 (100.0). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.26.

4-(4-Methoxy-3-methylphenyl)-5-methylhexanoic Acid (9) from Zinc Amalgam Reduction of Lactone 6. The Zn(Hg) was prepared by stirring for 5 min a mixture of 12 g of Zn dust, 1.2 g of $HgCl_2$, and 0.6 mL of concentrated HCl in 15 mL of H_2O, after which the aqueous solution was decanted. To the Zn(Hg) were added 7.5 mL of H_2O, 17.5 mL of concentrated HCl, 10 mL of toluene, and 5.0 g (20.2 mmol) of lactone **6**; the resulting mixture was refluxed vigorously for 62 h. At reaction times of 6, 12, and 18 h, 5-mL portions of concentrated HCl were added. After reflux, the cooled mixture was filtered, and the filtrate was extracted with Et_2O (6 × 50 mL). The ethereal portions were extracted with dilute aqueous NaOH (3 × 50 mL). The aqueous portions were acidified with concentrated HCl and extracted with Et_2O (6 × 50 mL). The combined ethereal portions were washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated under reduced pressure to provide 4.68 g (18.8 mmol, 93%) of carboxylic acid **9** as a greenish yellow oil: mp (of the S-benzylthiouronium hydrochloride derivative) 255–260 °C dec; TLC R_f 0.44 (EtOAc/hexane, 2/3); IR (neat) 2960 (OH), 1710 (C=O) cm^{-1}; NMR (CCl_4) δ 0.73, 0.97 (2 d, 6, J = 7 Hz, $CH(CH_3)_2$, 1.87–2.13 (4, CH_2CH_2), 2.15 (s, 3, $ArCH_3$), 3.73 (s, 3, $ArOCH_3$), 6.63–6.93 (3, ArH), and 11.71 ppm (s, 1, COOH).

4-(4-Methoxy-3-methylphenyl)-5-methylhexanoic Acid Prepared via Hexenoic Acids 8. The procedure used was similar to that described.[11] To keto ester **5** (35.4 g, 150 mmol, R = Me)[28] in benzene (80 mL) was added isopropylmagnesium bromide in 75 mL of Et_2O (prepared from 18.3 mL of isopropyl bromide and 5.47 g of magnesium). The reaction mixture was stirred with a mechanical stirrer and heated to reflux, using a Dean–Stark trap to remove the Et_2O, after which the heavy sludge was stirred for an additional 6 h at 95 °C. The reaction mixture then was cooled and acidified (dilute H_2SO_4), and Et_2O was added. The organic layer was washed (H_2O, 10% aqueous Na_2CO_3). The aqueous layer was extracted with Et_2O, acidified with dilute HCl, and reextracted with Et_2O. The first ether extract was added to the original organic layer from which starting material could be recovered. The second ether extract was washed (H_2O, saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to provide 24.0 g (96.7 mmol, 64.4%, 81% based on recovered keto ester) of the crude unsaturated acids **8**. This material was reduced to the saturated acid **9** without further purification.

A portion (11 g, 44.4 mmol) of the crude acids was dissolved in 200 mL of absolute EtOH containing 1.1 mL of 10% aqueous KOH, and 300 mg of 10% Pd/C was added. The contents were shaken on a Parr shaker under an H_2 atmosphere at 50 psi for 48 h, at which time the catalyst was removed by filtration, 1.7 mL of 1 N HCl was added, and the solvent was evaporated. The resulting material was dissolved in Et_2O, and the solution was filtered and concentrated to provide 10.25 g (41.0 mmol, 92.2%) of carboxylic acid **9**, characterized as described above.

1,2,3,4-Tetrahydro-4-isopropyl-7-methoxy-6-methyl-1-naphthalenone (10). Carboxylic acid **9** (4.59 g, 18.4 mmol) was mixed well with 30 g of polyphosphoric acid by stirring with a spatula and heated to 87 °C with continued stirring for 1 min, whereupon the mixture turned blood red. After being heated at 87 °C for an additional 30 min, a mixture of ice and water was added, and the resulting mixture was extracted with Et_2O (5 × 50 mL). The combined ethereal portions were washed (4 × 10 mL of saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to provide 4.15 g (17.9 mmol, 97.3%) of desired tetralone **10**: TLC R_f 0.63 (EtOAc/hexane, 1/1); UV max (95% EtOH) 322 nm (ϵ 3380), 265 (10090), 227 (16720); IR (neat) 1680 (C=O) cm^{-1}; NMR (CCl_4) δ 0.92 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.8–2.9 (CH_2CH_2), 2.18 (s, $ArCH_3$), 3.82 (s, 3, $ArOCH_3$), 6.90 and 7.28 (s, 2, ArH).

3,4-Dihydro-4-isopropyl-7-methoxy-1,6-dimethylnaphthalene (7-Methoxy-α-calacorene, 11). To a solution of methylmagnesium iodide in Et_2O [prepared from 2.76 g (19.4 mmol) of freshly distilled methyl iodide and 0.40 g (16.4 mmol) of Mg refluxed in 30 mL of Et_2O under N_2] at −10 °C was added with stirring 1.50 g (6.46 mmol) of tetralone **10** during a period of 30 min. The resulting reaction mixture was allowed to warm to room temperature (20 min) and then refluxed for 30 min, at which time the Et_2O was removed by distillation. To the cooled residue were added 20 mL of benzene, 20 mL of H_2O, and 20 mL of 4 N HCl. The mixture was stirred for 10 min, and then extracted with Et_2O (11 × 25 mL). The combined ethereal portions were washed with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 25 mL), and saturated aqueous NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated to give 1.61 g of crude product. Chromatographic purification of this material (50 g of silica gel; eluted with EtOAc/hexane, 1/9) provided 1.31 g (5.69 mmol, 88%) of desired dihydronaphthalene **11** as a homogeneous yellow oil: TLC R_f 0.69 (EtOAc/hexane, 1/1); UV max (95% EtOH) 222 nm (ϵ 2870), 267 (1170); IR (neat) 1610 (C=C), 1580, 1500 cm^{-1}; NMR (CCl_4) δ 0.77 and 0.85 (2 d, 6, $C(CH_3)_2$), 1.97 (s, 2, CH_2), 2.15 (s, 3, $ArCH_3$), 3.72 (s, 3, $ArOCH_3$), 5.53 (br s, 1, CH=C), 6.55 (s, 1, HCCOMe), and 6.72 (s, 1, HCCMe); mass spectrum (70 eV), m/z (relative intensity) 230 (12.2), 187 (100.0), 172 (31.6). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.59; H, 9.82.

1,2,3,4-Tetrahydro-1,2-dihydroxy-4-isopropyl-7-methoxy-1,6-dimethylnaphthalenes (12). To 1.50 g (6.54 mmol) of dihydronaphthalene **11** in 60 mL of acetone and 25 mL of H_2O at −25 °C was added with stirring under Ar 930 mg (6.89 mmol) of *N*-methylmorpholine *N*-oxide hydrate and 6.55 mL of a *freshly prepared*[29] *tert*-butyl alcohol solution of OsO_4. The mixture was allowed to warm to 23 °C and stirred for an additional 48 h, and then 700 mg of $Na_2S_2O_4$ and 3 g of Florisil were added. The resulting mixture was filtered, the acetone was removed under reduced pressure, the pH was adjusted to 2, and the mixture was extracted with EtOAc (6 × 30 mL). The combined extracts were washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to afford a brown oil. Purification of the crude product by chromatography on silica gel (60 g; EtOAc/pentane, 1/4 to 1/1) provided 1.62 g (6.13 mmol, 94%) of a colorless semisolid, found to be a mixture of diastereomers:[30] TLC R_f 0.36 (EtOAc/hexane, 1/1); NMR (CCl_4) δ 6.93 (s, 1), 6.83 (s, 1), 3.92 (br s, 2, OH), 3.73 (s, 3, OCH_3), 2.11 (s, 3, $ArCH_3$), 1.24 (s, 3, CH_3COH), 0.96 (d, 3, J = 7 Hz), 0.60 (d, 3, J = 7 Hz); TLC R_f 0.23 (EtOAc/hexane, 1/1), NMR (CCl_4) δ 6.93 (s, 1), 6.76 (s, 1), 4.38 (br s, 2, OH), 3.68 (s, OCH_3), 2.10 (s, 3, $ArCH_3$), 1.28 (s, 3, CH_3COH), 0.96 (d, 3, J = 7 Hz), 0.72 (d, 3, J = 7 Hz); mass spectrum (70 eV), m/z (relative intensity) 264 (32), 246 (16), 221 (54), 203 (100), 175 (63), 43 (63).

(28) Keto esters **5** (R = Et, Me) were prepared in 95% yields from *o*-methylanisole and succinic anhydride using the procedure described,[11a] followed by HCl-catalyzed esterification.

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(30) Assignment of the relative stereochemistry of the two diastereomers was not made. The diols were used as a mixture, since this stereochemical difference was removed during subsequent oxidations.

1-Hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2(1*H*)-naphthalenone (Lacinilene C Methyl Ether, 2) from Diols 12. To a mixture of diols **12** (718 mg, 2.72 mmol) and oxalyl chloride (0.240 mL, 3.0 mmol, freshly distilled) in 30 mL of CH_2Cl_2 stirring at −60 °C was added 0.410 mL (5.44 mmol) of Me_2SO over a period of 3 min. After the resulting mixture was stirred an additional 20 min at −78 °C, 2 mL of Et_3N was added, and the mixture was stirred 7 min at −70 °C before being allowed to warm to room temperature. After addition of 40 mL of H_2O, the layers were separated, the aqueous portion was extracted with CH_2Cl_2 (6 × 25 mL), and the combined organic portions were washed (2% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, saturated aqueous NaCl), dried ($MgSO_4$), and concentrated under reduced pressure to give 869 mg of the crude α-ketols **13** as a yellow oil.

The crude α-ketols and 1.0 g (4.41 mmol) of dichlorodicyanobenzoquinone were stirred in 25 mL of benzene for 24 h at room temperature, after which the solvent was evaporated under reduced pressure. The resulting oil was purified by chromatography on silica gel [first using 40 g and EtOAc/hexane (1/4) and then using 40 g and EtOAc/hexane (10/1 to 5/1)] to afford 482 mg (1.85 mmol, 68% yield based on diols **12**) of **2**[6] as yellow-orange crystals: mp 101–103 °C; ^1H NMR (CCl_4) δ 7.25 (s, 1), 7.14 (s, 1), 5.88 (s, 1), 3.93 (s, 3, OCH_3), 3.70 (br s, 1, OH), 3.20 (m, 1, $CHMe_2$), 2.21 (s, 3, $ArCH_3$), 1.43 (s, 3, CH_3COH), 1.26 (2 d, 6, J = 7 Hz (CH_3)$_2$CH); ^{13}C NMR ($CDCl_3$) δ 205.2 (C-2), 163.9 (C-4), 159.1 (C-7), 145.4 (C-9), 127.4 (C-3), 125.1 (C-5), 120.6 (C-10), 114.8 (C-6), 107.1 (C-8), 76.9 (C-1), 55.5 (C-16), 33.9 (C-11), 29.1 (C-12), 22.2 (C-14), 21.9, (C-15), 16.2 (C-13); mass spectrum, m/z (relative intensity) 261 (7), 260 (39), 245 (4), 232 (33), 217 (56), 202 (14), 190 (18), 189 (100), 175 (40).

1,2,3,4-Tetrahydro-4-isopropyl-7-methoxy-1,6-dimethyl-2-naphthalenone (15). Diols **12** (1.62 g, 6.13 mmol) and 0.7 g (3.68 mmol) of *p*-toluenesulfonic acid monohydrate were dissolved in 200 mL of benzene. The benzene was removed with gentle heating under reduced pressure. Saturated aqueous NaCl solution was added to the residue, and the resulting mixture was extracted with Et_2O (4 × 25 mL). The combined ethereal portions were washed (saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), and concentrated to give 1.465 g (5.95 mmol, 97%) of tetralone **15** as a dark yellow oil:[23] TLC R_f 0.65 (EtOAc/hexane, 1/1); NMR (CCl_4) δ 6.83 (br s, 1), 6.58 (br s, 1), 3.86 (s, 3, OCH_3), 3.30 (q, 1, J = 7 Hz,*H*CMe), 2.57 (br s, 2, $CH_2C{=}O$), 2.15 (s, 3, $ArCH_3$), 1.42 (d, 3, J = 7 Hz, CH_3CH), 0.88 (m, 6, (CH_3)$_2$CH). Tetralone **15** decomposed, forming six observable spots on TLC, upon storage at −15 °C for ca. 1 month, apparently the result of oxidation.

3,4-Dihydro-1-hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2(1*H*)-naphthalenone (13) from Hydroxylation of Tetralone 15. To a mixture of 131 mg (0.533 mmol) of tetralone **15** and 0.130 mL (0.616 mmol) of hexamethyldisilazane in 6 mL of CH_2Cl_2 was added 0.080 mL (0.563 mmol) of Me_3SiI at −10 °C under an Ar atmosphere. The mixture was stirred at −10 °C for 1 h and then allowed to warm to room temperature. After the mixture was cooled to −20 °C, 10 mL of cold, saturated aqueous $NaHCO_3$ was added, and the organic layer was washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to afford the intermediate silyl enol ether **16** as a dark yellow oil.

The crude silyl enol ether in 3 mL of *tert*-butyl alcohol containing 232 mg of 4% Triton B was treated with a mixture of *N*-methylmorpholine *N*-oxide monohydrate (69 mg, 0.54 mmol), 0.260 mL of a *tert*-butyl alcohol solution[29] of OsO_4 (0.01 mmol) and 0.3 mL of H_2O at 0 °C. The mixture was then stirred at 10 °C for 100 min, at which time 100 mg (0.48 mmol) of $Na_2S_2O_4$ and 0.5 g of Florisil were added. The suspension was filtered, and the pH of the filtrate was adjusted to 4 before extraction with EtOAc (2 × 20 mL). The combined organic portions were washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated under reduced pressure to give 118 mg of an oil. Purification of the product by chromatography (25 g of silica gel; EtOAc/hexane, 1/4) provided 80 mg (0.305 mmol, 57% based on tetralone **15**) of a greenish yellow oil, which was characterized by NMR before dehydrogenation (vide supra): NMR (CCl_4) δ 6.93 (s, 1), 6.83 (s, 1), 3.82 (s, 3, OCH_3), 2.4–3.3 (m, 2, $CH_2C{=}O$), 2.13 (s, 3, $ArCH_3$), ca. 0.90 (2 d, 6, J = 7 Hz).

1,7-Dihydroxy-4-isopropyl-1,6-dimethyl-2(1*H*)-naphthalenone (Lacinilene C, 1). Lacinilene C methyl ether (**2**; 10.4 mg, 0.040 mmol) was dissolved in 2 mL of a solution of CH_2Cl_2 containing 10% EtSH, and the resulting mixture was added to $AlCl_3$ (77.8 mg, 0.58 mmol) under a dry atmosphere. The solution was stirred for 2 h at room temperature and transferred directly onto a silica gel column (5 g, Baker 40–140 mesh). The EtSH was eluted from the column with hexane (50 mL), after which Et_2O/MeOH (9/1, 150 mL) was used to elute 6.7 mg (0.027 mmol, 68.0%) of **1**. Crystallization of this material from hexane/Et_2O gave 3.7 mg (0.015 mmol, 37.6%) of racemic lacinilene C, mp 65–77 °C.[6]

2-Hydroxy-4-isopropyl-7-methoxy-1,6-dimethylnaphthalene (2-Hydroxy-7-methoxycadalene, 4). To tetralone **15** (150 mg, 0.61 mmol) and Ac_2O (0.31 mL) in 5 mL of CCl_4 were added 2 drops of 70% $HClO_4$. The resulting mixture was stirred at room temperature for 3 h (becoming dark red), at which time it was poured into 40 mL of a 1:1 mixture of pentane and saturated aqueous $NaHCO_3$. Subsequently, solid $NaHCO_3$ was added with vigorous stirring as rapidly as foaming would permit until the aqueous phase remained slightly basic. After separation of the organic and aqueous phases, the aqueous portion was extracted with pentane (4 × 20 mL). The combined organic portions were dried ($MgSO_4$) and concentrated to give 171 mg (0.59 mmol, 97%) of enol acetates **17** as a wine red solid. Examination of the mixture of acetates by NMR indicated a 7:1 ratio of two isomers, which as a mixture were subjected to dehydrogenation without further purification.

A mixture of enol acetates **17** (346 mg, 1.20 mmol) and dichlorodicyanobenzoquinone (572 mg, 2.52 mmol) was stirred for 3.5 h in 25 mL of benzene at room temperature. The resulting dark green reaction mixture was placed onto a silica gel column (35 g) and eluted with EtOAc/hexane (4/1) to provide 305 mg (1.07 mmol, 89%) of the crude acetoxynaphthalene as a dark yellow oil: TLC R_f 0.57 (EtOAc/hexane, 1/1; NMR (CCl_4) δ 7.77, 7.00, 6.85 (3 s, 3, ArH), 3.77 (s, 3, OCH_3), 2.35 and 2.29 (2 s, 6, $ArCH_3$), 2.20 (s, 3, $CH_3C{=}O$), 1.35 (d, 6, J = 7 Hz, $C(CH_3)_2$).

The acetoxynaphthalene (305 mg, 1.07 mmol) was stirred in 10 mL of 0.3% NaOMe in MeOH at room temperature for 15 min. After subsequent evaporation of the solvent, the resulting yellow oil was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed (saturated aqueous NaCl), dried ($MgSO_4$), and concentrated to afford 232 mg (0.95 mmol, 88.9%, 76.6%, based on tetralone **15**) of **4** as white crystals. Recrystallization (Et_2O/hexane) provided an analytical sample (mp 168–169 °C) identical with natural material by spectral data as well as melting point.[5] This naphthol also was characterized as its 3,5-dinitrobenzoate ester, mp 217–217.5 °C, in excellent agreement with that reported.[23]

2,7-Dihydroxy-4-isopropyl-1,6-dimethylnaphthalene (2,7-Dihydroxycadalene, 3). To 2-hydroxy-7-methoxycadalene (**4**; 18.3 mg, 0.075 mmol) in CH_2Cl_2 (2.5 mL, dried over alumina) at 0 °C was added 0.023 mL of BBr_3, and the mixture was stirred for 5.5 h at 0 °C. The reaction mixture was then poured into an ice/water mixture and extracted with Et_2O. The ethereal solution was washed (10% $NaHCO_3$, H_2O, saturated aqueous NaCl), dried, and concentrated. The resulting product was purified by silica gel column chromatography, eluted with increasing concentrations of EtOAc in hexane to give recovered methyl ether **4** (3.5 mg, 0.014 mmol) and traces of lacinilene C (**1**) and its methyl ether (**2**), in addition to 11.9 mg (0.052 mmol, 68.9%, 84.5% based on recovered **4**) of 2,7-dihydroxycadalene (eluted with EtOAc/hexane, 20/80). The product, identical with that previously reported,[5] also was characterized as its bis(3,5-dinitrobenzoate) ester, mp 212–213 °C.

7-Hydroxy-4-isopropyl-1,6-dimethylnaphthalene (7-Hydroxycadalene, 19). A mixture of 7-methoxy-α-calacorene (**11**; 429 mg, 1.86 mmol), 10% Pd/C (84 mg), and decalin (10 mL) was refluxed under N_2 for 15 h, after which the catalyst was removed by filtration and washed with Et_2O. The combined organic solutions were concentrated. The product was purified by silica gel column chromatography, first eluting the decalin with hexane and then the desired product with $CHCl_3$. Recrystallization from hexane gave 242 mg (1.06 mmol, 57.2%) of 7-methoxycadalene (**19**), mp 65–66 °C.

A mixture of 7-methoxycadalene (242 mg, 1.06 mmol), BBr_3 (0.36 mL), and CH_2Cl_2 (10 mL) was stirred at room temperature under N_2 for 2.5 h, after which the mixture was poured into an ice/water mixture. The water was extracted with Et_2O and the

ethereal solution was washed (2% aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl), dried ($MgSO_4$), and concentrated. The crude product was recrystallized from ligroin to provide 194 mg (1.06 mmol, 85%) of 7-hydroxycadalene, mp 116–120 °C. The spectral data of this material were in agreement with those previously published for this compound.[26]

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Registry No. (±)-**1**, 87900-51-4; (±)-**2**, 56051-00-4; **3**, 77401-25-3; **4**, 68233-94-3; **4** 3,5-dinitrobenzoate, 68233-95-4; **5** (R = Et), 87843-16-1; (±)-**6**, 70143-23-6; **8** (isomer 1), 87843-17-2; **8** (isomer 2), 87843-18-3; (±)-**9**, 70143-24-7; (±)-**10**, 80736-45-4; (±)-**11**, 70143-25-8; (±)-**12** (isomer 1), 87843-19-4; (±)-**12** (isomer 2), 87843-20-7; **13**, 77996-13-5; **15**, 68233-93-2; (±)-**16**, 87843-21-8; (±)-**17** (isomer 1), 87843-22-9; **17** (isomer 2), 87843-23-0; **18**, 87843-24-1; **19**, 2102-75-2; isopropyl bromide, 75-26-3.

Applications of Intramolecular Amidomercuration. 2.[1] Synthesis of *trans*-5-Hydroxy-2-propylpiperidine, (±)-Pseudoconhydrine

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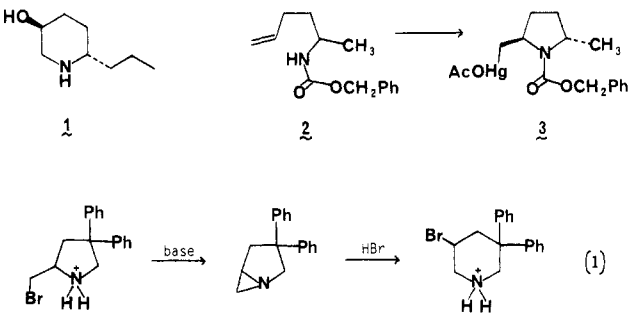
A method for the stereoselective conversion of δ-alkenyl carbamates into *trans*-2-alkyl-5-substituted-piperidines utilizing intramolecular amidomercuration as a key step has been developed. As a specific illustration of the method, a synthesis of one of the Hemlock alkaloids, (±)-pseudoconhydrine (*trans*-5-hydroxy-2-propylpiperidine, **1**) was completed. The organomercurial **7a** obtained from the intramolecular amidomercuration of 4-[(carbobenzyloxy)amino]-7-octene (**6**) was converted to the corresponding *trans*-5-(iodomethyl)-2-propylpyrrolidine derivative **7b**. Cleavage of the carbamate and treatment with base generated the bicyclic aziridine 2-*exo*-propyl-1-azabicyclo[3.1.0]hexane (**8a**). Treatment of this aziridine with excess trifluoroacetic acid gave ring opening to the disubstituted pyrrolidine derivative **9a** exclusively. Ring opening of the analogous aziridine **8b** with HCl gave mixtures of pyrrolidine **9b** and piperidine **10b**. However, these derivatives can be equilibrated through the neutral amine to a mixture consisting of ca. 85% of the piperidine derivative. Slow addition of trifluoroacetic acid to aziridine **8a** allowed for equilibration to piperidine **14** as the major product. Hydrolysis and purification gave pure racemic pseudoconhydrine. This synthetic sequence illustrates a synthetic equivalent to anti-Markovnikov cyclofunctionalization of δ-alkenyl carbamates. In addition, this study provided new information on the regiochemistry of ring opening of bicyclic aziridines.

As part of our investigation of the synthetic utility of intramolecular amidomercuration reactions,[1] we have examined the conversion of δ-alkenyl carbamates into *trans*-2-alkyl-5-substituted-piperidines. As a specific illustration of the utility of this method, we have completed a stereoselective synthesis of racemic pseudoconhydrine (**1**), one of the Hemlock alkaloids.[2] The synthesis is based on our previous demonstration that mercuric ion initiated cyclization of δ-alkenyl carbamates leads to formation of *trans*-pyrrolidine derivatives with high stereoselectivity (**2** → **3**)[1] and the reported[3] conversion of halomethylpyrrolidines into 3-substituted piperidines through bicyclic aziridine intermediates (e.g., eq 1). These studies have led also to important new observations regarding the regiochemistry of the ring opening of such bicyclic aziridines.



The carbamate **6** used for the synthesis of **1** was prepared in straightforward fashion. The known ketone **5**[2b] was prepared by oxidation of alcohol **4** obtained by addition of the Grignard reagent from 4-bromobutene to butyraldehyde. In analogy with our earlier preparation of **2**,[1] ketone **5** was converted to its oxime, reduced, and acylated with benzyl chloroformate to give **6** in 91% yield. The cyclization of this carbamate was effected by treatment with mercuric acetate in tetrahydrofuran. The resulting organomercury intermediate **7a** was treated with KI and then I_2[4] to give the iodo compound **7b** in 78% yield. This iodo compound could also be prepared by iodine-in-

(1) For paper 1 in this series, see: Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920–3922. We have applied the term amidomercuration to cyclizations involving both amide and carbamate functional groups. Cyclizations involving carbamates have been termed ureidomercuration by others (Danishefsky, S.; Taniyama, E.; Webb, R. R., II *Tetrahedron Lett.* **1983**, *24*, 11–14) even though rules of nomenclature indicate that "ureido" is a prefix for a NH_2CONH group: Rule C-971.2, IUPAC Rules for Nomenclature of Organic Compounds. See Riguady, J.; Klesney, S. P. "Nomenclature of Organic Chemistry", Sections A–F and H; Pergamon Press: New York, 1979; p 297.

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