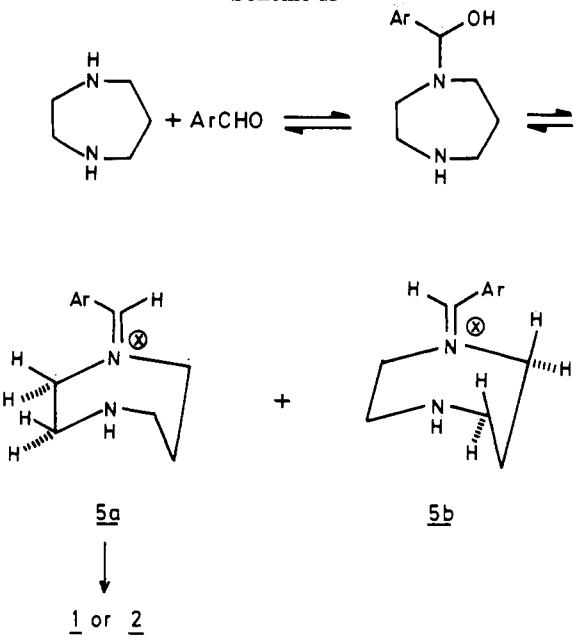
Scheme II



Satisfactory elemental analyses were obtained for new compounds **1b,c** and **2a,b**.

Acknowledgment. We gratefully acknowledge Prof. G. Govil, TIFR National NMR facility, Bombay, for 2D NOESY spectra on compound **1a**; we thank Dr. M. D. Nair and Dr. S. Selvavinayakam for helpful discussions.

Registry No. **1a**, 111159-67-2; **1b**, 111159-68-3; **1c**, 111159-69-4; **1d**, 111159-70-7; **1e**, 111159-71-8; **3a**, 111159-72-9; **3b**, 111159-73-0; *o*-phthalaldehyde, 643-79-8; *p*-phthalaldehyde, 623-27-8; 1,4-diazacycloheptane, 505-66-8; benzaldehyde, 100-52-7; 1-naphthalenecarboxaldehyde, 66-77-3; 9-anthracenecarboxaldehyde, 642-31-9; 2-hydroxy-1-naphthalenecarboxaldehyde, 708-06-5; 4-pyridinecarboxaldehyde, 872-85-5.

Improved Synthesis of 3-Substituted 7-Methoxybenzofurans, Useful Intermediates for Preparation of Morphine Analogues

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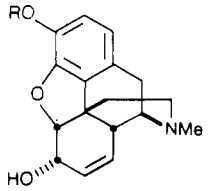
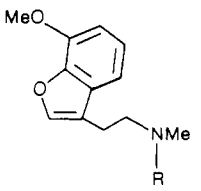
Interest in the synthesis of morphine (**1**), codeine (**2**), and their analogues and their pharmacologic properties as useful analgesics continues unabated. Several syntheses and synthetic approaches have been described recently.[3]

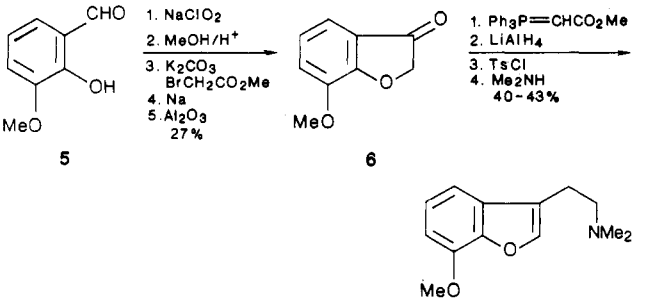


1, R=H
2, R=Me

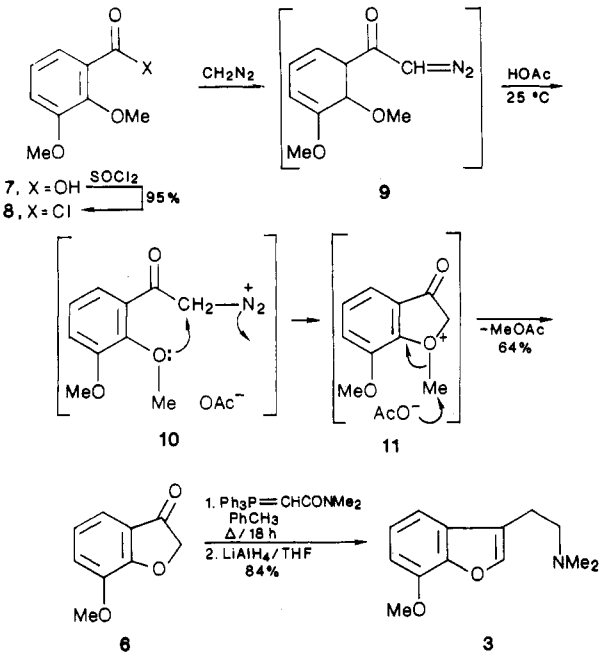


3, R=Me
4, R=H

For a proposed route to analgesics of the morphine class, we required a good supply of 3-[2-(dimethylamino)-ethyl]-7-methoxybenzofuran (**3**). Although this was an unknown compound, the analogous monomethyl amine **4** had been prepared by Ciganek and used in his synthesis of a morphine fragment.[4] However, this preparation requires nine steps from commercially available *o*-vanillin (**5**), affords **3** via the ketone **6** in reproducible yields of only



10–12% in our hands, and was therefore for us not applicable to the large-scale laboratory preparation of **3**. For this reason we have developed a rapid and efficient synthesis of **3** requiring only three operations from commercially available material.



2,3-Dimethoxybenzoic acid (**7**) was converted into the known acid chloride **8** in 95% yield by the standard method. Treatment of **8** with ethereal diazomethane followed by stirring the solution with glacial acetic acid at 25 °C afforded the ketone **6** in 64% yield. This reaction was described in 1956 by Richtzenhain and Alfredsson,[5] but their somewhat vague experimental description gives no

(1) UCLA Gold Shield Faculty Awardee, 1986–1988; Glenn T. Seaborg Awardee, 1987.
(2) Fellow of the Swiss Stiftung für Industriestipendien.

(3) (a) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473. (b) Weller, D. D.; Runyan, M. T. *Tetrahedron Lett.* **1986**, *27*, 4829. (c) Labidalle, S.; Min, Z. Y.; Reynet, A.; Thal, C.; Moskowitz, H. *Tetrahedron Lett.* **1986**, *27*, 2861. (d) Fujii, I.; Toyame, H.; Kanematsu, K. *Chem. Pharm. Bull.* **1986**, *34*, 4439. (e) Duthaller, R. O.; Ginsberg, D. *Helv. Chim. Acta* **1986**, *69*, 1559. (f) Dumont, R.; Newman, A. H.; Rice, K. C.; Brossi, A.; Toome, V.; Wegrzynski, B. *FEBS Lett.* **1986**, *206*, 125. (g) Schultz, A. G.; Shannon, P. J. *J. Org. Chem.* **1985**, *50*, 4421. (h) Schultz, A. G.; Lucci, R. D.; Napier, J. J.; Kinoshita, H.; Ravichandran, R.; Shannon, P.; Yee, Y. K. *J. Org. Chem.* **1985**, *50*, 217. (i) Handa, S.; Jones, K.; Newton, C. G.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1362.
(4) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.
(5) Richtzenhain, H.; Alfredsson, B. *Chem. Ber*, **1956**, *89*, 378.

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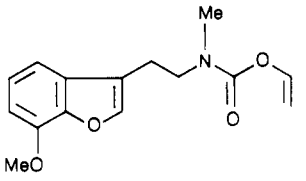
yield for the process.[6] The reaction presumably proceeds via the acyl diazonium acetate **10**, produced by protonation of the initially formed diazo ketone **9**. Intramolecular displacement of nitrogen from **10** by the lone pair of the *o*-methoxy group would give the oxonium acetate **11**, which would then lead to **6** by loss of methyl acetate. By this route, the ketone **6** is available from the acid **7** in only two steps in over 60% yield.

Conversion of **6** into the desired [(dimethylamino)-ethyl]benzofuran **3** was accomplished in a one-pot reaction. Condensation of the known [(*N*,*N*-dimethylcarbamoyl)-methylene]triphenylphosphorane (**12**)[7] with **6** in refluxing toluene for 18 h followed by removal of the toluene, addition of THF, and treatment at 0 °C with lithium aluminum hydride gave, after aqueous workup, the desired amine **3** in 84% yield. Thus this potential intermediate for the synthesis of morphine analogues is available in three steps from **7** in an overall yield of 51% by a reaction sequence that may be amenable to scale-up.

Finally, it should be pointed out that Ciganek's intermediate **4** can also be prepared via this route by treatment of **3** with vinyl chloroformate[10] and hydrolysis of the resultant vinyl carbamate **13**, in an overall yield of 70%.



13

Experimental Section

The IR spectra were recorded on a Perkin-Elmer 710B spectrometer. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker AM-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on an AEI MS-902 mass spectrometer. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use.

2,3-Dimethoxybenzoyl Chloride (8). A solution of 2,3-dimethoxybenzoic acid (**7**) (15.0 g, 82.4 mmol) in thionyl chloride (12 mL, 168 mmol) was refluxed for 20 min under nitrogen. The excess thionyl chloride was removed by distillation, and the residue was distilled in a Kugelrohr apparatus at 145 °C (0.02 Torr) to give 15.6 g (95%) of 2,3-dimethoxybenzoyl chloride as a colorless solid: mp 55–56 °C; IR ($CHCl_3$) 2970, 1770, 1470, 1420, 1310, 1265, 1080, 1000, 950, 910 cm^{-1}; MS (70 eV), *m/e* 202 (M^+, 4), 200 (M^+, 14), 166 (11), 165 (100), 122 (23), 121 (8), 107 (10), 92 (7), 77 (23), 63 (7), 53 (6), 51 (17), 50 (8), 36 (8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (1 H, dd, J = 3.9, 5.8 Hz), 7.13–7.16 (2 H, m, overlap), 3.92 (3 H, s), 3.90 (3 H, s).

7-Methoxy-3-benzofuranone (6). An ethereal diazomethane solution was prepared from diazald (5.90 g, 27.6 mmol) in 50 mL of ether and KOH (3.0 g, 53.6 mmol) in a mixture of 5 mL of water, 10 mL of ether, and 17 mL of 2-(2-ethoxyethoxy)ethanol according to a known procedure.[11] The obtained diazomethane solution was poured over 2,3-dimethoxybenzoyl chloride (**8**) (2.00 g, 10.0 mmol), and the resulting mixture was stirred at room temperature until no more gas evolution was observed (35 min). After evaporation of the solvent, the residue was dissolved in 20 mL of glacial acetic acid (strong gas and heat evolution) and stirred for 15 min at room temperature. The solvent was removed under reduced pressure, and the residue (1.80 g) was recrystallized from 25 mL of hot ether to give 1.05 g (64%) of 7-methoxy-3-benzofuranone (**6**) as slightly yellow crystals: mp 80–82 °C; recrystallization from ether gave crystals of mp 83–84 °C (lit.[5] mp 85 °C); IR ($CHCl_3$) 3000, 2930, 2840, 1710, 1600, 1500, 1440, 1270, 1180, 1160, 1090, 1035, 1000, 915, 825 cm^{-1}; MS (70 eV), *m/e* 165 (8), 164 (M^+, 100), 163 (8), 135 (72), 107 (30), 105 (6), 104 (7), 78 (6), 77 (18), 76 (39), 75 (7), 74 (6), 65 (23), 63 (10), 62 (5), 53 (5), 51 (13), 50 (13), 39 (11); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (1 H, d, J = 7.8 Hz), 7.11 (1 H, d, J = 7.8 Hz), 7.03 (1 H, t, J = 7.8 Hz), 4.68 (2 H, s), 3.97 (3 H, s).

***N*,*N*-Dimethyl-7-methoxy-3-benzofuranethylamine (3).** A mixture of 7-methoxy-3-benzofuranone (**6**) (5.29 g, 32.2 mmol) and [(*N*,*N*-dimethylcarbamoyl)methylene]triphenylphosphorane (**12**)[7] (12.3 g, 35.4 mmol) in 150 mL of toluene was refluxed under nitrogen for 18 h. The solvent was evaporated under reduced pressure and the residue diluted with 80 mL of dry THF and added at 0 °C to a suspension of lithium aluminum hydride (1.85 g, 48.7 mmol) in 250 mL of THF. After the reaction mixture was stirred for 10 min at 0 °C and 3 h at room temperature, 1.85 mL of water, 1.85 mL of 10% NaOH, and 5.6 mL of water were successively added to it. The resulting precipitate was removed by filtration and washed several times with ether. The combined ether portions were extracted with 250 mL of 1 N HCl, and the water phase was separated, made alkaline with 180 mL of 10% NaOH, and extracted three times with 200 mL of ether. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated and the residue distilled three times in a Kugelrohr apparatus at 80 °C (0.04 torr) to give 5.94 g (84%) of the amine **3** as a colorless liquid: IR ($CHCl_3$) 2930, 2860, 2820, 2780, 1640, 1560, 1490, 1460, 1430, 1360, 1260, 1170, 1090, 1055, 920 cm^{-1}; MS (70 eV), *m/e* 219 (M^+, 0.5), 201 (8), 78 (3), 77 (4), 58 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1 H, br s), 7.14–7.18 (2 H, m, overlap), 6.80 (1 H, dd, J = 3.2, 5.7 Hz), 4.00 (3 H, s), 2.84 (1 H, t, J = 7.4 Hz), 2.63 (1 H, t, J = 7.4 Hz), 2.32 (6 H, s). The HCl salt, mp 189–190 °C (ether/methanol), prepared by bubbling HCl into a solution of **3** in methylene chloride, was analyzed. Anal. Calcd for $C_{13}H_{18}NO_2Cl$: C, 61.05; H, 7.09. Found: C, 60.67; H, 7.12.

Ethenyl [2-(7-Methoxy-3-benzofuranyl)ethyl]methylcarbamate (13). A solution of vinyl chloroformate[10] (64 mg, 0.598 mmol) in 0.5 mL of dry dichloromethane was added at 0 °C under nitrogen to **3** (100 mg, 0.457 mmol) in 5 mL of dichloromethane. The reaction mixture was stirred for 18 h at room temperature, then poured on ice cold 1 N HCl, and extracted with ether. The organic layers were washed with 1 N bicarbonate, dried over Na_2SO_4, and concentrated under reduced pressure to give 101 mg (81%) of the vinyl carbamate **13**: IR ($CHCl_3$) 3020, 2940, 1705, 1640, 1620, 1590, 1490, 1440, 1400, 1360, 1270, 1190, 1180, 1160, 1100, 1050, 950, 870 cm^{-1}; MS (70 eV), *m/e* 275 (M^+, 56), 232 (56), 175 (71), 174 (43), 161 (19), 116 (11), 115 (12), 114 (71), 103 (12), 89 (8), 88 (9), 77 (13), 72 (100), 51 (7), 44 (76), 42 (26); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1 H, d, J = 10.8 Hz), 7.15–7.25 (3 H, m), 6.79–6.83 (1 H, m), 4.63 and 4.79 (1 H, dd, J = 14, 1.0 Hz), 4.40 and 4.47 (1 H, dd, J = 6.2, 1.0 Hz), 4.01 (3 H, s), 3.61 (2 H, t, J = 7.4 Hz), 2.88–2.97 (5 H, m); ^{13}C NMR (125 MHz) δ 145.7, 142.5 and 142.4, 141.8, 129.6, 123.4, 117.4 and 117.3, 111.8 and 111.6, 106.6, 95.4 and 95.2, 56.1, 49.2 and 48.6, 35.1 and 34.8, 22.8 and 22.0[12]

***N*-Methyl-7-methoxy-3-benzofuranethylamine (4).** Hydrogen chloride gas was bubbled through a solution of the urethane **13** (91 mg, 0.331 mmol) in 5 mL of dry dichloromethane for 45 min at room temperature. The solvent was removed and the residue dissolved in 5 mL of MeOH and stirred for 45 min at 50 °C. The mixture was poured into 1 N KOH and extracted with three portions of ether, the combined organic layers were washed twice with water and dried over Na_2SO_4, and the solvent was evaporated to give 59 mg (87%) of the amine **4** as a liquid: IR ($CHCl_3$) 2920, 2840, 2780, 1620, 1580, 1485, 1430, 1350, 1280, 1260,

(6) For further studies on this reaction, see: Dallacker, F.; Forb, W. *Justus Liebigs Ann. Chem.* **1966**, *694*, 98.

(7) This ylide was prepared by the method of Croce,[8] but instead of using the crude product, we first recrystallized **12** from ether to afford crystals of much higher melting point (170 °C) than that reported (151 °C).[8] Other examples of Wittig reactions of this type can be found in the work of Elix and co-workers.[9]

(8) Croce, P. D. *Ann. Chim.* (*Rome*) **1973**, *63*, 867 and references therein.

(9) Chan, J. H.-T.; Elix, J. A.; Ferguson, B. A. *Aust. J. Chem.* **1975**, *28*, 1097.

(10) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.

(11) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3. *Aldrich Tech. Info.* AL-131.

(12) Doubling of peaks is due to the presence of two conformers about the N–CO bond of the carbamate.

1170, 1090, 1050, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (1 H, s), 7.14–7.17 (2 H, m), 6.77–6.82 (1 H, m), 4.00 (3 H, s), 2.85–2.95 (4 H, m), 2.45 (3 H, s), 1.68 (1 H, br s).

Acknowledgment. We thank the National Institutes of Health (GM-31349) for financial support.

Registry No. 1, 57-27-2; 3, 111976-12-6; 4, 75611-13-1; 6, 7169-37-1; 7, 1521-38-6; 8, 7169-06-4; 12, 58131-63-8; 13, 111976-11-5; vinyl chloroformate, 5130-24-5.

A Transannulation Route to the [5.5.5.7]Fenestrane Ring System of Laurenene

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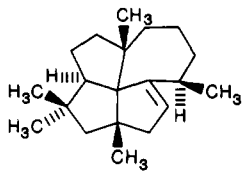
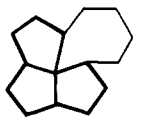
School of Chemistry, University of Hyderabad, Hyderabad 500 134, India

Received July 7, 1987

The diterpene hydrocarbon laurenene (1), isolated in 1979 from *Dacrydium cupressinum* by Corbett and coworkers, is unique among natural products in being the only fenestrane known to occur in nature.[1] The presence of a novel tetracyclic framework composed of three five-membered rings and a seven-membered ring, embellished with five asymmetric carbon centers and a network of methyl groups, makes laurenene an attractive target of synthesis. Basic to the synthesis of the natural product is the methodology for the construction of the [5.5.5.7]-fenestrane ring system 2 present in it. While the synthesis of several [4.4.4.5], [4.4.5.5], [5.5.5.5], and larger fenestranes have been reported[2,3] in recent years, the synthetic entry into the ring system 2 has not yet appeared in the literature.[3] We describe here a novel approach that has led to the attainment of a derivative of 2, albeit as a mixture of stereoisomers.



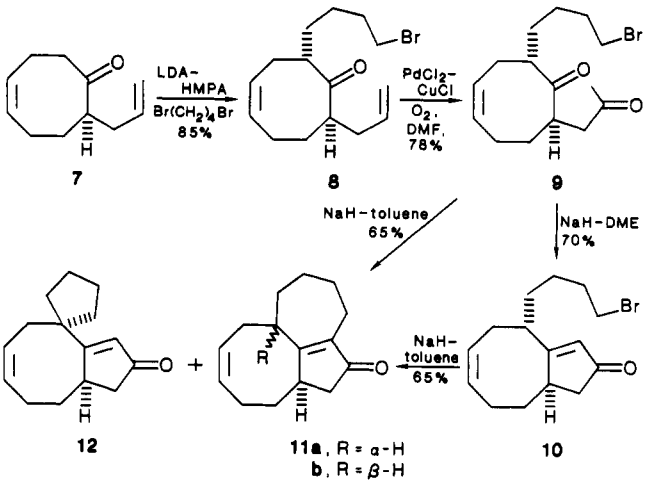
1



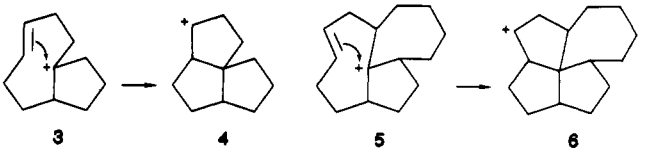
2

At the very outset, we recognized the carbocyclic ring system 2 as an angular triquinane (heavy lines) spanning a four-carbon bridge on the methylenes adjacent to the spirocenter. It was therefore tempting to adopt our general cationic transannulation approach[4] (3 → 4) to the angular triquinanes as the synthetic stratagem for the construction of the fenestrane ring system 2. Consequently, generation

Scheme I



of the bridged tricyclic cation 5 and its cyclization to 6 became our main concern.



3 4 5 6

Readily available[4,5] allylcyclooctenone 7 was selected as the starting point and regioselectively alkylated with 1,4-dibromobutane, under kinetically controlled conditions, to furnish the trans-dialkylated cyclooctenone 8, Scheme I. The allyl group in 8 was transformed into an acetonyl side chain through Wacker-type oxidation employing the Tsuji reaction conditions[4,6] to furnish the 1,4-diketone 9 in good yield. Internal aldol cyclization of 9 was achieved with sodium hydride under controlled conditions to deliver the bicyclic enone 10 as a single isomer. The structure of 10 was fully secured through its characteristic ^{13}C NMR lines at δ 207.6, 187.2, and 126.0 due to a β,β-disubstituted cyclopentenone moiety.[4,7]

The next step was crucial and required the four-carbon bridge formation through intramolecular bromide displacement from the α-position of the enone moiety in 10. This was realized through the dienolate generation with sodium hydride in refluxing toluene. A mixture of three tricyclic enones 11a,b and 12 (1:1) was obtained. The same mixture of three enones could be obtained directly from the diketone 9 on treatment with large excess of sodium hydride in boiling toluene. However, hydrogenolysis of the bromide in 9 was noticed as a competing reaction under these conditions. The three enones 11a,b and 12 could be separated through a combination of column chromatography and HPLC. The gross structure of 11a and 11b and their epimeric nature could be discerned from their spectral data. But, it was not possible to distinguish between them and, therefore, the epimeric mixture 11a,b was deployed for further reactions. The unwanted spiro enone 12 was readily identified on the basis of a quaternary sp^3 carbon resonance at δ 54.3 (s) in the ^{13}C NMR spectrum besides other complementary data.

With the acquisition of the tricyclic enones 11a,b, attention was turned toward the key transannular cyclization step 5 → 6. The enone mixture was exposed to a variety of protic acids (CF_3COOH, aqueous $HClO_4$, CF_3SO_3H) and

(1) (a) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774. (b) Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1791. (c) Hanton, L. R.; Simpson, J.; Weavers, R. T. *Aust. J. Chem.* **1983**, *36*, 2581.

(2) For a recent review, see: Venepalli, B. R.; Agosta, W. C. *Chem. Rev.* **1987**, *87*, 399. For some of the leading references in the area, see: Georgian, V.; Saltzman, M. *Tetrahedron Lett.* **1972**, 4315. Mitschka, R.; Cook, J. M.; Weiss, U. *J. Am. Chem. Soc.* **1978**, *100*, 3973. Luyten, M.; Keese, R. *Helv. Chim. Acta* **1984**, *67*, 2242. Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732.

(3) (a) For an approach toward laurenene, see: Crimmins, M. T.; Mascarella, S. W.; Bredon, L. D. *Tetrahedron Lett.* **1985**, *26*, 997. Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435 and private communication. (b) After completion of this manuscript, total syntheses of (±)-laurenene were reported: Tsunoda, T.; Amaike, M.; Tambunam, U. S. F.; Fujise, Y.; Ito, L.; Kodama, M. *Tetrahedron Lett.* **1987**, *28*, 2537. Crimmins, M. T.; Gould, L. D. *J. Am. Chem. Soc.* **1987**, *109*, 6199.

(4) Mehta, G.; Rao, K. S. *J. Am. Chem. Soc.* **1986**, 108, 8015.

(5) Apparau, M.; Barrella, M. *Tetrahedron* **1978**, *4*, 1817.

(6) Tsuji, J.; Schimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975.

(7) Mehta, G.; Pramod, K.; Subrahmanyam, D. *J. Chem. Soc., Chem. Commun.* **1986**, 247.

0022-3263/88/1953-0425$01.50/0