Conversion of Aldehyde 3 into Tambjamine D. A solution of the aldehyde 3 (4.7 mg) and isobutylamine (1 drop) in chloroform (5 mL) was stirred at 22 °C over molecular sieves (Type 3A pellets) for 2 h. The reaction product was filtered through silica gel with ethyl acetate as the eluant to yield tambjamine D (7; 3.0 mg, 53% theoretical), identical in all respects with the natural product.

LC Analysis of Tambjamines A–D (4–7) in *T. abdere* Exudate and Slime Trail. A specimen of *R. tigris* was allowed to attack an average sized specimen of *T. abdere* in a dish containing "Instant Ocean" synthetic seawater (100 mL). The *Tambje* exuded copious amounts of a yellow exudation from glands all over the dorsal surface. The animals were separated and removed. The dish and its contents were extracted with dichloromethane (3 × 75 mL), the combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed to yield a green oil (4.8 mg).

The concentrations of the tambjamines A–D (4–7) were determined by analytical LC by using known concentrations of pure compounds as standards. LC on an Alltech Spherisorb 5-μm C18-ODS column by using a linear gradient from 20% to 75% acetonitrile in 0.05 M pyridinium acetate buffer (pH 5.0) gave good separation of tambjamines A–D (retention times: A, 20.5 min; B, 13.5 min; C, 55.5 min; D, 61.0 min) that were detected by their UV absorption at 400 nm. Standard response curves of concentration vs. peak area (height × $W_{1/2}$) for each pure compound were used to calculate concentrations of the tambjamines in the exudate and slime trail (see Table I).

Two specimens of *T. abdere* were allowed to crawl over a bed of aquarium dolomite that had been washed with water, dichloromethane, deionized water, and synthetic seawater. The trials were marked with colored dolomite, the animals were carefully removed, and the dolomite on which the trail was laid was scooped up with a "lab scoop" spatula. The dolomite was washed with dichloromethane (3 × 200 mL), the combined extracts were dried over sodium sulfate, and the solvent was evaporated to yield a crude extract (3.1 mg) that was analyzed for tambjamines A–D as before (see Table I).

Acknowledgment. We thank James R. Lance for identifying the nudibranchs, Drs. D. F. and J. D. Soule for identifying the bryozoan, and Spencer Steinberg for suggesting the analytical method employed. Initial studies were performed by Dr. Chris Ireland and Robert W. Armstrong. This study was funded by a grant from the National Science Foundation (CHE-8121471).

Registry No. 1, 10476-41-2; 2, 85849-98-5; 3, 85849-99-6; 4, 85850-00-6; 5, 85850-01-7; 6, 85850-02-8; 7, 85850-03-9; 9, 85850-04-0; 10, 85850-05-1; 11, 85850-06-2; isobutylamine, 78-81-9.

Intramolecular Alkylation Route to the Bicyclo[3.3.1]nonane Ring System. A Total Synthesis of *dl*-Clovene

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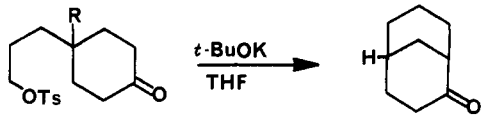
Received December 14, 1982

A formal total synthesis of *dl*-clovene (9) is described. The synthesis is highlighted by the efficient intramolecular alkylation of trisubstituted cyclohexenone **11b** to give 5-(2-ethylallyl)-1-methylbicyclo[3.3.1]non-2-en-4-one (**13b**) in 80% isolated yield. The preparation of **11b** follows an alkylation route starting with the enol ether 3 of cyclohexane-1,3-dione.

In 1966, Marvell and co-workers reported the first synthesis of a bicyclo[3.3.1]nonane by intramolecular enolate alkylation; e.g., **1a** → **2**.[1] The preparation of **1a** begins

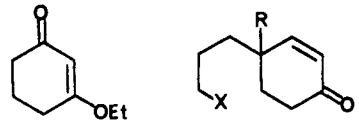


1a, R = H **2**

b, R = alkyl, aryl

by *p*-cyanoethylation of phenol and requires nine experimental steps. This strategy might not be readily adapted to synthesis of derivatives **1b** which have geminal ring disubstitution.[2]

The highly flexible 4,4-disubstituted cyclohexane ring synthesis developed by Stork and Danheiser[3] seems well suited to the preparation of cyclohexenones of type 4 from enol ether 3 of cyclohexane-1,3-dione. Cyclization of 4 would then provide bicyclo[3.3.1]nonanes with bridgehead substitution.



3 **4**

Cargill and Jackson report[4] that bicyclic enones such as **5a** give tricyclic enones (e.g., **6**) on internal α′-enolate alkylation.[5] This work was extended by Piers and coworkers to cyclizations of **5b,c**.[6] The Piers study is significant because experimental conditions were developed for nearly exclusive α′-alkylation to give α,β-enone **7** and α-alkylation to give β,γ-enone **8**.

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(4) R. L. Cargill and T. E. Jackson, *J. Org. Chem.*, **38**, 2125 (1973).

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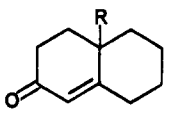
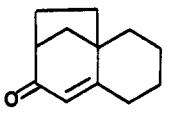


5a, R = CH_2CH_2Br
b, R = $CH_2CH_2CH_2Cl$
c, R = $CH_2CH_2CH_2I$



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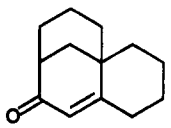

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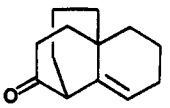
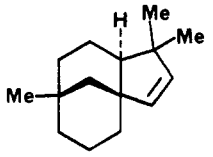


8

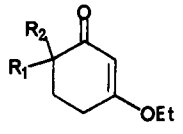
The bicyclo[3.3.1]nonane ring system as represented by structure **13** should be useful for a variety of synthesis applications. The α,β-unsaturated carbonyl group in **13** would be available for stereoselective addition reactions, ring modification processes (e.g., cleavage, expansion, and contraction), and other tactics directed at carbon-carbon bond formation. Herein, we describe an efficient bicyclo[3.3.1]nonane synthesis based on selective alkylations of enol ether **3**. An application of the method to synthesis of *dl*-clovene (**9**)[7] is presented. Clovene, an acid rearrangement product of caryophyllene, has been prepared from bicyclononane **14b** via enone **15** by Raphael and coworkers.[8] Bicyclononane **14b** is an intermediate in our formal total synthesis of **9**.

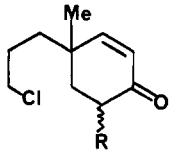


9

Results and Discussion

Alkylation of enol ether **3**[9] with lithium diisopropylamide (LDA) and methyl iodide gives **10a**, and this is converted to **10b** in 93% overall yield by a second alkylation (LDA



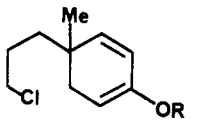


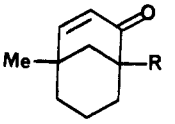
10a, R_1 = Me; R_2 = H
b, R_1 = Me; R_2 = $CH_2CH_2CH_2Cl$

11a, R = H
b, R = $CH_2C(=CH_2)Et$

and 1-bromo-3-chloropropane). Reduction of **10b** with lithium aluminum hydride, followed by acid-catalyzed hydrolysis–dehydration affords **11a** in 98% yield. The remaining carbon appendage is added by enolate alkylation of **11a** with 2-(bromomethyl)but-1-ene[10] to give trisubstituted cyclohexenone **11b** in 40% isolated yield.

Successful intermolecular reaction of the enolate derived from **11a** is dependent upon the reactivity of the electrophilic reagent. The lithium enolate of **11a** generated at −78 °C undergoes reaction with chlorotrimethylsilane to give dienol trimethylsilyl ether **12a** in nearly quantitative





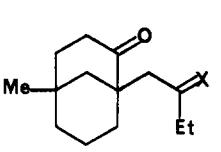
12a, R = $SiMe_3$
b, R = $SiMe_2t$-Bu

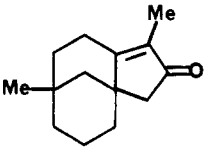
13a, R = H
b, R = $CH_2C(=CH_2)Et$

yield. Reaction of the enolate of **11a** with *tert*-butylchlorodimethylsilane (−78 °C to room temperature) is still effective but results in a mixture of **12b** and bicyclononenone **13a** in a ratio of 9.5:1. Bicyclononenone **13a** is obtained in 85% yield by warming the lithium enolate of **11a** to room temperature.

The desired intramolecular enolate alkylation is accomplished by treatment of **11b** with LDA at −78 °C and warming the resulting enolate in THF–HMPA solution to room temperature. Chromatographic separation of the reaction mixture gives pure bicyclononenone **13b** in 80% isolated yield. Thus intramolecular α'-enolate alkylation can be used for the construction of bridgehead-disubstituted bicyclo[3.3.1]nonanes from 4,4,6-trisubstituted cyclohexenones.

Conversion of **13b** to the Raphael clovene intermediate **14b** (and hence **15**) is accomplished by (1) conjugate reduction of **13b** with K-Selectride (Aldrich)[11] followed by oxidative workup to give bicyclononane **14a** (77%) and (2) ozonolysis of **14a** in methanolic solution[12] (49% isolated yield).





14a, X = CH_2
b, X = O

15

While spectral data for **14b** are completely compatible with the structural assignment, scant spectral data for **14b** are available in the literature[8] for comparison, and thus, **14b** was converted to enone **15** by the published procedure.[8a]

Summary

With this formal total synthesis of *dl*-clovene, we have demonstrated the simplicity and efficiency of the intramolecular alkylation route to the bicyclo[3.3.1]nonane ring system. Applications of this methodology to other syn-

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thesis problems will be reported in the future.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer Model 137 spectrophotometer. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer Model R600 nuclear magnetic resonance spectrometer at 60 MHz and on a Varian Model XL200 NMR spectrometer at 200 MHz with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer as well as on a Finnigan OWA-1020 GC/MS system. UV spectra were recorded on a Perkin-Elmer Model 552 spectrophotometer. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI, and by Galbraith Laboratories, Inc., Knoxville, TN. Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Associates preparative LC 500 unit by using Prep Pak 500 silica gel cartridges or on a Waters 1 in. × 1 ft steel Prep column packed with E. Merck Art. Kieselgel 60 (40–63-μm silica gel). Preparative thin-layer chromatography was carried out on plates prepared from E. Merck AG Darmstadt silica gel PF-254 or GF-254.

6-(3-Chloropropyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one (10b). A solution of lithium diisopropylamide (0.07 mol) was prepared at −20 °C from diisopropylamine (7.18 g, 0.071 mol) and *n*-butyllithium (2.4 M, 9.95 mL, 0.07 mol) in dry tetrahydrofuran (THF, 65 mL). After 0.5 h the solution was cooled to −78 °C, and a solution of 3-ethoxy-6-methyl-2-cyclohexen-1-one (**10a**)[3] (9.96 g, 0.064 mol) in dry THF (40 mL) was added dropwise. After the addition was complete the solution was stirred for 45 min at −78 °C. A solution of 1-bromo-3-chloropropane (20.15 g, 0.120 mol) in dry THF (40 mL) was added dropwise at −78 °C. When the addition was complete, the mixture was stirred at −78 °C for 1 h after which cooling was discontinued. The reaction was stirred for 24 h at room temperature and then quenched with water (20 mL). The solvent was removed on a rotary evaporator and the residue dissolved in ether (50 mL). The ether solution was washed with water (3 × 20 mL) and brine (3 × 20 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent on a rotary evaporator gave **10b** (14.4 g, 98%). Analytical samples were prepared by HPLC (3:1 hexane–ethyl acetate): ^1H NMR δ 1.1 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz), 1.6–2.1 (m, 6 H), 2.46 (t, 2 H, J = 7 Hz), 3.55 (m, 2 H), 3.93 (q, 2 H, J = 7 Hz), 5.28 (s, 1 H); IR (neat) 1660, 1620 cm^{-1}; mass spectrum, m/e (relative intensity) 230 (M^+, 2.2), 202 (8.2), 154 (100). Anal. Calcd for $C_{12}H_{19}ClO_2$: C, 62.46; H, 8.29. Found: C, 62.72; H, 8.33.

4-(3-Chloropropyl)-4-methyl-2-cyclohexen-1-one (11a). To a dry flask equipped with a nitrogen inlet, reflux condenser, and magnetic stirring bar was added dry ether (15 mL). After the mixture was cooled to 0 °C, 0.96 mL (0.96 mmol) of a 1 M solution of lithium aluminum hydride was added. A solution of **10b** (0.43 g, 1.9 mmol) in ether (1 mL) was added dropwise. The mixture was stirred for 15 min. The reaction was quenched with saturated ammonium chloride solution (5 mL), after which ether (30 mL) was added. The mixture was washed with water (3 × 10 mL) and brine (3 × 10 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated, the residue was dissolved in absolute ethanol (10 mL), and hydrochloric acid solution (2 mL, 10%) was added. After stirring at room temperature for 45 min, the mixture was neutralized with sodium bicarbonate (5% solution). The resulting solution was dissolved in ether (20 mL) and washed with brine (1 × 10 mL). The aqueous layer was extracted with ether (2 × 10 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated to afford **11a** (0.29 g, 82%). Analytical samples were prepared by HPLC (4:1 hexane–ethyl acetate): ^1H NMR δ 1.16 (s, 3 H), 1.48–2.06 (m, 6 H), 2.46 (m, 2 H), 3.56 (t, 2 H, J = 6 Hz), 5.91 (d, 1 H, J = 10 Hz), 6.7 (d, 1 H, J = 10 Hz); IR (neat) 1670 cm^{-1}; mass spectrum, m/e 186 (M^+, 16), 158 (33), 144 (59), 109 (84), 41 (100). Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.09. Found: C, 64.53; H, 8.13.

4-(3-Chloropropyl)-4-methyl-6-(2-ethylallyl)-2-cyclohexen-1-one (11b). Lithium diisopropylamide (11.57 mmol) was generated in dry THF (10 mL) from *n*-butyllithium (11.57 mmol) and diisopropylamine (12.5 mmol) at −20 °C. The reaction mixture was cooled to −78 °C, and a solution of **11a** (1.79 g, 9.63 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred for 1 h at −78 °C. 2-(Bromomethyl)but-1-ene (2.87 g, 19.3 mmol) was added followed by hexamethylphosphoramide (2.59 g, 14.5 mmol). The reaction was stirred for 30 min at −78 °C, for 4 h at −40 to −50 °C, and then for 15 h at −20 °C, during which time a dark red coloration appeared. The reaction mixture was quenched at −20 °C with a saturated solution of ammonium chloride, and the solvent was removed on a rotary evaporator. The residue was dissolved in ether (50 mL), washed with water (4 × 50 mL) and brine (2 × 50 mL), and dried over anhydrous magnesium sulfate. Removal of the solvent gave a crude oil which was purified by HPLC (8:1 hexane–ethyl acetate) to yield **11b** as a mixture of diastereomers: 0.98 g (40%); ^1H NMR δ 1.05 (t, 3 H, J = 7 Hz), 1.1 and 1.18 (2 overlapping s, 3 H), 1.33–3.2 (m, 11 H), 3.55 (t, 2 H, J = 6 Hz), 4.78 (d, 2 H, J = 6 Hz), 5.92 (d, 1 H, J = 10 Hz), 6.63 (d, 1 H, J = 10 Hz); IR (neat) 1680, 1650 cm^{-1}; mass spectrum, m/e 254 (M^+, 2.0), 186 (13), 178 (11), 158 (47), 41 (100). Anal. Calcd for $C_{15}H_{23}ClO$: C, 70.71; H, 9.09. Found: C, 70.80; H, 9.01.

5-(3-Chloropropyl)-5-methyl-2-(trimethylsiloxy)-1,3-cyclohexadiene (12a). Lithium diisopropylamide (0.42 mmol) was prepared at −10 °C in dry THF (1 mL). After the mixture was cooled to −78 °C a solution of **11a** (0.071 g, 0.38 mmol) in dry THF (2 mL) was added dropwise. The resulting solution was stirred at this temperature for 40 min. Trimethylsilyl chloride (0.05 g, 0.46 mmol) was added quickly. The reaction mixture was maintained at −78 °C for 1.5 h and then allowed to slowly come to room temperature. Pentane was added and the resulting slurry filtered through Celite. Removal of the solvent under reduced pressure afforded **12a**: 0.098 g, (99%); ^1H NMR δ 0.19 (s, 9 H), 1.16–1.92 (m, 4 H), 2.07 (dd, 1 H, J = 20, 6 Hz), 2.21 (dd, 1 H, J = 20, 6 Hz), 3.52 (t, 2 H, J = 6 Hz), 4.8 (m, 1 H), 5.52 (d, J = 8 Hz), 5.64 (dd, J = 8, 2 Hz); IR (neat) 1655, 1601 cm^{-1}.

2-(*tert*-Butyldimethylsiloxy)-5-(3-chloropropyl)-5-methyl-1,3-cyclohexadiene (12b). Lithium diisopropylamide (0.79 mmol) was generated at −20 °C in dry THF (2 mL). The reaction mixture was cooled to −78 °C, and a solution of **11a** (0.097 g, 0.52 mmol) in dry THF (2 mL) was added dropwise. After 45 min a solution of *tert*-butyldimethylsilyl chloride (0.100 g, 0.66 mmol) in dry THF (2 mL) was added dropwise followed by hexamethylphosphoramide (0.12 g, 0.67 mmol). The solution was stirred for 1.5 h at −78 °C and then allowed to warm to room temperature. After 18 h at room temperature, water (3 mL) was added. The solvent was removed under reduced pressure and the residue partitioned between ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (2 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL) and brine (2 × 10 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave an oil (0.15 g), which was shown to be a mixture of **11a** (40%), **13a** (5.7%), and **12b** (54%) by ^1H NMR analysis. The ^1H NMR spectrum of the enol ether **12b** had the following characteristic peaks: δ 4.77 (m, 1 H), 5.51 (d, 1 H, J = 10 Hz), 5.63 (dd, 1 H, J = 10, 2 Hz).

1-Methylbicyclo[3.3.1]non-2-en-4-one (13a). Lithium diisopropylamide (1.6 mmol) was generated in dry THF (4 mL) at −20 °C. The reaction mixture was then cooled to −78 °C. A solution of **11a** (0.203 g, 1.09 mmol) in dry THF (2 mL) was added dropwise. The resulting solution was stirred for 50 min, and then hexamethylphosphoramide (0.23 g, 1.31 mmol) was added. The solution was stirred for 20 min at this temperature, and then the cooling bath was removed. After the mixture was stirred for 26 h at room temperature, water (3 mL) was added. The solvent was removed on a rotary evaporator and the residue partitioned between ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (2 × 10 mL). The combined organic extracts were washed successively with water (3 × 30 mL) and brine (2 × 20 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent provided **13a** as a yellow oil (0.139 g, 85%) which appeared to be of good purity by ^1H NMR analysis. An analytical sample was prepared by HPLC (15:1 hexane–ethyl acetate): ^1H NMR δ 1.12 (s, 3 H), 1.32–1.67 (m, 6 H), 1.76 (m, 1 H), 2.06 (m, 1 H), 2.55 (br s, 1 H), 6.17 (d, 1 H, J = 10 Hz), 6.64 (dd, 1 H, J = 10, 2 Hz); IR (neat) 1670, 1601 cm^{-1}; mass spectrum, m/e 150 (M^+, 100), 135 (17), 122 (29). Anal.

Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.09; H, 9.43.

5-(2-Ethylallyl)-1-methylbicyclo[3.3.1]non-2-en-4-one (13b). Lithium diisopropylamide (4.25 mmol) was generated in dry THF (20 mL) at -20 °C and cooled to -78 °C. A solution of **11b** (0.90 g, 3.5 mmol) in dry THF (22 mL) was added dropwise over 25 min. After the resulting solution was stirred at -78 °C for 1 h, hexamethylphosphoramide (1.27 g, 7.08 mmol) was added. Stirring was continued at -78 °C for 15 min, and then the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and was stirred for 26 h, after which water was added, and the solvent was removed under reduced pressure. The residue was partitioned between ether (40 mL) and water (20 mL). The combined aqueous layers were extracted with ether (2 × 20 mL). The combined organic extracts were washed with water (4 × 80 mL) and brine (1 × 100 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure provided a yellow oil (0.77 g, quantitative) which appeared to be of good purity by ^{1}H NMR analysis. An analytical sample was prepared by HPLC (25:1 hexane–ethyl acetate): 0.6 g, (80%); ^{1}H NMR δ 0.98 (t, 3 H, J = 7 Hz), 1.13 (s, 3 H), 1.23–2.13 (m, 11 H), 2.83 (d, 1 H, J = 16 Hz), 4.71 (d, 2 H, J = 10 Hz), 6.1 (d, 1 H, J = 10 Hz), 6.54 (dd, 1 H, J = 10, 2 Hz); IR (neat) 1675, 1640 cm^{-1}; mass spectrum, m/e 218 (M$^+$, 32), 203 (13), 189 (99), 41 (100); UV (MeOH) λ_{max} 231 nm (ϵ 7400). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.78; H, 10.13.

5-(2-Ethylallyl)-1-methylbicyclo[3.3.1]nonan-4-one (14a). A solution of enone **13b** (0.174 g, 0.8 mmol) in dry THF (10 mL) was cooled to -78 °C. K-Selectride (1 M, 0.88 mL) was added dropwise to the reaction mixture. The solution was stirred for 1 h at -78 °C and 1 h at 0 °C. Sodium hydroxide solution (3 N, 1.5 mL) was added, the cooling bath was removed, and hydrogen peroxide (30%, 0.5 mL) was slowly added. The resulting milky white suspension was stirred for 18 h at room temperature. The aqueous layer was separated and extracted with ether (3 × 15 mL). The combined organic fractions were washed with water (2 × 20 mL), 1 N $NaHSO_3$ solution (2 × 20 mL), and brine (2 × 20 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded **14a**, which was chromatographed on HPLC (25:1 hexane–ethyl acetate): 0.136 g (77% isolated yield); ^{1}H NMR δ 0.98 (t, 3 H, J = 7 Hz), 1.03 (s, 3 H), 1.17–2.87 (m, 16 H), 4.72 (d, 2 H, J = 10 Hz); IR (neat) 1700 cm^{-1}; mass spectrum, m/e 220 (M$^+$, 62), 191 (100), 163 (90). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.57; H, 11.00.

5-Methyl-2-oxo-1-(2-oxobutyl)bicyclo[3.3.1]nonane (14b). A solution of ketone **14a** (0.093 g, 0.42 mmol) in dry methanol (50 mL) was cooled to -78 °C. Ozone was passed through the solution to saturation as evidenced by development of a deep blue coloration. The reaction mixture was stirred for 30 min at -78 °C, the cold bath was removed, and the mixture was stirred until the blue coloration disappeared. After 20 min, the mixture was recooled to -78 °C, and dimethyl sulfide (3 mL) was slowly added. The reaction mixture was gradually warmed to 0 °C over 1.5 h and stirred for an additional 4 h at 0 °C. After the mixture was stirred for 12 h, the solvent was distilled from the mixture under reduced pressure, and the residue was dissolved in ether (75 mL). The ether extract was washed with water (3 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded crude diketone **14b**, which was chromatographed by HPLC (25:1 hexane–ethyl acetate) to give **14b**: 0.046 g (49%); ^{1}H NMR δ 1.01 (t, 3 H, J = 6 Hz), 1.03 (s, 3 H), 1.08–1.94 (m, 10 H), 2.22 (d, 1 H, J = 16 Hz), 2.28–2.45 (m, 3 H), 2.78–3.01 (m, 1 H), 3.08 (d, 1 H, J = 16 Hz); IR (neat) 1710 cm^{-1} (lit.[8a,b] 1710 cm^{-1}); mass spectrum, m/e 222 (M$^+$, 39), 207 (64), 193 (100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.63; H, 10.17.

4-Demethylclov-4-en-3-one (15). The diketone **14b** (0.028 g, 0.13 mmol) was reacted with KOH in refluxing methanol according to the published procedure.[8a,b] The product was purified by preparative TLC (SiO_2, 3:1 hexane–ethyl acetate) to give **15**: 0.016 g (63%); ^{1}H NMR δ 0.90 (s, 3 H), 1.16–2.0 (m, overlapping s at 1.65, 13 H), 2.18 (d, 1 H, J = 18 Hz), 2.28 (d, 1 H, J = 18 Hz), 2.8 (m, 2 H); IR (neat) 1690, 1640 cm^{-1} (lit. 1690, 1630 cm^{-1}); UV (EtOH) λ_{max} 244 nm (ϵ 13 900) [lit. 244 (12 800)]. The 2,4-dinitrophenylhydrazone was isolated in the form of red plates: mp 221–223 °C (lit. mp 223–225 °C); UV ($CHCl_3$) λ_{max} 395–399 nm (ϵ 30 400) [lit. 393–397 (30 800)]; ^{1}H NMR δ 0.91 (s, 3 H), 1.19–2.04 (m overlapping s at 1.84, 13 H), 2.37 (d, 1 H, J = 17 Hz), 2.48 (d, 1 H, J = 17 Hz), 2.69 (m, 2 H), 7.37 (s, 1 H), 7.99 (d, 1 H, J = 9.8 Hz), 8.26 (dd, 1 H, J = 10, 2.5 Hz), 9.14 (d, 1 H, J = 2.6 Hz).

Acknowledgment. This work was supported by the National Institute of General Medical Science (Grant No. GM 26568). We thank R. A. Raphael and J. S. Roberts for assistance with spectral data relating to the synthesis of *dl*-clovene. NMR spectra were recorded on a Varian XL-200 instrument purchased with funds provided, in part, by a National Science Foundation Department Instrumentation Grant.

Registry No. (±)-**9**, 3852-30-0; (±)-**10a**, 85909-15-5; (±)-**10b**, 85909-16-6; (±)-**11a**, 85909-17-7; (±)-*cis*-**11b**, 85909-18-8; (±)-*trans*-**11b**, 85909-19-9; (±)-**12a**, 85909-20-2; (±)-**12b**, 85909-21-3; (±)-**13a**, 85909-22-4; (±)-**13b**, 85909-23-5; (±)-**14a**, 85909-24-6; (±)-**14b**, 85909-25-7; (±)-**15**, 85909-26-8; (±)-**15** 2,4-dinitrophenylhydrazone, 85923-33-7; $ClSiMe_2$-*t*-Bu, 18162-48-6; 1-bromo-3-chloropropane, 109-70-6; 2-(bromomethyl)but-1-ene, 59032-45-0.

Synthesis of Conformationally Defined Analogues of Norfenfluramine. A Highly Stereospecific Synthesis of Amines from Alcohols in the Benzobicyclo[2.2.1]heptene System[1a,b]

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Received October 12, 1982

The synthesis of 5-, 6-, 7-, and 8-(trifluoromethyl)benzonorbornen-2-yl alcohols **6a–9a** (exo) and **11a-14a** (endo) and an examination of the stereospecificity of the conversion to amines via phthalimides are reported. The exo alcohols were prepared from 5-(trifluoromethyl)benzonorbornadiene (**16**) and 6-(trifluoromethyl)benzonorbornadiene (**23**) by hydroboration–oxidation. The endo alcohols were available from the corresponding exo alcohols by oxidation to the benzonorbornen-2-ones **24** (5-CF_3), **25** (6-CF_3), **26** (7-CF_3), and **27** (8-CF_3) followed by diborane reduction. While in the presence of the electron-withdrawing CF_3 group the exo alcohols gave predominantly the endo amines, the endo alcohols afforded exclusively the exo amines.

As part of a search for the explanation of the dramatic pharmacological differences between amphetamine and its *m*-(trifluoromethyl)-*N*-ethyl analogue, fenfluramine (**1**, Chart I), and on the basis of our initial highly successful

0022-3263/83/1948-2321$01.50/0