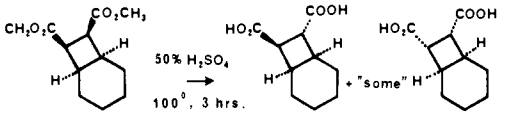
undergoes hydrolysis to a urea–acid in mild base (2.8 N NaOH, 45 °C, 2 days), whereas the minor isomer resists both hydrolysis and epimerization even under much more forcing conditions (10 N NaOH, 70 °C, 2 days), assuming an analogy with the report (T. Kunieda and B. Witkop, *J. Am. Chem. Soc.*, **93**, 3478, 3493 (1971)) that head-to-tail *exo*-thymine dimer hydrolyzes in aqueous base much more readily than does head-to-head *endo*-thymine dimer.

(28) 5% SE-30, 170 °C; R_f(**10t**) = 9.7 min; R_f (**10c**) = 10.9 min.
(29) Prepared from **11** (F. V. Brutcher and D. D. Rosenfeld, *J. Org. Chem.*, **29**, 3154 (1964)) by catalytic hydrogenation followed by LAH reduction.
(30) Prepared from **12** (G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957)) by LAH reduction.
(31) These results will be the subject of a forthcoming paper.
(32) See C. Galli, G. Illuminati, and L. Mandolini, *J. Am. Chem. Soc.*, **95**, 8374 (1973), and references cited therein.
(33) J. Put and F. C. De Schryver, *J. Am. Chem. Soc.*, **95**, 137 (1973).
(34) The rate of hydrolysis of esters decreases with increasing steric hindrance in base (see E. A. S. Cavell, N.B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960); E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961); also, footnote 27) and in dilute acid (N. B. Chapman, J. Shorter, and K. J. Toyne, *J. Chem. Soc.*, 2543 (1961)), although the rate increases with increasing steric hindrance in 95% H_2SO_4 (H. Van Bekkum, H. M. A. Buurmans, B. M. Wepster, and A. M. Van Wijk, *Recl. Trav. Chim. Pays-Bas*, **88**, 301 (1969)).
(35) Prepared from cyclohexen-4-yl bromoacetate and 2,4-bis(trimethylsiloxy)pyrimidine by the procedure of E. Wittenburg, *Chem. Ber.*, **101**, 2132 (1968).
(36) (a) H. Yoshioka, T. J. Mabry, and A. Higo, *J. Am. Chem. Soc.*, **92**, 923 (1970); (b) K. Ohga and T. Matsuo, *Bull. Chem. Soc. Jpn.*, **43**, 3505 (1970).
(37) Bruce A. Pearlman, *J. Am. Chem. Soc.*, following paper in this issue.
(38) G. Fuchs and N. Hellstrom, *Lantbrukshoegsk. Ann.*, **30**, 615 (1964); *Chem. Abstr.*, **63**, 6850g (1965).
(39) The acetyl substituent of **28** is presumed to have the exo configuration because it is expected to enolize under the reaction conditions (H. Schechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, **84**, 2905 (1962)), and the exo isomer is expected to be more stable than the endo isomer by analogy with the result indicated below (R. Robson, P. W. Grubb, and J. A. Barltrop, *J. Chem. Soc.*, 2153 (1964)).



(40) B. E. Cross, J. F. Grove, and A. Morrison, *J. Chem. Soc.*, 2498 (1961).
(41) B. Bellau and D. Dvornik, *Can. J. Chem.*, **43**, 2545 (1965).
(42) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
(43) Prepared by LAH reduction (ether, Δ, 19 h, 90%) of cyclohexene-3-carboxylic acid, which was prepared by a double-Birch reduction of benzoic acid by using the procedure developed by F. Camps, J. Coll, and J. Pascual (*J. Org. Chem.*, **32**, 2563 (1967)) for double-Birch reductions of substituted benzoic acids.
(44) Prepared from 5-hydroxymethyluracil (R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959)) by treatment with excess ethereal CH_2N_2 in methanol at room temperature followed by stirring in neat $SOCl_2$ at room temperature for 3 h.
(45) (a) A. J. Birch, *J. Chem. Soc.*, 593 (1946); (b) A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8**, 1 (1972).
(46) Prepared in 77% yield by treatment of a cold (−78 °C) solution of 4-hydroxycyclohexene and 1.2 equiv of maleoylglycyl chloride (L. Paul, A. Dittmar, and C. Rusch, *Chem. Ber.*, **100**, 2757 (1967)) in methylene chloride with 1.4 equiv of triethylamine followed by warming to room temperature.
(47) Prepared in 61% yield by treatment of an ice-cooled solution of **5**[37] and 1.4 equiv of maleoylglycyl chloride in methylene chloride with 2.0 equiv of triethylamine.
(48) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

A Total Synthesis of Reserpine[1a]

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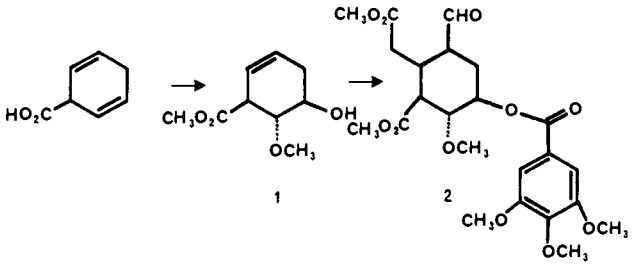
Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. *Received February 24, 1978*

Abstract: Woodward reserpine precursor **2** has been synthesized from 1,4-dihydrobenzoic acid, using the novel methodology described in the preceding paper.

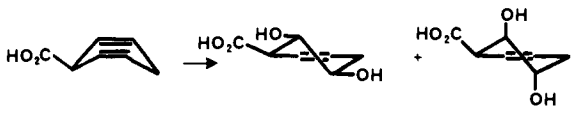
Introduction

The preceding paper[2] describes a method for effecting the equivalent of a de Mayo reaction with formyl acetic ester. In this paper, we report that application of this method to olefin **1** affords Woodward reserpine precursor **2**, and that olefin **1** is available by a short (four step) sequence from 1,4-dihydrobenzoic acid.



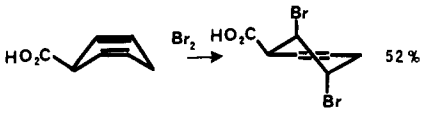
1 2

Synthesis of 1. The strategy of using 1,4-dihydrobenzoic acid[3] (see Experimental Section for an improved method of preparation) as the starting material for preparation of **1** is superficially attractive because the only difference between **1** and 1,4-dihydrobenzoic acid is that the former has two oxygen functionalities instead of a double bond. Moreover, this strategy is advantageous in practice: treatment of 1,4-dihydrobenzoic acid with 1 equiv of performic acid at room temperature for 30 h, then at reflux for 1 h, followed by boiling in water for 4.5 h (to hydrolyze the formates) affords the desired "diequatorial" diol **3** in multi-gram quantities.



3 4

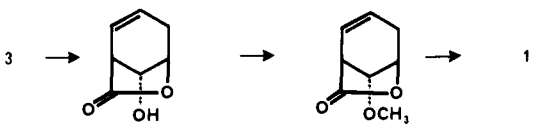
Presumably, the undesired "diaxial" isomer **4** is the major product of this reaction,[4] by analogy with the report that the major product of bromination of 1,4-dihydrobenzoic acid is the diaxial isomer **5**.[5] However, **3** is formed in sufficiently high



5

yield that this method of preparation is attractive.

Of course, diol **3** is of no value unless its C-4 hydroxyl can be selectively methylated. However, in fact, this can be accomplished straightforwardly by the sequence of thermolysis (180 °C, 1.5 h), methyl etherification (Ag_2O, CH_3I, crushed $CaSO_4$),[6] and methanolysis (H_2SO_4, CH_3OH, Δ, 2 h).



6 7

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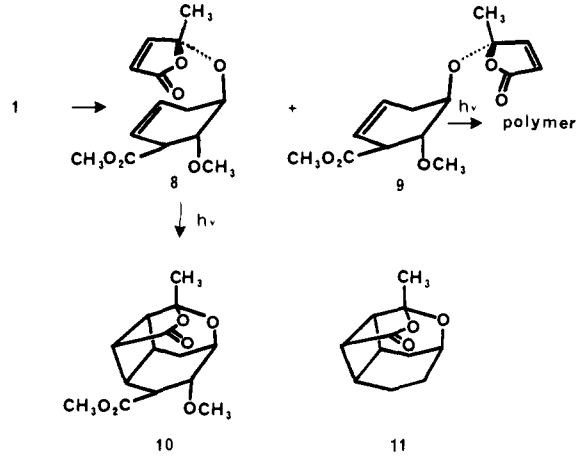
Thus, a procedure for the preparation of multi-gram quantities of **1** has been found.

Synthesis of Woodward Reserpine Precursor 2. The double bond of **1** was then subjected to the aldehydo ester functionalization sequence that we had developed[2] for this application.

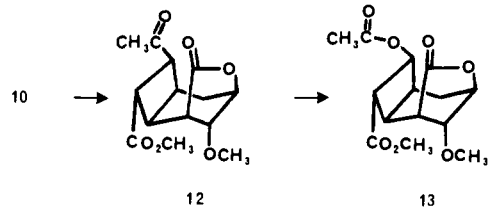
First, **1** was treated with the pseudo-acid bromide of *cis*-β-acetylacrylic acid[7] in the presence of Ag_2O and crushed $CaSO_4$. As with 4-hydroxycyclohexene, the product was a 1:1 mixture of diastereomeric ketals (**8** and **9**). However, in this case, the two ketals have sufficiently different mobilities on silica gel that they can be separated cleanly by routine column chromatography. Also, the undesired ketal **9** can be converted back into **1** quantitatively by refluxing in acidic methanol. Thus, the yield of **8** from **1** is essentially quantitative rather than 50%.



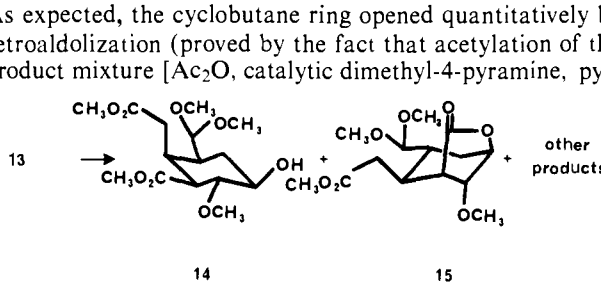
Ketal **8** was then converted into the desired cyclobutane **10** in 30% yield by photolysis in 0.003 M acetone solution.

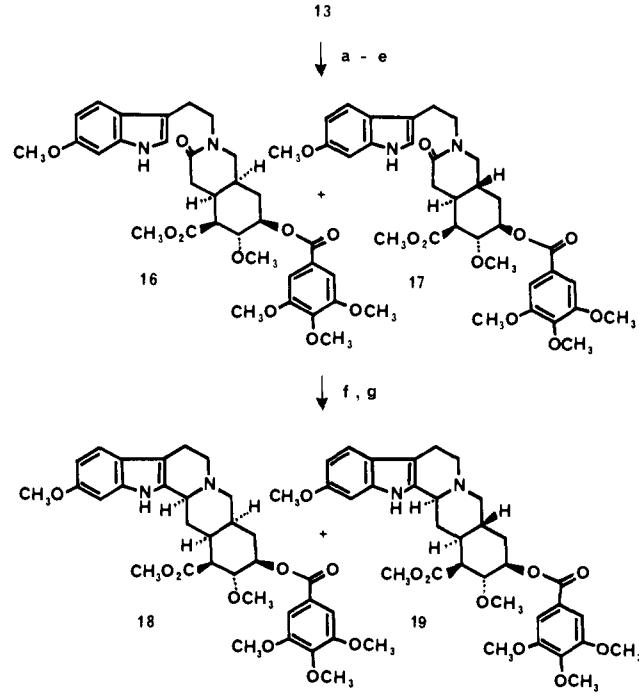
The sequence[2] that had been used for the unmasking of the latent aldehydo ester functionality of the adduct **11** was then applied to **10.**

First, **10** was subjected to refluxing in acidic methanol. As expected from the model studies, the ketal bridge underwent methanolysis and the liberated methyl ketone epimerized to the exo configuration.[8] In addition, the liberated hydroxyl group formed a lactone with the carbomethoxy substituent of the cyclohexane ring; however, this transformation is irrelevant for synthetic purposes because none of the five contiguous asymmetric centers on the cyclohexane ring become inverted. The methyl ketone **12** was then converted into the corresponding acetate **13** by treatment with trifluoroperacetic acid.[9]



Acetate **13** was then refluxed in acidic methanol for 48 h. As expected, the cyclobutane ring opened quantitatively by retroaldolization (proved by the fact that acetylation of the product mixture [Ac_2O, catalytic dimethyl-4-pyramine, pyr, room temperature, 1 h] afforded no starting material **13** by NMR). Also, the lactone ring underwent methanolysis to the extent of 56%.[10,12] The crude dimethyl acetal **14** (which could not be rigorously purified) was then successively 3,4,5-trimethoxybenzoylated and hydrolyzed to give an oil which displayed all the spectral characteristics expected of Woodward reserpine precursor **2**. To prove this assignment, this oil was converted by a variation[13] of the original Woodward procedure[14] into a crystalline material, **18**, mp (vac) = 146-149 °C, all of the spectra (^1H NMR, ^{13}C NMR, IR, MS, and UV) and TLC mobility (15% ethyl acetate/methylene chloride, Al_2O_3) of which were identical with those of an authentic sample of 3-epireserpine,[15,16] prepared by acetic acid catalyzed equilibration of natural reserpine.[17]





(a) H_2SO_4, CH_3OH, Δ; (b) $((CH_3O)_3C_6H_2CO)_2O$, 4-$(CH_3)_2N$-C_5H_4N, pyr; (c) HOAc, H_2O; (d) 6-methoxytryptamine, C_6H_6/CH_3OH; (e) $NaBH_4$, CH_3OH; (f) $POCl_3$, Δ; (g) $NaCNBH_3$, HOAc

Thus, the olefin functionalization method described in the preceding paper can, in fact, be used to produce Woodward reserpine precursor **2** from 1,4-dihydrobenzoic acid.

Experimental Section

Routine nuclear magnetic resonance (NMR) spectra were taken on Varian T-60, CFT-20 (80 MHz), and HA-100 spectrometers.

Exact mass measurements were determined on either a VG 7070 or an AEI MS9 spectrometer.

1,4-Dihydrobenzoic Acid.[3] The Birch reduction of benzoic acid yields a product (1,4-dihydrobenzoic acid) that is base sensitive[5] and an inorganic byproduct (the metal salt of the proton source) that is a base. Thus, the very nature of the reaction is such that the product is vulnerable to isomerization under the conditions of its formation. Indeed, we found that, with sodium and ethanol as the reducing agent and proton source, isomerization and subsequent over-reduction is avoided only by employing relatively high dilution conditions (the procedure in ref 3 prescribes 60 mL of ammonia and 10 mL of ethanol[18] per g of benzoic acid): presumably, over-reduction occurs in more concentrated reaction mixtures because precipitated salts tend to impede stirring, which causes there to be local areas in which overheating occurs. To prepare large amounts of material, we found that the following procedure, which uses lithium[19] as the reducing agent, to be preferable.

A 5-L three-necked round-bottomed flask equipped with mechanical stirrer, Dewar condenser, and gas inlet tube was flamed out under nitrogen, then filled with benzoic acid (160.0 g, 1.31 mol). The flask was then cooled to −78 °C and enough ammonia distilled in to

dissolve most of the benzoic acid (ca. 3 L). The solution was then treated with lithium metal (31.7 g, 4.53 mol) bit by bit, then with anhydrous ethanol (161.0 g, 3.50 mol) dropwise over a period of 20 min. The reaction mixture was then allowed to stir at reflux for 30 min, recooled to −78 °C, and quenched carefully with ammonium chloride (270.0 g, 5.05 mol). The ammonia was then allowed to evaporate (some sort of external heating is a virtual necessity) and the white solid residue taken up in 1 L of water, washed with ether (2 × 500 mL),[18] covered with 500 mL of ether, and acidified to pH 1 with concentrated HCl, taking care by external cooling that the internal temperature not exceed ca. 23 °C. The ether layer was then separated and the aqueous layer extracted with ether (2 × 500 mL). The combined extracts were then dried ($MgSO_4$), concentrated, and the residual liquid distilled (95–101 °C/1.1 mm) to afford a colorless liquid: yield, 153.3 g (1.24 mol, 94%); NMR (80 MHz) 2.70 (2 H, d, J = 9 Hz), 3.78 (1 H, t, J = 9 Hz), 5.87 (4 H, s), 9.12 (1 H, s); IR (film) 1650, 1710, 2500–3500; MS (EI) 124 (M^+, 10%), 79 (100).

4α,5β-Dihydroxycyclohexene-3β-carboxylic Acid, γ-Lactone (6). A solution of 30% H_2O_2 (138.7 g, 1.22 mol) in 800 mL of 88% formic acid was cooled to 0 °C and treated with 1,4-dihydrobenzoic acid (151.7 g, 1.22 mol). After 5 h at 0 °C and 30 h at room temperature, the black reaction mixture was refluxed for 1 h, the formic acid removed in vacuo, 600 mL of water added, and the reaction mixture refluxed for 4.5 h. Some insoluble brown material was then filtered off, the filtrate concentrated, and the residual orange oil heated at 183 °C (bath temperature) until water ceased to be evolved (ca. 1.5 h). The pot residue, an orange solid mass, was then taken up in 1525 mL of 8.2% $NaHCO_3$ and extracted with methylene chloride (7 × 200 mL). The extracts were then dried ($MgSO_4$) and concentrated to a reddish oil weighing 22.8 g. Chromatography (40% ethyl acetate/chloroform, silica gel, medium pressure) gave a colorless oil that crystallized on standing, pure by NMR. Yield: 5.8% (overall from 1,4-dihydrobenzoic acid). Three recrystallizations from ethyl acetate/hexane gave colorless prisms, mp 69.5–71.5 °C; NMR (100 MHz) 2.4–2.6 (2 H, mult), 3.10 (1 H, t, J = 6 Hz), 3.51 (1 H, s; disappears on addition of D_2O), 4.54 (2 H, br s), 5.74 (1 H, t, J = 8 Hz), 5.96 (1 H, t, J = 8 Hz); IR (KBr) 1630, 1790, 3390; MS (EI) 140 (M^+, 5%), 105 (100). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.90; H, 5.78.

5β-Hydroxy-4α-methoxycyclohexene-3β-carboxylic Acid, γ-Lactone (7). A solution of alcohol **6** (1.111 g, 7.94 mmol) in 12 mL of methyl iodide stirred over crushed $CaSO_4$ (4.03 g, 29.7 mmol) was treated with Ag_2O (3.002 g, 12.94 mmol) and the reaction mixture stirred vigorously at room temperature for 18 h, at which time a TLC (1:1 ethyl acetate/chloroform, SiO_2) indicated that all the starting material had been consumed. The crude reaction mixture was then filtered through celite, washing with 70 mL of methylene chloride, and the filtrate concentrated in vacuo in the hood to leave a pale yellow oil, consisting of a single component plus polar material by TLC (8% ethyl acetate/chloroform, SiO_2). Yield: 1.152 g. This oil was then chromatographed on silica gel by using medium pressure to afford the title compound in pure form (by NMR) as a colorless oil: yield, 0.8505 g (5.53 mmol, 70%); NMR (100 MHz) 2.45 (2 H, mult), 3.19 (1 H, tt, J = 5, 1 Hz), 3.37 (3 H, s), 4.11 (1 H, td, J = 5, 1 Hz; simplifies to d, J = 5 Hz on irr at 3.19), 4.63 (1 H, mult; simplifies to d, J = 5 Hz on irr at 2.45), 5.6–6.0 (2 H, mult); IR (KBr) 1650, 1790; MS (EI) 154 (M^+, 5%), 109 (100). Anal. Calcd for $C_8H_{10}O_3$: m/e 154.0630. Found: m/e 154.0628.

3β-Carbomethoxy-5β-hydroxy-4α-methoxycyclohexene (1). A solution of lactone **7** (0.8505 g, 5.53 mmol) in 20 mL of methanol was treated with concentrated H_2SO_4 (20 drops) and refluxed for 3 h. The acid was then neutralized with solid $NaHCO_3$ (1.79 g, 21.4 mmol) and the methanol removed in vacuo to leave a white solid residue, which was thoroughly extracted with 80 mL of methylene chloride. The extracts were then dried ($MgSO_4$) and concentrated to yield a faintly yellow oil, homogeneous by TLC (1:1 ethyl acetate/chloroform, SiO_2) and NMR: yield, 0.9745 g (5.25 mmol, 95%); NMR (100 MHz) 2.0–2.6 (2H, mult.), 3.13 (1H, s; disappears on addition of D_2O), 3.20 (1 H, mult), 3.50 (3 H, s), ca. 3.7 (1 H, mult), 3.73 (3 H, s), 5.42 (1 H, d, J = 5 Hz), 5.68 (1 H, mult); IR (film) 1660, 1745, 3450; MS (EI) 186 (M^+, 1.0%), 74 (100). Anal. Calcd for $C_9H_{14}O_4$: m/e 186.0892. Found: m/e 186.0894.

2,5-Dihydro-5-methyl-2-oxo-5*R*-(3′β-carbomethoxy-4′α-methoxycyclohexen-5′β-yl)oxyfuran (8). A solution of alcohol **1** (6.266 g, 33.7 mmol) and *cis*-β-acetylacrylic acid, pseudo-acid bromide[7] in 50 mL of methylene chloride was stirred over 10 g of crushed $CaSO_4$ for 10 min, then treated with Ag_2O (12.16 g, 52.4 mmol) and stirred at room temperature for 24 h, then filtered through celite. The filtrate contained some residual starting alcohol by TLC (8% ethyl acetate/chloroform, SiO_2), so it was treated with more pseudo-acid bromide (3.549 g, 20.01 mmol), powdered $CaSO_4$ (15 g), and Ag_2O (4.605 g, 19.86 mmol), and stirred at room temperature for 19 h. The reaction mixture still contained some starting alcohol by TLC, so it was again filtered, treated with more pseudo-acid bromide (3.545 g, 20.05 mmol), powdered $CaSO_4$ (25 g), and Ag_2O (4.656 g, 20.08 mmol), and allowed to stir at room temperature for another 28 h, then filtered through celite and concentrated to yield a brownish oil weighing 15.04 g, which was carefully chromatographed on 300 g of silica gel (2% ethyl acetate/chloroform eluent) to give a pale yellow oil, R_f 0.45 (25% ethyl acetate/chloroform, SiO_2). Yield: 4.965 g (17.62 mmol, 52%). Two recrystallizations from benzene/hexane gave white prisms, mp 83–85 °C; NMR (80 MHz) 1.67 (3 H, s), 2.3 (2 H, br mult), 3.1–3.7 (3 H, patterns obscured), 3.52 (3 H, s), 3.73 (3 H, s), 5.53 (2 H, mult), 6.16 (1 H, d, J = 5.5 Hz), 7.21 (1 H, d, J = 5.5 Hz); IR (KBr) 1610, 1650, 1735, 1770; MS (EI) 282 (M^+, 1.2%), 97 (100). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.72; H, 6.49.

Further elution gave 5.776 g of another yellow oil: R_f 0.39; NMR (80 MHz) 1.66 (3 H, s), 2.1–2.6 (2 H, br mult), 3.2–3.9 (3 H, patterns obscured), 3.50 (3 H, s), 3.73 (3 H, s), 5.60 (2 H, br s), 6.14 (1 H, d, J = 5.7 Hz), 7.15 (1 H, d, J = 5.7 Hz); IR (film) 1740, 1770.

The more polar component, **9**, was then recycled to **1** by the following procedure: A solution of **9** (4.874 g, 17.29 mmol) in 50 mL of methanol was treated with 40 drops of concentrated H_2SO_4, refluxed for 20 h, and then quenched with 3.3 g of solid $NaHCO_3$. The methanol was then evaporated and the light yellow solid residue thoroughly extracted with 100 mL of methylene chloride. The extracts were then concentrated to a yellow oil weighing 5.426 g, which was then chromatographed on 70 g of silica gel (10% ethyl acetate/chloroform eluent) to give a pale yellow oil, identified as **1** by NMR and IR. Thus, the calculated yield of **8** (based on unrecovered **1**) is 106%.

Cyclobutane 10. A solution of ketal **8** (2.554 g, 9.07 mmol) in 3.01 L of acetone was divided into seven equal portions and each portion photolyzed internally through a Pyrex filter for 3.5 h. The acetone was then evaporated to leave a brown oil weighing 3.129 g. Chromatography on 70 g of silica gel (chloroform eluent) afforded a pale yellow oil, homogeneous by TLC (1:1 ethyl acetate/chloroform, silica gel) and NMR (except for singlets at 2.19 and 1.27 ppm). Yield: 0.780 g (2.76 mmol, ≤ 30.5%). All attempts to crystallize this oil met with failure. However, it must be reasonably pure, judging by the respectable yields of subsequent transformations: NMR (100 MHz) 1.61 (3 H, s), 1.71 (2 H, t, J = 3), 2.2 (1 H, mult), 2.56 (1 H, dd, J = 9, 6 Hz), 2.75 (1 H, dt, J = 2.5, 8 Hz), 3.30 (1 H, dd, J = 9.5, 1 Hz), ca. 3.4 (1 H, pattern obscured), 3.47 (3 H, s), 3.74 (3 H, s), 4.21 (1 H, dt, J = 1.5, 3 Hz), 4.32 (1 H, d, J = 9.5 Hz); IR (film) 1735, 1770; MS (EI) 282 (M^+, 8%), 43 (100). Anal. Calcd for $C_{14}H_{18}O_6$: m/e 282.1103. Found: m/e 282.1108.

Methyl Ketone 12. A solution of **10** (0.648 g, 2.30 mmol) in 15 mL of methanol was treated with 15 drops of concentrated H_2SO_4, refluxed for 11 h, allowed to cool to room temperature, neutralized with 1.0 g of solid $NaHCO_3$, and the methanol evaporated to leave a yellow solid residue, which was thoroughly extracted with 50 mL of methylene chloride. The extracts were then concentrated to a reddish oil, pure by NMR. Yield: 0.588 g (2.08 mmol, 91%). Crystallization from ethyl acetate/hexane gave white prisms, mp 136–137.5 °C; NMR (100 MHz) 1.9 (2 H, br mult), 2.18 (3 H, s), 2.6–2.9 (2 H, br mults), 3.11 (1 H, t, J = 5.5 Hz), 3.3–3.9 (2 H, patterns obscured), 3.38 (3 H, s), 3.72 (3 H, s), 4.07 (1 H, t, J = 5.5 Hz), 4.70 (1 H, dt, J = 6, 3 Hz); IR (KBr) 1710, 1735, 1790; MS (EI) 282 (M^+, 37%), 43 (100). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.48; H, 6.55.

Acetoxycyclobutane 13. A solution of methyl ketone **12** (0.588 g, 2.08 mmol) in 20 mL of methylene chloride stirred over solid Na_2HPO_4 (2.360 g, 16.63 mmol) was cooled to 0 °C and treated with a solution of trifluoroperacetic acid[9] in methylene chloride, prepared in advance by mixing 90% H_2O_2 (0.362 g, 9.60 mmol) and trifluoroacetic anhydride (2.438 g, 11.61 mmol) in 20 mL of methylene chloride initially at 0 °C, then at room temperature for 30 min. The reaction mixture was allowed to stir at room temperature for 2 h, then poured into a solution of 8 g of Na_2SO_3 and 8 g of Na_2CO_3 in 100 mL of water, and extracted with methylene chloride (3 × 35 mL), and the extracts dried ($MgSO_4$) and concentrated to leave 0.463 g of a col-

orless oil. Column chromatography on 13 g of silica gel (chloroform eluent) gave a white solid. Yield: 0.369 g (1.238 mmol, 59%). Recrystallization from chloroform/ether gave colorless prisms, mp 145–146 °C; NMR (100 MHz) 1.90 (1 H, ddd, J = 15, 9, 2.5 Hz; simplifies to dd, J = 15, 9 Hz on irr at 4.69), 2.04 (3 H, s), 2.39 (1 H, ddd, J = 15, 2.5, 1 Hz; simplifies to dd, J = 15, 1 Hz on irr at 4.69), 2.48 (1 H, ddt, J = 1, 8, 9 Hz; simplifies to dt, J = 1, 9 Hz on irr at 5.12), 2.93 (1 H, dt, J = 5.5, 9 Hz), 3.07 (1 H, t, J = 5.5 Hz; simplifies to d, J = 5.5 Hz on irr at 4.05), 3.34 (1 H, dd, J = 9, 8 Hz), 3.39 (3 H, s), 3.73 (3 H, s), 4.05 (1 H, t, J = 5.5 Hz), 4.69 (1 H, dt, J = 5.5, 2.5 Hz), 5.12 (1 H, t, J = 8 Hz); IR (KBr) 1735, 1775; MS (CI) 299 ($M^+ + 1$, 100%). Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.17; H, 5.99.

2,3-*seco*-3-Oxoreserpine (16). A solution of acetoxycyclobutane **13** (49 mg, 0.164 mmol) in 12 mL of methanol was treated with 12 drops of concentrated H_2SO_4 and refluxed for 48 h. The acid was then neutralized with 0.621 g of solid $NaHCO_3$ and the methanol evaporated to leave a white solid, which was thoroughly extracted to give 54 mg of a pale yellow oil: NMR (80 MHz) 1.7–3.0 (mults), 3.31–3.51 (numerous singlets), 3.66 (s), 3.68 (s), 3.8–4.4 (mults), 4.66 (mult), 5.15 (s); IR (film) 1735 (vs), 1780 (m), 3480 (br, s).

A 28.1-mg quantity of the above oil was taken up in 1.2 mL of pyridine, treated with 3,4,5-trimethoxybenzoic anhydride[20] (0.122 g, 0.301 mmol) and dimethyl-4-pyramine (0.055 g, 0.45 mmol), and the reaction mixture stirred at room temperature for 21 h. The excess anhydride was then hydrolyzed by the addition of 1.0 mL of water and the reaction mixture diluted with 50 mL of methylene chloride, washed successively with 50 mL of cold 5% HCl and 50 mL of 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 44.9 mg of a pale yellow oil: NMR (80 MHz) 1.7–3.0 (mults), 3.32–3.69 (numerous singlets), 3.91 (s), 3.94 (shoulder), ca. 4.0–4.3 (several mults), 4.73 (0.44 H, mult), 4.8–5.3 (mults), 5.15 (s), 7.29 (1.12 H, s), 7.36 (s); IR (film) 1710 (s), 1730 (s), 1775 (m).

This oil (44.9 mg) was then taken up in 3.0 mL of 50% aqueous acetic acid, stirred at room temperature for 23 h, poured cautiously into 50 mL of 5% $NaHCO_3$, and extracted with methylene chloride (2 × 25 mL), and the extracts dried ($MgSO_4$) and concentrated to yield a colorless oil: yield, 33.7 mg; NMR (80 MHz) 1.6–3.0 (mults), 3.29–3.49 (numerous singlets), 3.67 (s), 3.69 (s), 3.91 (s), 3.94 (s), 4.72 (0.39 H, mult), 5.00 (0.33 H, mult), 5.31 (0.28 H, mult), 7.28 (2 H, s), 9.59–9.75 (1 H, several doublets and singlets); IR (film) 1715 (s), 1725 (s), 1735 (s), 1780 (m), 2730 (w), 2845 (m), 2950 (s); MS (EI) 482 (M^+, 22%), 195 (100). Anal. Calcd for $C_{23}H_{30}O_{11}$: *m/e* 482.179. Found: *m/e* 482.117. This oil decomposes to nonaldehydic compounds upon chromatography (silica gel).

Following the procedure of Woodward,[14] the above-described oil (33.7 mg) was taken up in 2.0 mL of benzene, treated with a solution of 6-methoxytryptamine[14] (23.4 mg, 0.123 mmol) in 2.0 mL of 5:1 benzene/methanol, and allowed to stir at room temperature for 15 min. The solvents were then evaporated (the temperature of the solution being kept at or below ca. 45 °C at all times) to give a yellow oil: IR (film) 1630 (s), 1665 (m), 1715 (s), 1735 (s), 1780 (m), 3385 (br, s).

This oil was immediately taken up in 7 mL of methanol, treated with $NaBH_4$ (74 mg, 1.94 mmol), and stirred at room temperature (cooling being required to moderate the reaction between the $NaBH_4$ and the methanol) until the last of the $NaBH_4$ had been spent (ca. 5 min); the reaction mixture was then refluxed for 8 min, poured into 50 mL of 5% HCl, and extracted with methylene chloride (2 × 25 mL), and the extracts dried ($MgSO_4$) and concentrated to a pale yellow oil. To recover any material which might have been lost by saponification, this oil was taken up in 1.0 mL of dioxane, treated with excess ethereal CH_2N_2 at room temperature for 2 min; then the solvents were evaporated. The residue, a yellow oil, was then taken up in 1.2 mL of pyridine, treated with 3,4,5-trimethoxybenzoic anhydride (0.104 g, 0.256 mmol) and dimethyl-4-pyramine (0.052 g, 0.43 mmol), stirred at room temperature for 12 h, then worked up as before to give a yellow foam weighing 33.2 mg. Rough preparative TLC (silica gel, 8% methanol/ethyl acetate, R_f 0.40) afforded a yellow oil, consisting of a 3:2 mixture of **16** and **17** (determined by integration of the C-17 methoxyl and C-18 proton regions of the NMR): yield, 13.8 mg (0.0221 mmol, 26% from **13**); NMR (80 MHz) 1.4–3.1 (13 H, mults), 3.38 (1.1 H, s), 3.50 (1.9 H, s), 3.74–3.82 (6 H, several singlets), 3.92 (6 H, s), 3.96 (3 H, s), ca. 4.0 (1 H, pattern obscured), 4.88 (ca. 0.6 H, br mult), 5.34 (ca. 0.4 H, narrow mult), 6.8–7.8 (5 H, mults), 7.32 (2 H, s). Rechromatography of this yellow oil (3% methanol/ethyl acetate, silica gel, R_f 0.42) afforded the title compound in pure form as a pale green oil: yield, 9.2% from **13**; NMR (80 MHz) 1.4–3.1 (13 H, mults), 3.50 (3 H, s), 3.74 (3 H, s), 3.77 (3 H, s), 3.92 (9 H, s), ca. 4.0 (1 H, pattern obscured), 4.89 (1 H, mult), 6.8–7.8 (5 H, mults), 7.32 (2 H, s); IR ($CHCl_3$) 1590, 1630, 1715, 1735, 3450; MS (EI) 624 (M^+, 3.4%), 173 (100). Anal. Calcd for $C_{33}H_{40}O_{10}N_2$: *m/e* 624.268. Found: *m/e* 624.264.

3-Epireserpine (18). A solution of the 3:2 mixture of **16** and **17** (13.8 mg, 0.0133 mmol of **16** plus 0.0088 mmol of **17**) in 1.6 mL of freshly distilled $POCl_3$ was refluxed in a scrupulously dried apparatus for 2 h, then the $POCl_3$ evaporated. The residue, a dark yellow glass, was immediately taken up in 2.0 mL of glacial acetic acid, treated with $NaCNBH_3$ (0.198 g, 3.14 mmol), stirred at room temperature for 3 min, poured cautiously into 50 mL of 10% aqueous ammonia, extracted with methylene chloride (2 × 25 mL), and the extracts dried (K_2CO_3) and concentrated to leave a dark yellow glass. Preparative TLC (alumina, 11% ethyl acetate/methylene chloride, R_f 0.52) afforded the title compound as a pale yellow oil. Yield: 5.4 mg (0.0089 mmol, 67% from **16**). Crystallization from methanol gave 3.7 mg (0.0061 mmol, 46%) of clusters of needles, mp (vac) 146–149 °C. The ^1H NMR, ^{13}C NMR, IR, mass, and UV spectra were all absolutely superimposable on those of natural 3-epireserpine, prepared by acetic acid catalyzed epimerization of reserpine.[17] The synthetic material also had the same R_f on alumina TLC as the natural material (0.46; 15% ethyl acetate/methylene chloride): NMR (80 MHz) 1.6–3.0 (14 H, mults), 3.45 (3 H, s), 3.81 (3 H, s), 3.84 (3 H, s), 3.87 (6 H, s), 3.88 (3 H, s), ca. 4.0 (1 H, pattern obscured), 5.06 (1 H, mult), 6.7–7.7 (4 H, mults), 7.28 (2 H, s); ^{13}C NMR (pyr-d_5) 22.6, 28.4, 31.0, 35.2, 37.8, 51.2, 52.5, 53.5, 55.5, 56.2, 60.0, 60.7, 61.0, 78.4, 78.7, 95.7, 107.6, 108.7, 118.8, 122.3, 126.1, 134.8, 138.2, 143.4, 153.8, 156.4, 165.8, 172.3; IR ($CHCl_3$) 1715, 1735, 2760, 2810, 3490; MS (EI) 608 (M^+, 100%); UV (CH_3CN) λ_{max} 296 nm (ϵ 10 360), 266 nm (ϵ 18 290). Anal. Calcd for $C_{33}H_{40}O_9N_2$: *m/e* 608.273. Found: *m/e* 608.269.

3,20-Diepireserpine (19). Isolation of the band of R_f 0.25 off the plate in the above-described experiment afforded a pale yellow oil, identified as the title compound by its spectral properties[21] and synthetic origin. Yield: 3.1 mg (0.0051 mmol, 58% from **17**). Crystallization from methanol gave 2.4 mg (0.0039 mmol, 44%) of clusters of needles, mp (vac) 142–149 °C: NMR (80 MHz) 1.5–3.1 (14 H, mults), 3.33 (3 H, s), 3.52 (3 H, s), 3.82 (3 H, s), 3.89 (3 H, s), 3.92 (6 H, s), ca. 4.0 (1 H, pattern obscured), 5.42 (1 H, mult), 6.7–7.5 (4 H, mults), 7.30 (2 H, s); IR ($CHCl_3$) 1710, 1740, 2735, 2800, 3440; MS (EI) 608 (M^+, 4%), 195 (100). Anal. Calcd for $C_{33}H_{40}O_9N_2$: *m/e* 608.273. Found: *m/e* 608.271.

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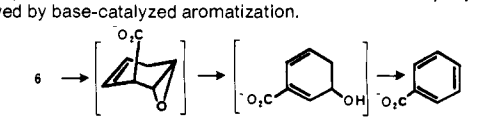
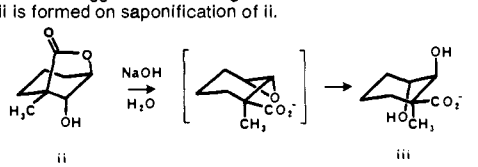
References and Notes

(1) (a) Excerpted from Ph.D. thesis, Columbia University, 1976; *Diss. Abstr. Int. B*, **37**, 5091 (1977); order no. 77-8263. (b) Present address: The Upjohn Company, Kalamazoo, Mich. 49001.
(2) B. A. Pearlman, *J. Am. Chem. Soc.*, preceding paper in this issue
(3) M. E. Kuehne and B. F. Lambert, *Org. Synth.*, **5**, 400 (1973).
(4) The ratio of **3** to **4** was not determined because purification at this stage was not necessary for synthetic purposes. However, the 5.8% yield of lactone **6** is a lower limit, and this is high enough to permit preparation of **6** in batches of > 10 g with no undue inconvenience.
(5) H. Plieninger and G. Ege, *Chem. Ber.*, **94**, 2088 (1961).
(6) Attempts to effect methyl etherification of **6** that employed basic conditions (for example, NaH/CH_3I/THF) resulted in its decomposition to benzoic acid. One possible mechanism consists of isomerization to epoxy acid (i) followed by base-catalyzed aromatization.



i

Moffatt[6a] has suggested an analogous mechanism to rationalize the fact that iii is formed on saponification of ii.

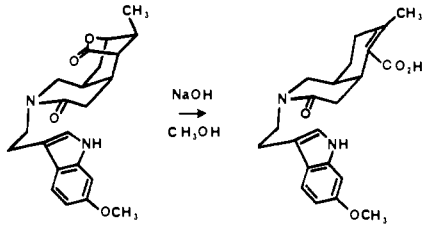


ii iii

Precedent for this mechanism is provided by the fact that several rigid 1,2-*trans*-diaxial hydroxy acetates are known to react with aqueous base to form epoxides.[6b] Another possible mechanism for the aromatization of **6** is that is opens to iv

iv

as v is known to do[6c]



and then dehydrates. Still another possibility is that **6** polymerizes to a polyester, which then would dehydrate. (a) J. S. Moffatt, *J. Chem. Soc.*, 2595 (1963); (b) M. Davis and V. Petrow, *ibid.*, 2536 (1949); (c) I. Ernest and B. Kakac, *Collect. Czech. Chem. Commun.*, **29**, 2663 (1964).

(7) G. Fuchs and N. Hellstrom, *Lantbrukshoegsk. Ann.*, **30**, 615 (1964); *Chem. Abstr.*, **63**, 6850g (1965).

(8) See footnote 39 of reference 2; the epimerization of the acetyl substituent to the exo configuration may, in fact, be crucial for the success of the Baeyer–Villiger oxidation.

(9) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(10) The NMR and IR spectra of the methanolysis product mixture both indicate the presence of some unopened lactone (NMR: δ = 4.66 ppm; IR: ν = 1780 cm^{-1}). However, the exact amount cannot be determined because the spectra contain no absorptions characteristic of the hydroxy ester. Fortunately, the NMR spectrum of the product of 3,4,5-trimethoxybenzoylation of the hydroxy ester/lactone mixture (see Experimental Section) has not only the multiplet at 4.73 ppm characteristic of the proton at C-18 α to the lactone but also a singlet at 7.29 ppm, which is characteristic of the protons at C-2,6 of the trimethoxybenzoate substituent. By comparing the integrals of these two signals, the ratio of hydroxy ester to lactone (not necessarily **14** to **15**) may be inferred to be 56:44 ($-\Delta F$ = 0.16 kcal/mol). Refluxing the methanolysis mixture for additional time (up to 5 days) does not alter its NMR spectrum perceptibly, so presumably this 56:44 ratio is the equilibrium value. In general, bridged γ-lactones are less stable than the corresponding hydroxy esters by significantly more than 0.16 kcal. For example, *cis*-3-hydroxycyclohexanecarboxylic acid is 1.51 kcal more stable (in H_2O at 100 °C) than the corresponding lactone (extrapolated to 1.88 kcal at 65 °C, using $\Delta F = \Delta H - T\Delta S$ with ΔH = 5.39 kcal and ΔS = 10.4 eu).[11] Presumably, the hydroxy ester fraction of the methanolysis mixture is favored over the lactone fraction by only 0.16 kcal because the carbomethoxymethyl substituent of the hydroxy ester is axial: indeed, the two 1,3-diaxial repulsions of the carbomethoxymethyl substituent might be expected to be especially severe, since it is buttressed against two vicinal cis substituents.[11]

(11) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

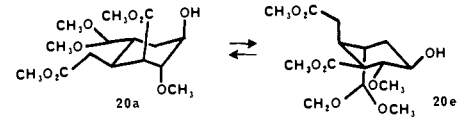
(12) The rate of acid-catalyzed hydrolysis of bridged γ-lactones such as **15** to hydroxy acids is known to be quite sensitive to steric hindrance.[11] Since there is an acetic ester appendage near the lactone ring of **15**, it could not be predicted before the fact whether the lactone ring would undergo acid-catalyzed methanolysis at an appreciable rate. The fact that it does is, therefore, fortunate.

(13) (a) L. Velluz, G. Muller, R. Joly, G. Nomine, J. Mathieu, A. Allais, J. Warnant, J. Valls, R. Bucourt, and J. Jolly, *Bull. Soc. Chim. Fr.*, 673 (1958); (b) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956); J. Weichet, K. Pelz, and L. Blaha, *Collect. Czech. Chem. Commun.*, **26**, 1529 (1961).

(14) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(15) We chose to convert our sample of 2,3-*seco*-3-oxoreserpine (**16**) into 3-epireserpine (**18**) rather than reserpine because reduction of 3(14)-dehydroreserpine to 3-epireserpine with $NaCNBH_3$ is cleaner than reduction to reserpine with zinc (see M. Protiva, J. O. Jilek, I. Ernest, and L. Novak, *Tetrahedron Lett.*, 11, 12 (1959); see also ref 13).

(16) This sequence affords a small amount of 3,20-diepireserpine (**19**) in addition to the desired 3-epireserpine (**18**). Thus, partial loss of configuration at C-20 occurs during some step in our sequence. Presumably, the methanolysis of **13** yields no **20**, since both chair conformers of **20** are quite unstable relative to **14**: **20e** has an axial dimethyl acetal substituent, and **20a** has a carbomethoxy group, hydroxyl group, and hydrogen in a 1,3,5-triaxial relationship, the free energy of which is presumably roughly comparable to that of the axial conformer of *cis*-3-hydroxycyclohexanecarboxylic acid, which is 3.5–4.4 kcal (in H_2O at 100 °C),[11] whereas **14** has only an axial carbomethoxymethyl group (even if it is doubly buttressed). Assuming that the unidentified impurities in the sample of **14** (perhaps pseudo esters and/or enol–lactone) do not give rise to **19**, the conclusion would be that 3,4,5-trimethoxybenzoate of **14** undergoes acetic acid catalyzed hydrolysis to **2** with partial loss of configuration at C-20.



This partial loss of configuration during hydrolysis was unexpected, since dimethyl acetals of simple aldehydes undergo acetic acid catalyzed hydrolysis with retention of configuration at the α carbon (see, inter alia, G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979)). Of course, it is also conceivable that the two buttressing interactions of the carbomethoxymethyl substituent of **14** are so serious that the equilibrium ratio of **14** to **20** is 312. If so, the conclusion that **14** hydrolyzes with loss of configuration at C-20 would be unnecessary.

(17) A. J. Gaskell and J. A. Joule, *Tetrahedron*, **23**, 4053 (1967).

(18) Removal of the ethanol prior to acidification is necessary if formation of ethyl dihydrobenzoate is to be avoided (B. Ganem, G. W. Holbert, L. B. Weiss, and K. Ishizumi, *J. Am. Chem. Soc.*, **100**, 6483 (1978)). Because the procedure of ref 3 prescribes use of a particularly large excess amount of ethanol, its removal becomes a technical problem, requiring evaporation. With our procedure, no more than the minimum amount of ethanol is used, and enough of this is evidently removed by washing the ammonium carboxylate solution with ether prior to acidification that esterification does not occur.

(19) Over-reduction occurs in the Birch reduction of cumic acid with sodium as the reducing agent, but not with lithium (F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967)).

(20) Prepared from 3,4,5-trimethoxybenzoyl chloride by treatment with 1.2 equiv of sodium 3,4,5-trimethoxybenzoate in refluxing benzene for 2 h: yield, 63% (after purification by three recrystallizations from ethyl acetate); mp 159–160 °C.

(21) The relatively low field chemical shift of the C-18 proton (5.42 ppm) might be due to its being equatorial (see E. L. Eliel and M. H. Gianni, *Tetrahedron Lett.*, 97 (1962); E. Premuzic and L. W. Reeves, *J. Chem. Soc.*, 4817 (1964)) or to ring E having some preferred conformation other than a chair.