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Biomimetic Transformations among Monomeric Macroline-Related Indole Alkaloids[1]

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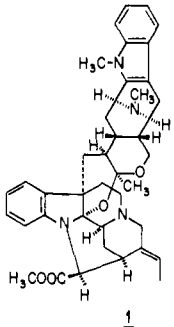
Abstract: The monomeric base macroline **5**, previously utilized in biomimetic syntheses of the *Alstonia* bisindole alkaloids villalstonine (**1**), alstonisidine (**2**), macralstonine (**3**), and macralstonidine (**4**), was converted to the monomeric alkaloid alstonerine (**10**) by an epoxidation–dehydration sequence. Alstonerine (**10**) was converted by reduction followed by acid-catalyzed rearrangement into N_b-methyl-N_b,21-secotalpinine (**20**), and alstonisine (**21**) into talpinine (**18**) by twofold reductive rearrangement. Model experiments bearing upon these interconversions are described. The nature of the biogenetic "macroline equivalent" is discussed in the light of these results. During model reactions performed to develop a biomimetic pathway to the pyridinoindole base suaveoline (**30**), a new, potentially general synthesis of 2-alkyl- and 3-alkylpyridines, utilizing dihydropyran as starting material, was developed.

In previous work in our laboratory, the *Alstonia* bisindole alkaloids villalstonine (**1**),[2] alstonisidine (**2**),[2] macralstonine (**3**),[3] and macralstonidine (**4**)[4] were synthesized by acid-cat-



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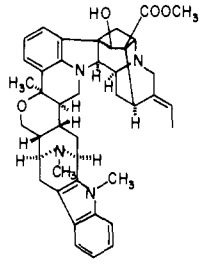

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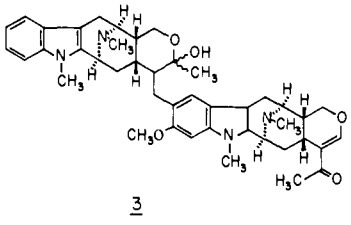

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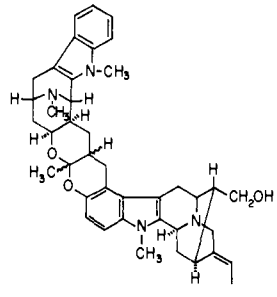

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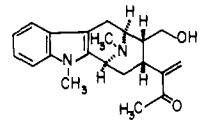
alyzed Michael-type and vinylogous Michael-type reactions between macroline **5** and respectively pleiocarpamine (**6**), quebrachidine (**7**), alstophylline (**8**), and N_a-methylsarpagine (**9**). Although macroline itself has not been encountered as a natural product, the notable directness and stereospecificity of these syntheses have led us to consider macroline or an "equivalent" as a likely biogenetic precursor of the bisindoles **1**–**4**, and to regard the syntheses therefore as biomimetic. In this paper we report our work on biomimetic transformations



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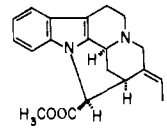

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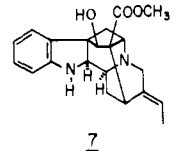

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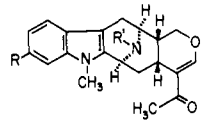
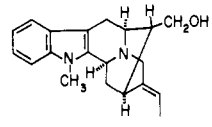


8; R = OCH_3, R' = CH_3
10; R = H, R' = CH_3
24; R = H, R' = $COCF_3$
25; R = H, R' = $COCH_3$



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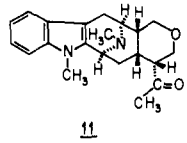
among some monomeric alkaloids. First we consider alkaloids closely related to macroline itself by virtue of carbon skeleton and natural occurrence, and then we discuss interconversions connecting the macroline bases with other indole alkaloids so as to suggest the likelihood of biogenetic relationships.

Alstophylline (**8**) and alstonerine (**10**) are the known alkaloids closest to macroline (**5**), so we investigated first the conversion **5** → **10**. In view of the importance of Michael-type reactions in the bisindole syntheses, we envisaged a Michael-type ring closure of macroline followed by dehydrogenation to give **10**. Macroline was recovered unchanged after exposure



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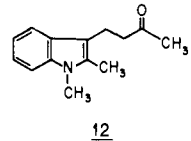

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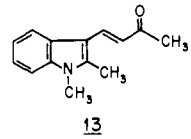

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to various aqueous acid conditions (0.2 N HCl, 20 °C for 12 h, or 2 N HCl, reflux, 4 h) but was converted by methanolic sodium methoxide into an approximately 1:1 equilibrium mixture of **5** and a new compound, $C_{21}H_{26}N_2O_2$. This com-

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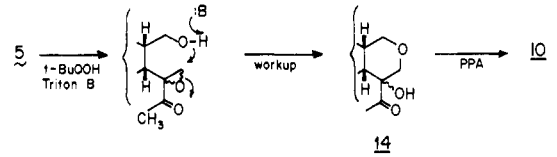
Scheme I. Conversion of Macroline (**5**) into Alstonerine (**10**).



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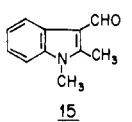
pound showed ν_{max} 1700 cm^{-1} (nonconjugated ketone), and the NMR spectrum lacked olefinic protons. These data are in accord with structure **11**; the stereochemistry shown for the acetyl substituent (equatorial) is supported by the NMR spectrum, in which the signal from the acetyl methyl group is shifted upfield, at δ 1.82. Models show that the acetyl group in the equatorial configuration lies directly in the shielding zone of the indole ring. Treatment of either pure **11** or **5** with methanolic sodium methoxide yielded approximately 1:1 mixtures of both compounds, but with potassium *tert*-butoxide/*tert*-butyl alcohol the equilibrium was shifted markedly toward **11.** Attempts to dehydrogenate **11** to **10** were based upon results from model studies. These employed the ketone **12,** readily prepared from 1,2-dimethylindole and methyl vinyl ketone in acetic anhydride/acetic acid.[5] Compound **12** with dichlorodicyanobenzoquinone (DDQ) in dioxane gave the enone **13** in good yield, but compound **11** was recovered unchanged under the same conditions. The reasons for this unreactivity are not obvious. Attempted bromination of **12** led to a complex mixture of products, and attempted bromination of **11** with bromine/acetic acid or with cuprous bromide[6] was unrewarding. The dehydrogenation pathway was then abandoned in favor of oxygenation; if the enone of macroline could be converted into the α,β-epoxide, internal displacement and dehydration would lead to alstonerine (**10**). Epoxidation of macroline (**5**) to a transient α,β-epoxide without causing N_b-oxide formation was achieved with *tert*-butyl hydroperoxide in benzene containing Triton B,[7] conditions which did not degrade the indole function of **12** and were unreactive to tertiary amines. Two products were isolated as a mixture (2:1, NMR); spectral data suggest that they are the diastereomeric ring-closed α-ketols **14,** probably arising as shown in Scheme I, via a transient epoxide. The ketol mixture on dehydration with freshly prepared polyphosphoric acid gave alstonerine (**10**). (During model reactions for these conversions, we treated the enone **13** with hydrogen peroxide–NaOH; the only isolable product was the aldehyde **15,** otherwise best prepared by Vilsmeier reaction on 1,2-dimethylindole. Probably an epoxide **16** is formed initially, and subsequently undergoes hydrolysis and retro-aldol loss of hydroxyacetone. Hydrogen peroxide was essential for the reaction.)



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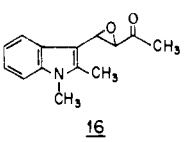

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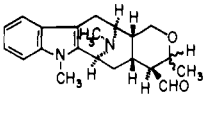
This synthesis of alstonerine, involving epoxidation, Michael reaction, and dehydration, employs reactions which have ample biochemical precedent; it can thus be regarded as biomimetic. Moreover, since the absolute configuration of macroline is known (from that of villalstonine (**1**)[8]), the absolute configuration of alstonerine (**10**) and, almost certainly, alstophylline (**8**), whose $[\alpha]_D$ is comparable, can be inferred. The absolute configuration of macralstonine follows as shown in **3.**

We then considered some other alkaloids structurally similar to macroline. The root bark of *Pleiocarpa talbotii* Wernham yields, among other compounds, talcarpine (**17**) and talpinine (**18**).[9] These structures relate macroline formally to the sarpagine group, which is represented among the *Alstonia* bisindoles by the nonmacroline half of macralstonidine (**4**), N_a-methylsarpagine. Reduction of alstonerine with sodium borohydride led to a mixture of alcohols **19.** On treatment with 0.2 N HCl at 20 °C this mixture gave a new compound, whose characteristic mass and infrared spectra were identical with those reported for N_b-methyl-N_b,21-secotalpinine (**20**).[9] Compound **20** presumably arises by hydrolysis of the enol ether followed by cyclic ether formation. Schmid and his co-workers[9] have described heating compound **20** to give talcarpine (**17**), which is epimeric with **20** at the formyl-bearing carbon.



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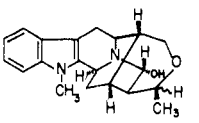

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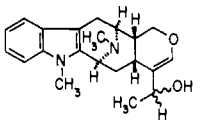

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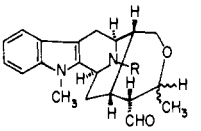
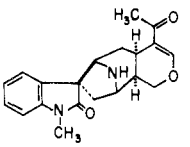


20; R = H
27; R = $COCH_3$

If in compound **20** the N_b-methyl group is replaced by hydrogen, carbinolamine formation is possible with the formyl group and talpinine (**18**) results. Among the monomeric *Alstonia* bases, only alstonisine (**21**)[10] has a secondary N_b, although a Polonovski-type[11] demethylation of alstonerine would yield a precursor suitable for conversion into talpinine. Since alstonisine was in hand from *A. muelleriana*,[10,12] we considered its conversion into talpinine first. This would involve double reduction and rearrangement steps, in the oxindole and the acetyldihydropyran parts of the molecule. Precedent exists for the reductive rearrangement of 3,3-disubstituted oxindoles; e.g., compound **22** with lithium aluminum hydride gives, after mild acidic workup (spectroscopic grade ethanol), the indole



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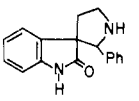

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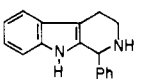
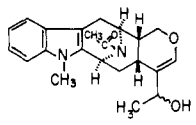


23.[13] This observation parallels other reductions of oxindole alkaloids with lithium aluminum hydride[14,15] or oxindole-derived imino ethers with sodium borohydride.[16] In compounds such as **22** the bond migrating from the 3 position is that to the carbon bonded to N_b. Reduction of alstonisine with lithium aluminum hydride (2 equiv) in ether followed by workup with 0.2 N HCl gave, in low yield, an alkaloid identical in spectral properties (IR and the extremely characteristic mass spectrum) with talpinine (**18**) and giving the same Ce(IV) color reactions. Further, we treated the synthetic talpinine (**18**) with methyl iodide in benzene[9], obtaining N_b-methyl-N_b,21-secotalpinine (**20**), identical with that prepared from alstonerine. Authentic samples of the *Pleiocarpa talbotii* alkaloids were unfortunately unavailable for comparison with our synthetic products. However, the infrared and NMR spectral properties of our materials were in excellent accord with those reported in the literature.[9] Moreover, the mass spectra of alkaloids in this series are exceptionally diagnostic of structural and stereochemical features; for example, Schmid and his co-workers[9] noted the characteristic difference in the intensities of the peaks at *m/e* 310 in the spectra of **17** and **20.** This difference arises from decarbonylation at the epimeric centers. Our synthetic sample of **20** gave an appropriately intense peak at *m/e* 310, as well as the other reported characteristic peaks. Our synthetic materials also displayed the very characteristic color reactions with cerium(IV) sulfate noted by Schmid and his co-workers.[9] In an attempted further interlocking conversion, we have

treated alstonerine N_b-oxide (prepared from the alkaloid with *m*-chloroperbenzoic acid) with trifluoroacetic anhydride to obtain the N_b-trifluoroacetyl-N_b-demethyl derivative **24.**[11] Since the yield in this conversion was surprisingly low, we also prepared the acetamido analogue **25.** Compound **25** on reduction with sodium borohydride gave a substance whose spectral and chromatographic characteristics were fully consistent with its being a mixture of the diastereomeric alcohols **26.** This mixture, which was not separated chromatographi-



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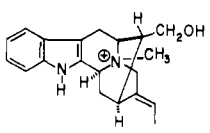
cally, gave with 0.2 N HCl a single compound having spectral and chromatographic properties (especially the characteristic mass spectrum and Ce(IV) color reaction) completely consistent with its formulation as the secotalpinine analogue **27.** However, attempted hydrolysis of the acetamide function to generate talpinine (performed on a minute scale) led only to general decomposition. Further work on N_b-demethyl compounds in these series is underway.

In view of the known oxidative conversion of indole alkaloids to spirooxindoles[17] by such reagents as *tert*-butyl hypochlorite and lead tetraacetate, which can be regarded as biomimetic reactions, we had earlier[18] tried unsuccessfully to convert alstonerine into N_b-methylalstonisine. This oxidation may be more difficult to effect with an N_a-methylated than an unalkylated indole.

The relationships disclosed in this work between alstonerine and alstonisine and the *Pleiocarpa talbotii* alkaloids are of considerable phytochemical interest. A possible pathway can now be traced to these alkaloids and the *Alstonia* bisindoles from bases such as quebrachidine (**7**). Oxidative cleavage of the cyclopentanol ring of **7** with loss of carbon would give the sarpagine skeleton (as in **9**). The N_a-methylated derivative of a sarpagine-type compound such as macusine B (**28**)[19] would, on oxygenation of the ethylidene side chain to an acetyl group, provide a β-ketoammonium salt **29,** which would readily ring open to macroline. To a suitably oxygenated derivative such as **29,** and to macroline (**5**) itself, talpinine, talcarpine, macroline, and its monomeric relatives can be connected by simple modifications. The *Alstonia* bisindoles would arise by reactions between macroline and "precursor" bases in the ajmaline and sarpagine series. A "macroline equivalent" such as **29** would be water soluble, which could explain the failure to observe it hitherto. Work on the water-soluble constituents of *A. muelleriana* is underway in our laboratory. This biogenetic hypothesis for the macroline bases, which displays structural variety and economy of derivation, should be tested with labeled precursors.



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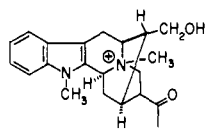

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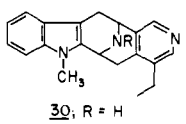
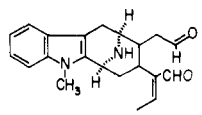


30, R = H

32; R = CH_3



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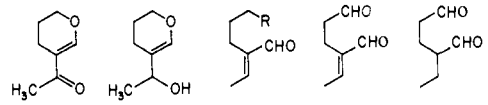
Suaveoline (**30**),[20] from *Rauvolfia suaveolens,* also has the carbon skeleton of the macroline bases; and, although a neat and plausibly biomimetic synthesis of N_b-methylsuaveoline from ajmaline has been achieved,[19] we considered the alternative possibility that suaveoline might arise by the action of ammonia on the enedialdehyde **31.** We thus sought to prepare the N_b-methyl analogue **32** from alstonerine. In order to conserve alstonerine, we developed model chemistry which has led to a convenient synthesis of 2- and 3-alkylpyridine derivatives from dihydropyran.

Acetyl chloride reacted smoothly with dihydropyran (dichloromethane solution, −78 °C) in the presence of aluminum chloride to give the ketone **33,** a direct analogue of alstonerine. Reduction of **33** with sodium borohydride gave the somewhat unstable alcohol **34,** which with dilute aqueous acid hydrolyzed and dehydrated to give the hydroxy enal (**35,** R = OH), in apparently stereochemically homogeneous condition. Oxidation of **35** (R = OH) with pyridinium chlorochromate or Kornblum oxidation of the tosylate of **35** gave **36.** Compound **36** resisted conversion to 3-ethylpyridine with ammonia under a variety of conditions; but the saturated dialdehyde **37** prepared from **36** by catalytic hydrogenation reacted with hy-



33 34 35 36 37

droxylamine hydrochloride to give 3-ethylpyridine. Attempts to apply these reactions to a synthesis of N_b-methylsuaveoline (**32**) from alstonerine, however, have been unsuccessful. In all cases the hydrolysis and rearrangement of the borohydride reduction product of alstonerine has led to N_b-methyl-N_b,21-secotalpinine (**20**), and no products analogous to **35** could be obtained in adequate yield under solvolysis conditions. The model compound's greater rotational freedom after hydrolysis of the dihydropyran ring may be the cause of this different behavior compared with the alkaloids. These results suggest that suaveoline arises in nature by reactions closer to those performed by the French workers[19] than to ours; interestingly, *R. suaveolens* has not to our knowledge yielded any other macroline bases.

The synthesis of 3-ethylpyridine from **33** described above can be envisaged to extend to other 3-substituted pyridines by using different acyl chlorides in the initial Friedel-Crafts reaction. Moreover, 2-noralkylpyridines are accessible from the same acyldihydropyrans; compound **33** with 2 N HCl at 100 °C undergoes hydrolysis and retro-aldol reaction to give 6-hydroxyhexan-2-one, which on oxidation and treatment with hydroxylamine hydrochloride gives, although in lower yield, 2-picoline.

Experimental Section

Microanalyses, unless otherwise stated, were by Spang Microanalytical Laboratory, Ann Arbor, Mich. UV absorption spectra were measured on a Cary 14 spectrophotometer and IR spectra with a Perkin-Elmer 567 spectrophotometer. NMR spectra were taken with a Varian T-60 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were taken with a Nuclide I-90G instrument and optical rotations with a Perkin-Elmer 140 polarimeter. Analytical thin layer chromatography was performed on Eastman Chromagram silica gel plates in 90:10 dichloromethane–acetone unless otherwise specified. TLC plates were visualized with long-wavelength UV light and a spray of a saturated solution of cerium(IV) sulfate in 50% aqueous sulfuric acid, or with iodine where indicated.

Preparation of Dihydroalstonerine. Macroline **5**[2] (50 mg, 0.15 mmol) in methanol (3 mL) was added rapidly to a solution of sodium (0.12 g) in methanol (3 mL), and the solution stirred for 4 h. TLC showed the presence of a new product as well as starting material. After 4 h the reaction mixture was diluted with water (15 mL) and extracted with chloroform (3 × 15 mL). The chloroform extracts were combined, dried over anhydrous potassium carbonate, and concentrated under vacuum. The product was then chromatographed on silica

gel (Woelm, activity II) and eluted with acetone. Fractions 2 and 3 (5-mL fractions) yielded pure dihydroalstonerine (**11**, 19 mg) while fractions 4, 5, and 6 yielded the uncyclized macroline.

Repetition of the above experiment on the macroline obtained from fractions 4, 5, and 6 yielded an additional 9 mg of dihydroalstonerine. Dihydroalstonerine recrystallized twice from 95% ethanol had mp 216 °C; IR (film) 2920, 1700, 1475, 750 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (4 H, m, aromatic protons), 3.62 (3 H, s, N_a-methyl), 2.36 (3 H, s, N_b-methyl), 1.82 (3 H, s, MeC=O). Anal. Calcd for $C_{21}H_{26}N_2O_7$: C, 74.52; H, 7.73; N, 8.27. Found: C, 74.22; H, 7.86; N, 8.25.

The position of equilibrium between **5** and **11** was estimated as follows. Macroline **5** (1 mg) was dissolved in freshly prepared methanolic sodium methoxide as above. TLC indicated the production of a material (**11**) at R_f 0.8 after 5 h. The intensity of the spot at R_f 0.8 appeared during 3 h to intensify, while that at R_f 0.7 diminished in intensity until both appeared approximately equally intense. No further change in intensity of either spot was noted after 48 h.

Dihydroalstonerine (**11**, 1 mg) was dissolved in freshly prepared methanolic sodium methoxide. TLC indicated the production of a slower material at R_f 0.7 (identical with macroline **5**). TLC indicated that an approximately 1:1 mixture of dihydroalstonerine and macroline was present after 24 h.

Macroline **5** (1 mg) was dissolved in freshly prepared potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction was followed by TLC which indicated that after 4 h only traces of **5** remained in the reaction mixture. An identical reaction run using **11** (1 mg) produced only traces of **5**.

Preparation of 1,2-Dimethyl-3-(3′-oxobutyl)indole (12). 1,2-Dimethylindole (2.9 g, 0.02 mol) was dissolved in glacial acetic acid (12 mL), and acetic anhydride (4 mL) and then methyl vinyl ketone (4.2 g, 0.02 mol) were added. The solution was allowed to stand at room temperature for 5 min, at which point the reaction became markedly exothermic. The reaction mixture was then heated on a steam bath for 30 min. At the end of this time the reaction mixture was poured into ice-water (100 mL) and allowed to stand for 10 min. A dark yellow oil separated out and the aqueous supernatant was decanted off. The supernatant was extracted with chloroform (3 × 25 mL). The chloroform extracts were combined with the dark yellow oily product, and the solution was dried over anhydrous potassium carbonate and concentrated under reduced pressure. The dark yellow oil thus obtained was chromatographed on silica gel (50 g). Elution with benzene gave a yellow oil (2.1 g, 50%). The analytical sample was prepared by distillation at 170 °C (0.7 mmHg): IR (neat) 3030, 2910, 1710 (s, C=O), 1610, 1470, 740 cm^{-1} (s, aromatic ortho disubstitution); NMR ($CDCl_3$) δ 7.6–6.9 (4 H, m, aromatic protons), 3.56 (3, H, s, indolic N-methyl), 3.2–2.5 (4 H, m, $-CH_2CH_2-$), 2.38 (3 H, s, indolic CCH_3), 2.08 (3 H, s, $OCCH_3$). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.95; N, 6.50. Found: C, 78.08; H, 7.95; N, 6.51.

Dehydrogenation of 1,2-Dimethyl-3-(3′-oxobutyl)indole (12) with Dichlorodicyanoquinone (DDQ). Compound **12** (0.5 g, 2.32 mmol) dissolved in 1,4-dioxane (25 mL, filtered through a column of neutral alumina, activity 1) was added dropwise to a solution of DDQ (0.52 g, 2.3 mmol) in dioxane (25 mL). The solution immediately turned dark green, with evident warming. The green color quickly discharged, followed by copious precipitation of dichlorodicyanohydroquinone. The hydroquinone was removed by filtration and the resultant dark red solution chromatographed on Florisil and eluted with chloroform. The yellow eluate crystallized on removal of solvent. Recrystallization from ethanol (95%) yielded 0.393 g (80%) of **13**: mp 115–116 °C; IR (neat) 3030, 2920, 1650, 1620, 1600, 1415, 1260, 750 cm^{-1}; NMR ($CDCl_3$) δ 7.85 (1 H, d, J = 16 Hz, vinylic proton), 7.3 (4 H, m, aromatic protons), 6.75 (1 H, d, J = 16 Hz, vinylic proton), 3.69 (3 H, N-methyl), 2.48 (3 H, s, $O=CCH_3$), 2.38 (3 H, s, indolic C-methyl). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.08; N, 6.56. Found: C, 78.69; H, 7.06; N, 6.53.

Attempted Dehydrogenation of Dihydroalstonerine (11) with DDQ. To a solution of dihydroalstonerine (**11**, 15 mg, 0.00443 mmol) in freshly distilled dioxane (2 mL) was added DDQ (10.2 mg, 0.0045 mmol). The solution was stirred at room temperature for 24 h, then analyzed by TLC, which indicated that no reaction had occurred. Filtration of the mixture through a Pasteur pipet containing Florisil (2 g) removed the DDQ, and concentration of the dioxane solution under reduced pressure afforded dihydroalstonerine (**11**, 7 mg).

This material (7 mg) was dissolved in dioxane (3 mL) and DDQ (6 mg) added. The solution was stirred until all reagents were in solution; then *p*-toluenesulfonic acid (2 mg) was added. The solution was refluxed for 1 h, cooled, basified with ammonia, and extracted with chloroform (3 × 5 mL). The chloroform extracts were combined, dried over anhydrous sodium carbonate, and concentrated under reduced pressure. Thin layer chromatography indicated that unreacted dihydroalstonerine was still present, although, among other products, a new spot had appeared at R_f 0.5. Co-TLC with alstonerine indicated that the new spot in the mixture was not alstonerine. Owing to the limited amount of dihydroalstonerine available this reaction was not further investigated.

Oxidation of Compound 13 with Alkaline Hydrogen Peroxide. Compound **13** (2.35 mmol, 500 mg) and 3.6 mL of 2 N aqueous sodium hydroxide in methanol (10 mL) were refluxed for 2 h. TLC indicated that no reaction had occurred. Hydrogen peroxide (30%, 2 mL) was then added and the reaction refluxed for an additional 15 min. The reaction mixture was cooled to 20 °C and extracted with chloroform (3 × 15 mL). The chloroform extracts were washed with water and dried over potassium carbonate. The chloroform solution was concentrated to small volume and chromatographed on silica gel (2 g) in a Pasteur pipet. A yellow, crystalline product (150 mg) was thus obtained. Recrystallization from ethanol yielded 42 mg of **15** as yellow needles: mp 128–130 °C; IR (film) 3030, 2920, 2810, 2715, 1640, 1390, 750 cm^{-1}; NMR ($CDCl_3$) δ 9.5 (1 H, s, aldehyde proton), 7.2 (4 H, m, aromatic protons), 3.5 (3 H, s, N-methyl). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.08. Found: C, 76.44; H, 6.57; N, 8.14.

Preparation of 15 by Vilsmeier Acylation. 1,2-Dimethylindole (6.15 g) dissolved in dimethylformamide (5 mL) was added dropwise to a solution of dimethylformamide (14.4 mL) and phosphorus oxychloride (4.3 mL) cooled to −10 °C and mechanically stirred. The reaction mixture, which rapidly became an orange paste, was stirred at −10 °C for 1 h, then quenched with ice (30 g), added all at once. Sodium hydroxide solution (18.75 g in 50 mL of water) was added dropwise. The reaction mixture was then rapidly heated to boiling, then immediately cooled to 20 °C. The precipitate which formed was filtered off and recrystallized from ethanol (95%) to give **15**, mp 128–130 °C, identical with that prepared above, by TLC, NMR, and infrared spectra (lit.[21] mp 128–130 °C).

Reaction of Macroline 5 with *tert*-Butyl Hydroperoxide and Triton B. To a solution of macroline (50 mg, 0.15 mmol) in benzene (1 mL), *tert*-butyl hydroperoxide (freshly distilled, 40% in methanol, 1 μL) was added. The solution was stirred at room temperature for 24 h, then the solvent removed under reduced pressure. The resulting glass was dissolved in a minimum quantity of acetone and chromatographed on an analytical silica gel plate (E. Merck, 0.25 mm) developed in acetone. Three bands were seen, at R_f 0.50, 0.52, and 0.7. These bands were excised and extracted with acetone–methanol (10:1). The bands at R_f 0.50 and 0.52 (Ce(IV), brown) could not be separated without much loss and were obtained together as a glass (15 mg). This product appeared to be a mixture (2:1, NMR) of the diastereomeric α-ketols **14**: IR (film) 3400 (O–H), 1705 (strong C=O), 1610 (indole C=C), 1100 (C–O–C), and 750 cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.18 (4 H, m, aromatic protons), 3.60 (3 H, s, N_a-methyls), 2.38, 2.36 (3 H, two singlets, N_b-methyls), 2.20, 2.17 (3 H, two singlets, COMe); mass spectrum *m/e* (rel intensity) M^+, 354 (30.8), 353 (100), 338 (16.3), 337 (48.2), 310 (39.2), 242 (30.8), 197 (89.4), 183 (14.7), 182 (32.9), 181 (14.8), 170 (20.5), 168 (10.9). The band at R_f 0.7 (Ce(IV), brown, 15 mg) was shown by co-TLC and its infrared spectrum to be dihydroalstonerine.

Preparation of Alstonerine (10). The mixed α-ketols (7.5 mg) were dissolved in freshly prepared polyphosphoric acid (86% P_2O_5) (1 mL) at room temperature and the solution stirred for 24 h. Water (10 mL) was then added and the solution neutralized with dilute ammonium hydroxide. Extraction with chloroform (3 × 25 mL) followed by drying over anhydrous potassium carbonate for 1 h and concentration of the extracts under reduced pressure yielded a glassy product. An infrared spectrum of this crude product showed close similarity to that of pure alstonerine (especially the characteristic bands at 1650, 1620, and 1200 cm^{-1}). Chromatography of this product on an analytical TLC plate (silica gel) developed in methylene chloride–acetone (10:1) showed one major component and a small amount of a fluorescent impurity. Excision of the major band and extraction with acetone–methanol (10:1) gave the major component as a pure compound (1 mg), identical with natural alstonerine by co-TLC and mass spectrometry: mass spectrum *m/e* (rel intensity) 337 (16.6), M^+ 336 (33.3), 267 (6.6), 212 (10.6), 197 (73.3), 183 (10.0), 182 (10.0), 181 (48.0), 170 (100), 149 (18.0), 109 (6.6), 98 (19.3).

Reduction of Alstonerine with Sodium Borohydride. Alstonerine (50 mg, 0.15 mmol) was dissolved in anhydrous methanol (2 mL) and the solution cooled to 0 °C. Sodium borohydride (100 mg) was then added all at once and the solution stirred at this temperature for 15 min, then allowed to warm to room temperature. The solution was stirred for 24 h, then diluted with water (25 mL), and extracted with methylene chloride (2 × 25 mL). The extracts were combined, dried over anhydrous potassium carbonate, and concentrated under reduced pressure. Chromatography of this material on a silica gel preparative plate (Merck 0.5 mm, 30% acetone-methylene chloride) yielded after excision and extraction (acetone-methanol, 10:1) 42.6 mg of diastereomeric alcohols, **19**, as a glass: IR (film) 3410, 1650 (C=CHOR), 1465, 1175, 1069, 910, 739 cm^{-1}; NMR ($CDCl_3$) δ 7.60-7.18 (m, aromatic protons) 6.32 (s, C=CHOR), 3.58 (s, N_a-methyl) 2.38 (s, N_b-methyls), 1.2, 0.92 (two doublets each, J = 6 Hz); mass spectrum *m/e* (rel intensity) 339 (2.8), M^+ 338 (10.0), 320 (14.1), 197 (19.6), 170 (19.9), 111 (16.5), 109 (13.4), 101 (18.0), 97 (20.6), 95 (16.7), 85 (13.5), 83 (21.3), 81 (18.2), 71 (22.1), 60 (22.5), 59 (48.4), 57 (39.9), 55 (28.4), 43 (100), 41 (20.0).

Rearrangement of the Alcohols 19 to N_b-Methyl-N_b,21-secotalpinine (20). The alcohols **19** (20 mg, 0.6 mmol) were dissolved in 0.2 N HCl (2 mL) and stirred at room temperature for 2 h. The reaction mixture was then neutralized with dilute ammonia and extracted with chloroform (3 × 10 mL). The extracts were combined and dried for 2 h over anhydrous sodium carbonate. Concentration of the chloroform extracts followed by preparative thin layer chromatography on silica gel (Merck, 0.5 mm, acetone) indicated that two new products had been produced. Excision of the major band at R_f 0.5 followed by extraction of the silica gel with acetone-methanol (10:1) produced pure N_b-methyl-N_b,21-secotalpinine (15 mg) with properties identical with those given in the literature.[9] Ce(IV), blue; IR (film) 2710, 1715 (CHO), 1465, 1170, 1106, 1060, 740 cm^{-1}; NMR ($CDCl_3$) δ 9.35 (broad singlet, CHO), 7.6-7.18 (m, aromatic protons), 3.45 (s, N_a-methyl), 2.36 (s, N_b-methyl), 1.19 (d, J = 6 Hz, CH_3CH); mass spectrum *m/e* (rel intensity) 339 (18.4), M^+ 338 (58.8), 311 (13.8), 310 (52.9), 225 (26.5), 224 (11.2), 197 (100), 196 (20.1), 183 (19.7), 182 (26.7), 183 (23.0), 170 (23.1), 144 (15.7), 70 (96).

Preparation of Talpinine 18 from Alstonisine (21). Alstonisine (**21**, 30 mg, 0.088 mmol) was dissolved in anhydrous diethyl ether (4 mL) and lithium aluminum hydride (7.0 mg, 0.176 mmol) added at once. The reaction mixture was stirred at room temperature for 1 h, and then worked up by slow addition of water followed by acidification with 0.2 N HCl. The acidified solution was stirred at 20 °C for 10 min, then basified with saturated sodium carbonate solution. The aqueous solution was then extracted with methylene chloride (3 × 10 mL), and the extracts were combined and dried over anhydrous sodium carbonate. The sodium carbonate was filtered off and the methylene chloride solution concentrated under reduced pressure. Chromatography of the residue on a silica gel analytical plate (0.25 mm) in 10% acetone-methylene chloride indicated the presence of many bands, two of which appeared to be major components at R_f 0.45 and 0.40. The band at R_f 0.45 was excised and extracted with acetone. The acetone was removed under reduced pressure to yield a homogeneous, glassy alkaloid (1.5 mg), identical in spectral and chromatographic properties with those reported in the literature for talpinine **21**.[9] Ce(IV), light green → violet; IR (film) 3360 (broad), 2920, 1470, 1130, 745 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 324 (75), 306 ($M - H_2O$), 196 (30), 184 (40), 183 (100), 182 (33), 181 (16), 170 (20), 168 (15), 152 (14).

Conversion of Talpinine 19 into N_b-Methyl-N_b,21-secotalpinine (20). Talpinine **19** (from above, 1 mg) was dissolved in anhydrous benzene (1 mL) and methyl iodide (1.4 μL) added. The solution was stirred at 20 °C for 24 h and monitored at 2-h intervals by TLC (silica gel, 10% acetone-methylene chloride). After 3 h a new spot appeared at R_f 0.6, which had the same R_f and Ce(IV) color reaction (blue) as a sample of synthetic N_b-methyl-N_b,21-secotalpinine. After 24 h only traces of talpinine were present. Co-TLC of the reaction product and synthetic N_b-methyl-N_b,21-secotalpinine showed identity in three solvent systems.

Preparation of Alstonerine *N*-Oxide. To a solution of alstonerine (33.6 mg, 0.1 mmol) dissolved in anhydrous methylene chloride (10 mL) was added *m*-chloroperbenzoic acid (85%, 22 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched by the rapid addition of 10% sodium bicarbonate solution (1 mL). The mixture was stirred for 3 min and the bicarbonate layer removed. The organic phase was washed with water (2 × 3 mL) and dried over anhydrous sodium carbonate. The sodium carbonate was filtered off and the solvent concentrated under reduced pressure. Chromatography on silica gel (0.5 mm, ethyl acetate-methanol, 2:1) indicated one major product at R_f 0.1. This band was excised and extracted with methanol. removal of solvent produced alstonerine *N*-oxide as a colorless glass (25 mg): Ce(IV) brown-pale gray; IR (film) 3700-3100 (broad), 1650, 1615, 1470, 1205, 750 cm^{-1}; NMR ($CDCl_3$) δ 7.53 (1 H, s, C=C-OR), 7.45-7.0 (4 H, m, aromatic protons), 3.70 (3 H, s, N_a-CH_3), 3.26, (3 H, s, N_b-CH_3), 2.06 (3 H, s, $COCH_3$); mass spectrum *m/e* (rel intensity) M^+ 352 (88), 267 (20), 239 (18), 224 (20), 212 (15), 197 (81), 181 (92), 170 (100), 144 (17). The material was used directly in succeeding experiments.

Polonovski Rearrangement of Alstonerine N_b-Oxide to Noralstonerine-N_b-trifluoroacetamide (24). Alstonerine *N*-oxide (20.3 mg, 0.05 mmol) was dissolved in methylene chloride (3 mL) and the solution cooled to 0 °C. Trifluoroacetic anhydride (distilled from P_2O_5, 14 μL, 0.1 mmol) was then added via syringe, and the reaction mixture stirred at 0 °C for 1 h. The yellow solution was then concentrated under reduced pressure to remove trifluoroacetic anhydride. The residue was neutralized with 10% sodium bicarbonate solution, extracted with methylene chloride (3 × 5 mL), and dried over anhydrous sodium carbonate. The solution was concentrated under reduced pressure and the product chromatographed on a silica gel preparative plate (0.5 mm, 10% acetone-methylene chloride) which indicated three major components and a large number of minor products. A systematic examination of all products by infrared and mass spectrometry indicated that the product at R_f 0.9 was noralstonerine-N_b-trifluoroacetamide (**24**, 3 mg): IR (film) 2930, 1685, 1655, 1620, 1199, 1145, 745 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+, 418 (100), 321 (3.0), 280 (26.1), 279 (52.9), 183 (28.5), 182 (15.1), 181 (14.1), 170 (39.9), 168 (13.1), 144 (17.1).

Polonovski Rearrangement of Alstonerine N_b-Oxide with Acetic Anhydride. Alstonerine N_b-oxide (35 mg, 0.1 mmol) was dissolved in acetic anhydride (freshly distilled, 1 mL). The solution was heated on a steam bath for 1 h, after which water (10 mL) was added and the solution basified with concentrated ammonium hydroxide. The aqueous solution was extracted with chloroform (3 × 10 mL), and the extracts were combined and dried over anhydrous sodium carbonate. The solution was then filtered and concentrated to a small volume under reduced pressure. Chromatography of the residue on silica gel analytical plates (0.25 mm, 10% acetone-methylene chloride) indicated one major component at R_f 0.85. Excision of this band and extraction with methanol yielded 10 mg of the microcrystalline acetamide **25**: IR (film) 2920, 1650-1620 (broad), 1470, 1199, 735 cm^{-1}; NMR ($CDCl_3$) δ 7.5 (s, C=CHOR), 7.4-7.0 (m, aromatic protons), 3.66 (s, N_a-methyl), 2.20 (s, O=CCH_3), 2.16 (s, O=CCH_3); mass spectrum *m/e* (rel intensity) M^+, 364 (100), 336 (52.8), 321 (13.1), 267 (6.7), 226 (31.3), 225 (36.2), 197 (47.9), 184 (13.9), 183 (62.1), 182 (27.6), 181 (58.2), 171 (21.2), 170 (97.7), 169 (3.8), 168 (27.3).

Reduction of Noralstonerine-N_b-acetamide (25) with Sodium Borohydride to the Alcohols 26. Noralstonerine-N_b-acetamide (**25**, 10 mg, 0.03 mmol) was dissolved in anhydrous methanol (1 mL) and sodium borohydride (10 mg) added. The solution was stirred at room temperature for 3 h, then water (5 mL) added and the solution extracted with chloroform (3 × 5 mL). The chloroform extracts were combined, dried over anhydrous sodium carbonate, concentrated under reduced pressure to a small volume, and chromatographed on an analytical silica gel plate (10% acetone-methylene chloride). Two bands were present, at R_f 0.7 and 0.1. The band at R_f 0.7 gave talpinine-N_b-acetamide (3 mg), identified by its infrared and mass spectrum: Ce(IV) reaction (green-violet); IR (film) 2925, 2845, 2720, 1725, 1635, 1440, 1100, 750 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+, 366 (100), 338 (10), 323 (10), 322 (10), 251 (8), 225 (20), 196 (15), 183 (60), 181 (62), 170 (25), 168 (23).

Preparation of 5-Acetyl-2,3-dihydro-4*H*-pyran (33). To a suspension of anhydrous aluminum chloride (3.3 g, 25 mmol) in anhydrous methylene chloride (25 mL) was added acetyl chloride (2 g, 25 mmol). The aluminum chloride immediately dissolved and the reaction mixture was then cooled to −78 °C. Dihydropyran (2 g, 23.8 mmol) dissolved in methylene chloride (15 mL) was then added dropwise such that the temperature never exceeded −70 °C. Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, then quenched in ice water (50 mL). The lower organic layer was separated, neutralized with aqueous sodium carbonate, washed with water (2 × 50 mL), and dried over anhydrous sodium carbonate. Concentration

of the methylene chloride extract under reduced pressure followed by distillation at 45 °C and 0.01 mmHg gave 5-acetyl-2,3-dihydro-4*H*-pyran (**33,** usually ca. 3 g) sufficiently pure for subsequent reaction. For analytical characterization, three Kugelrohr distillations (attended by polymerization) were performed to give pure **33** (400 mg) as a crystalline solid: mp 31 °C; IR (neat) 1650, 1620 (RO-C=CCOMe), 1395, 1170, 635 cm^{-1}; NMR ($CDCl_3$) δ 7.6 (1 H, s, -C=CHOR), 4.06 (2 H, t, J = 5 Hz, CH_2OR), 2.28-2.20 (5 H, s, partially obscuring a triplet methylene and COMe protons), 1.95 (2 H, m, J = 5 Hz, methylene protons). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.98; O, 25.36. Found: C, 66.6; H, 8.0; O, 25.4. The compound gradually decomposed on storage at 0 °C; the combustion analysis was performed on freshly distilled material by Dr. C. K. Fitts, Carlisle, Mass.

Reduction of 5-Acetyl-2,3-dihydro-4*H*-pyran (33) with Sodium Borohydride. 5-Acetyl-2,3-dihydro-4*H*-pyran (1 g, 7.9 mmol) was dissolved in methanol (20 mL) at 0 °C and sodium borohydride (0.3 g) added. The reaction mixture was stirred at room temperature for 24 h. Water (25 mL) was then added and the aqueous solution extracted with diethyl ether (liquid-liquid extractor, 24 h). The ether layer was dried over anhydrous sodium carbonate, concentrated to a small volume, and distilled. The 2′-hydroxy-5-ethyl-2,3-dihydro-4*H*-pyran (**34,** 0.82 g, 81%) was obtained at 57 °C and 0.01 mmHg: R_f 0.45 (brown, I_2); IR (neat) 3400 (O-H, strong), 1660 (C=COR), 1240, 1150, 1070, 920, 850 cm^{-1}; NMR ($CDCl_3$) δ 6.40 (1 H, s, vinyl ether proton), 4.4-3.80 (3 H, m, CH_2OR, R_2CHOR), 2.80-2.50 (1 H, broad s, -OH), 2.20-1.80 (4 H, m, CH_2CH_2), 1.28 (3 H, d, J = 7 Hz, CH_3CHROH). The compound deteriorated on storage too quickly for accurate analytical data to be obtained.

Hydrolysis of 2′-Hydroxy-5-ethyl-2,3-dihydro-4*H*-pyran (34) with 2 N HCl. To 2 N HCl (75 mL) was added 2′-hydroxy-5-ethyl-2,3-dihydro-4*H*-pyran (2.3 g). The solution was stirred for 1 min, basified to pH 9 with dilute ammonia, and extracted with chloroform (25 mL) and diethyl ether (2 × 50 mL). The organic phases were combined, dried over anhydrous potassium carbonate, concentrated to a small volume under reduced pressure, and distilled. The product, (*E*)-4-formyl-4-hexenol (**35,** R = OH) (1.5 g, 65.2% yield), was obtained at 87 °C and 0.01 mmHg as a colorless oil: IR (neat) 3400 (strong, OH), 2870, 2720, 1670 (strong, CHO), 1640, 1060 cm^{-1}; NMR ($CDCl_3$) δ 9.36 (1 H, s, CHO), 6.60 (1 H, q, J = 7 Hz, CH_3C=C), 1.80-1.40 (2 H, m, $-CH_2-$). Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.43; O, 24.96. Found: C, 65.71; H, 9.33; O, 24.82.

Reaction of 2′-Hydroxyethyl-2,3-dihydro-4*H*-pyran (34) with *p*-Toluenesulfonyl Chloride. 2′-Hydroxy-5-ethyl-2,3-dihydro-4*H*-pyran (**34,** 54 mg, 0.42 mmol) was dissolved in pyridine (1 mL, dried over KOH). The solution was cooled to 0 °C and freshly recrystallized *p*-toluenesulfonyl chloride (160 mg, 0.84 mmol) added. The reaction mixture was held at 3 °C for 24 h, then poured into ice-water (25 mL). The solution was acidified with dilute HCl (0.1 N) and extracted with chloroform (3 × 10 mL). The chloroform extracts were combined and dried over anhydrous sodium carbonate and solvent was removed under reduced pressure. The product (**35,** R = OTs) (120 mg, 84% yield) was a colorless oil which could not be distilled without decomposition: IR (neat) 2720, 1680, 1640, 1598, 1360, 1176, 930, 818, 740, 665 cm^{-1}; NMR ($CDCl_3$) δ 9.93 (1 H, s, CHO), 7.60 (4 H, d, d, J = 8 Hz, aromatic protons), 6.58 (1 H, q, J = 7 Hz, C=CHMe), 3.98 (2 H, t, J = 6 Hz, CH_2OTs), 2.44 (3 H, s, aromatic methyl), 2.28 (2 H, m, $-CH_2-$), 2.0 (3 H, d, J = 7 Hz, C=$CHCH_3$), 1.76 (2 H, m, CH_2). This material was characterized as the derived phthalimide (**35,** R = phthalimido).

Preparation of (*E*)-4-Formyl-4-hexenyl-1-phthalimide. To a solution of (*E*)-4-formyl-4-hexenyl 1-tosylate (**35,** R = OTs) (1 g, 3.54 mmol) in freshly distilled dimethylformamide (20 mL) was added potassium phthalimide (654 mg, 3.54 mmol). The reaction mixture was stirred at room temperature for 24 h. TLC indicated that a new product, R_f 0.8, was produced, although a large quantity of starting material was still present. The reaction mixture was then heated to 90 °C under nitrogen and monitored by TLC. At the end of 2 h no starting material was found and the reaction mixture was quenched in ice water (100 mL). Extraction of the aqueous solution with chloroform (3 × 25 mL) was followed by repeated washing of the organic phase with water, to remove residual dimethylformamide. The organic phase was then dried over anhydrous sodium carbonate and solvent removed under reduced pressure to leave a white solid. The solid was recrystallized from 95% ethanol to yield needles of **35** (R = phthalimido): mp 113-114 °C; IR (film) 1705, 1670, 1640, 1400, 722, 715 cm^{-1}; NMR ($CDCl_3$) δ 9.33 (1 H, s, CHO), 7.72 (4 H, m, aromatic protons), 6.57 (1 H, q, J = 7 Hz, C=$CHCH_3$), 1.90 (6 H, m, $CH_2CH_2CH_2$). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.07; H, 5.87; N, 5.44. Found: C, 69.95; H, 5.89; N, 5.50.

Preparation of (*E*)-4-Formyl-4-hexenal (36) by Kornblum Oxidation of (*E*)-4-Formyl-4-hexen-1-yl Tosylate (35, R = OTs). A solution of anhydrous sodium bicarbonate (1 g) in anhydrous dimethyl sulfoxide (20 mL, distilled from calcium hydride) was prepared in a three-necked flask equipped with a dropping funnel, thermometer, and nitrogen atmosphere. The solution was heated (oil bath) to 150 °C and (*E*)-4-formyl-4-hexen-1-yl tosylate (1 g) added. The solution was maintained at 150 °C for exactly 3 min, then rapidly cooled to room temperature, added to water (500 mL), and extracted with chloroform (3 × 50 mL). The chloroform extracts were combined, dried over anhydrous sodium carbonate, and concentrated under reduced pressure to yield an oily product (225 mg). Chromatography of this material on a silica gel preparative plate (Merck, 0.5 mm) in chloroform yielded a new product (**36**) (R_f 0.8, 100 mg) as a colorless oil: IR (neat) 2915, 2815, 2710, 1715 (strong, CHO), 1665, 1640, (α,β-unsaturated CHO), 1175, 755 cm^{-1}; NMR ($CDCl_3$) δ 9.76 (1 H, t, J = 1 Hz, saturated -CHO), 9.38 (1 H, s, α,β-unsaturated CHO), 6.64 (1 H, q, J = 6 Hz, C=$CHCH_3$), 2158 (4 H, s, $-CH_2CH_2-$), 2.03 (3 H, d, J = 6 Hz, C=$CHCH_3$).

The dialdehyde **36** could not be purified by distillation as partial polymerization resulted. The compound also rapidly decomposed on storage, even at low temperature, and was thus prepared only when it was to be used immediately.

Oxidation of (*E*)-4-Formyl-4-hexenol (35, R = OH) with Pyridinium Chlorochromate. Pyridinium chlorochromate (2.59 g, 12 mmol) was dissolved in methylene chloride (25 mL, dried by filtration through aluminum oxide). To this solution was added (*E*)-4-formyl-4-hexenol (1 g, 8 mmol) with constant stirring. The reaction mixture was stirred at room temperature for 2 h, then diluted with diethyl ether (125 mL). The resulting brown suspension was rapidly filtered through a column of silica gel (50 g) and the eluate concentrated under reduced pressure to a yellow oil. This oil was distilled at 76 °C and 0.01 mmHg to yield (*E*)-4-formyl-4-hexenal (0.542 g), which was slightly contaminated with polymeric products. Chromatography of the crude product (100 mg) on a silica gel preparative plate ($CHCl_3$) produced pure (*E*)-4-formyl-4-hexenal (**36**) with infrared, NMR, and TLC behavior identical with those of (*E*)-4-formyl-4-hexenal prepared by Kornblum oxidation. For preparative purposes the initial distillation only is required. Since the pyridinium chlorochromate oxidation was easier than the Kornblum oxidation, the former synthesis was utilized exclusively for preparative work.

Hydrogenation of (*E*)-4-Formyl-4-hexenal. To a solution of (*E*)-4-formyl-4-hexenal (1.2 g) dissolved in anhydrous methanol (stored over Raney nickel) was added palladium on charcoal (10%, 50 mg). The solution was then hydrogenated at atmospheric pressure, absorbing 150 mL of hydrogen (70% of theoretical). The catalyst was filtered off through a Celite filter pad and the solvent removed under reduced pressure. TLC of the reaction mixture indicated that a new product had been obtained along with unreacted starting material. VPC of the reaction mixture on a 2-ft Triton X column (10%) at 150 °C also showed that the major component of the reaction mixture was a new product. An infrared spectrum taken of the crude reaction mixture showed a strong O-H peak at 3410 cm^{-1}, aldehydic absorptions at 2710 and 1720 cm^{-1} (strong), and only a small amount of carbonyl absorption attributable to starting material, at 1670 cm^{-1}. An NMR ($CDCl_3$) taken of the crude reaction mixture was consistent with the presence of the saturated dialdehyde **31** and its enol-lactol tautomers. Two new aldehyde peaks appeared at δ 9.46 and 9.60 as multiplets. The ethylidene methyl doublet present in the starting dialdehyde had also been replaced by a broadened triplet at δ 1.10. The new product also did not quench long-wavelength UV light. Since its R_f was very close to that of the starting material, the crude mixture was employed directly in the next step.

Preparation of 3-Ethylpyridine. The crude 2-ethyl-1,5-pentanedialdehyde **31** (500 mg, 4 mmol) was dissolved in methanol (15 mL) and hydroxylamine hydrochloride (1 g, 14.3 mmol) added. The solution was refluxed under nitrogen for 5 h, during which time it turned deep red. Methanol was then removed under reduced pressure and the solution basified with sodium hydroxide (10%) and steam distilled until oily droplets ceased to appear in the distillate. The distillate was then extracted with chloroform (3 × 25 mL). The chloroform solution was dried over anhydrous sodium carbonate and concentrated to a

colorless oil under reduced pressure. Distillation of the oil gave pure 3-ethylpyridine (350 mg) which was characterized as its picrate, recrystallized as yellow needles from 95% ethanol, mp 127–128 °C (lit.[22] 128.1 °C). The IR and NMR spectra of the pyridine were identical with literature data.[23]

Preparation of 6-Hydroxyhexan-2-one. 5-Acetyl-2,3-dihydro-4*H*-pyran (**33**, 5.2 g, 41 mmol) was dissolved in 2 N HCl (100 mL) and the reaction mixture refluxed for 4 h. The solution was then neutralized with dilute ammonia and extracted with chloroform (3 × 25 mL). The chloroform solution was dried over anhydrous sodium carbonate and concentrated to a light yellow oil. Distillation of this oil at 65 °C and 0.7 mmHg produced pure 6-hydroxyhexan-2-one as a colorless liquid (4.0 g, 84%): IR (neat), 3400, 2975, 1710, 1370, 1230, 1090, 1040, 760 cm^{-1}; NMR ($CDCl_3$) δ 4.10, (1 H, broad s, OH), 3.55 (2 H, broad t, CH_2OH), 2.49 (2 H, broad t, $CH_2C{=}O$), 2.13 (3 H, s, CH_3CO), 1.8–1.35 (4 H, m, CH_2CH_2); cf. ref 24.

Preparation of 5-Oxohexanal. To a solution of anhydrous sodium acetate (246 mg, 3 mmol) and pyridinium chlorochromate (324 mg, 1.5 mmol) dissolved in anhydrous methylene chloride was added 6-hydroxyhexan-2-one (116 mg, 1 mmol). The reaction mixture was stirred for 3 h and monitored by TLC until all starting material had disappeared. The reaction mixture was then diluted with diethyl ether (100 mL) and rapidly filtered through a silica gel column (10 g). The solvent was removed under reduced pressure and the resultant oil distilled at 0.1 mmHg and 65 °C. 5-Oxohexanal was thus obtained as a colorless liquid, whose spectral data were consistent with the assigned structure: IR (neat) 2710, 1715, 1360, 1170 cm^{-1}; NMR ($CDCl_3$) δ 9.86 (s, CHO), 2.70 (broad t, CH_2), 2.36 (s, $-CH_3CO$), 1.8 (m, CH_2); cf. ref 25. This material was used directly to prepare 2-methylpyridine.

Preparation of 2-Methylpyridine. To a solution of hydroxylamine hydrochloride (2.32 g, 33.34 mmol) in anhydrous methanol (50 mL) was added 5-oxohexanal (1.9 g, 16.67 mmol). The solution was refluxed for 6 h under nitrogen, and the solvent then removed under reduced pressure. The dark yellow oil was then basified with 10% sodium hydroxide and steam distilled until no more oily droplets were found in the distillate. The aqueous solution was then extracted with chloroform (3 × 25 mL). The chloroform extract was dried over anhydrous sodium carbonate, concentrated, and distilled. The NMR spectrum of the distillate (0.1 g) was identical with that of authentic 2-methylpyridine. The picrate of the synthetic 2-methylpyridine and of an authentic sample had identical melting points, 163–164 °C.

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