(KBr) 1750 ($\nu_{C=O}$), 1040 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_5P$: C, 53.34; H, 5.60; P, 11.46. Found: C, 52.94; H, 5.61; P, 11.47.

3-(Carboxymethyl)-2-oxo-5-phenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5e): white crystals; mp 118–121 °C; ^1H NMR ($CDCl_3$) δ 2.4–3.0 (m, 2), 3.3–4.6 (m, 5), 6.9–7.9 (m, 5), 9.85 (s, 1); IR (KBr) 3400, 1730 ($\nu_{C=O}$) 1640 ($\nu_{C=O}$), 1035 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_7P$: C, 48.01; H, 4.36; P, 10.32. Found: C, 47.65; H, 4.80; P, 10.60.

5-Methoxy-2-oxo-7,7,8,8-tetramethyl-1,4,6,9-tetraoxa-5-phosphaspiro[4.4]nonane (5f). An equimolar (3 mmol) mixture of **1c**, **4a**, and diphenyl disulfide in acetonitrile (4 mL) was kept at room temperature with stirring under nitrogen. After 24 h, acetonitrile and benzenethiol were removed completly in vacuo, and the residue was subjected to the recrystallization as above: white crystals; mp 87–89 °C; ^1H NMR ($CDCl_3$) δ 1.3 (m, 12), 3.63 (d, J_{P-H} = 14 Hz, 3) 4.19 (d, J_{P-H} = 14 Hz, 2); IR (Nujol) 1755 ($\delta_{C=O}$), 1060 (ν_{P-O-C}) cm^{-1}. Anal. Calcd for $C_9H_{17}O_6P$: C, 42.86; H, 6.80; P, 12.28. Found: C, 42.54; H, 7.12; P, 12.32.

***S*-Phenyl *O*-[2-(Phenylthio)ethyl] Phenylphosphonothioate (10).** Equimolar (3 mmol) amounts of **1a** and diphenyl disulfide were dissolved in diethyl ether (6 mL), and the mixture was kept at room temperature under a nitrogen atmosphere for 3 h. On removing diethyl ether in vacuo a colorless viscous oil was given. It was then purified by the preparative TLC (silica gel–chloroform, R_f 0.4–0.5) to yield **10**: 92%; ^1H NMR ($CDCl_3$) δ 3.10 (t, J_H = 7 Hz, 2), 4.3 (m, 2), 7.0–7.8 (m, 15); ^{31}P NMR ($CDCl_3$ from 85% H_3PO_4) 41 ppm; IR (film) 1230 ($\nu_{P=O}$), 1060 (ν_{P-O-C}), 1000 cm^{-1} Anal. Calcd for $C_{20}H_{19}O_2PS_2$: C, 62.16; H, 4.96; P, 8.01. Found: C, 61.94; H, 4.94; P. 8.05.

Registry No. **1a**, 1006-83-3; **1b**, 695-11-4; **1c**, 14812-60-3; **2a**, 107-21-1; **2b**, 120-80-9; **2c**, 126-30-7; **2d**, 109-83-1; **3a**, 34736-73-7; **3b**, 71559-31-4; **3c**, 80317-87-9; **3d**, 80317-88-0; **3e**, 34736-72-6; **4a**, 79-14-1; (±)-**4b**, 598-82-3; (±)-**4c**, 90-64-2; **4d**, 594-61-6; (*S*)-**4e**, 97-67-6; **5a**, 75631-05-9; (±)-**5b**, 80317-89-1; (±)-**5c**, 80317-90-4; **5d**, 75631-06-0; (*S*)-**5e**, 80317-91-5; **5f**, 80317-92-6; **10**, 80317-93-7; diphenyl disulfide, 882-33-7.

Synthetic Studies in the Ajmaline Series[1]

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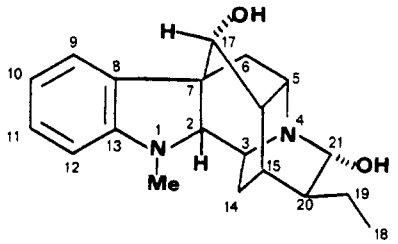
An approach to the Rauwolfia alkaloid ajmaline (1) is described. The bicyclic indole system **13a** was prepared by Fischer indole synthesis from either of the 9-azabicyclo[3.3.1]nonan-2-one derivatives **8** and **10**. Differentiation of a symetrically functionalized diol **6** by using poly(vinylpyridinium chlorochromate) (PVPCC) is described. The preparation of the indole system **13a** is discussed with appropriate reference to the stereochemical aspects involved. Further elaboration of **13a** to the tricyclic compounds **31** and **32** is presented.

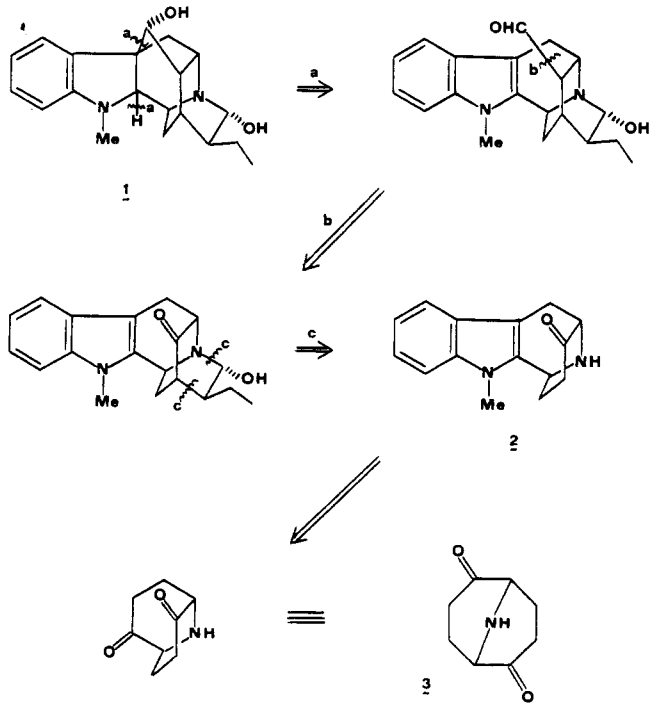
The appeal of the antiarrhythmic[3] Rauwolfia alkaloid ajmaline (1) to synthetic chemists has been the inherent



1 Ajmaline

challenge of preparing such a highly fused ring system. Previous syntheses of ajmaline,[4] isoajmaline,[5] and an elegant partial synthesis[6] have employed quite different approaches to control of stereochemistry and ring formation; however, all of these syntheses have shared the common feature of the Pictet–Spengler reaction in linking carbons 2 and 3. Because of this common feature, all of these previous syntheses[4–6] have utilized preformed indolic starting materials such as *N*-methyltryptophan and *N*-methylindole acetic acid.

Scheme I. Retrosynthetic Analysis of Ajmaline



In examining a number of alternative approaches to ajmaline, we were attracted to the possibility of constructing the indole moiety de novo. In particular, as shown in Scheme I, the series of retrosynthetic disconnections a–c gave the attractive intermediate **2**, which,

(1) Contribution No. 614 from the Institute of Organic Chemistry.
(2) Syntex Postdoctoral Fellow: (a) 1977–1979; (b) 1979–1980.
(3) Petter, A.; Engelmann, K. *Arzneim.-Forsch.* **1974**, *24*, 876.
(4) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506.
(5) Mashimo, K.; Sato, Y. *Tetrahedron* **1970**, *26*, 803.
(6) van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136.

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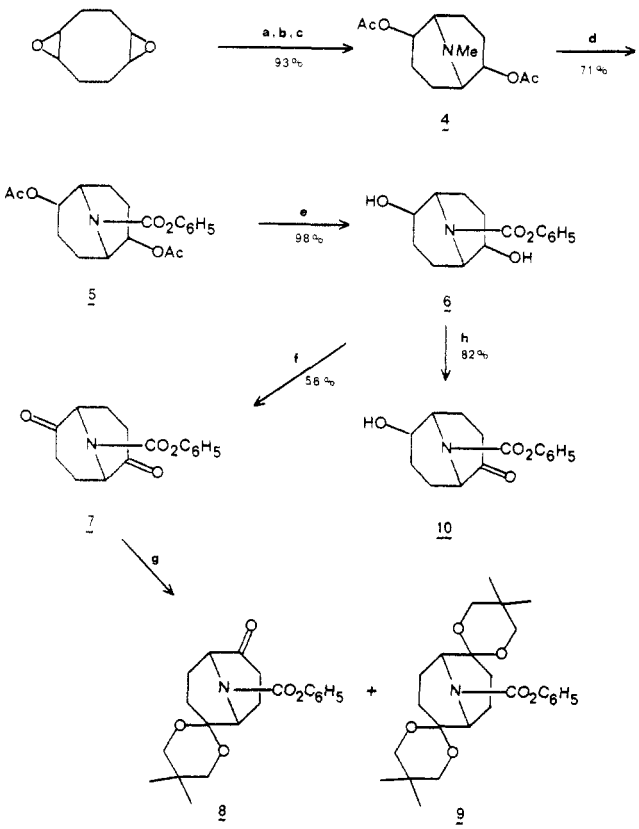
Scheme II. Formation of the 9-Azabicyclo[3.3.1]nonane System[a]

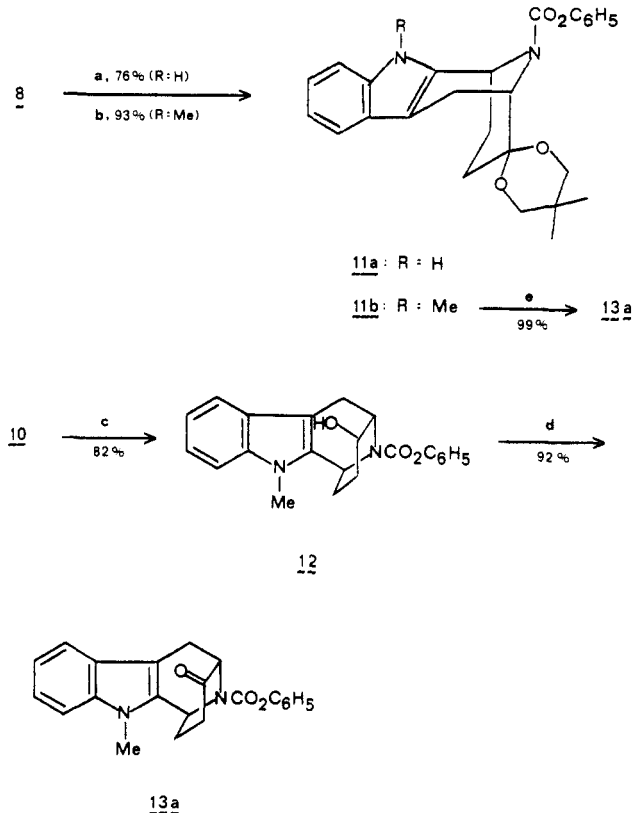


[a] (a) CH_3NH_2, CH_3OH, H_2O, 85 °C, 18 h; (b) Ac_2O, pyr, room temperature, 16 h; (c) 300 °C, 15 min; (d) $ClCO_2C_6H_5$, LiI, acetone, 0 °C, 40 min; 25 °C, 3.5 h; (e) K_2CO_3, CH_3OH, H_2O, room temperature, 2 h; (f) PCC, $CHCl_3$, 26 h; (g) 2,2-dimethylpropanediol, *p*-TsOH, toluene, reflux, 3.25 h; (h) PVPCC, CH_2Cl_2, room temperature, 7 days.

upon further disconnection, gave the 9-azabicyclo[3.3.1]-nonane system **3**. Since, in principle, there existed two fine methods for proceeding in the synthetic direction from **3** to **2**, namely, the Fischer indole synthesis and the Gassman indole synthesis,[7] we decided to investigate the synthetic counterpart to Scheme I.

Synthesis of the 9-Azabicyclo[3.3.1]nonane System. Efficient procedures were developed for making the diacetate **4**[8] and for transforming it into *N*-carbophenoxy diol **6**. We opted for the conversion of the *N*-methyl group in **4** to the *N*-carbophenoxy group at this early stage in order to have crystalline, lipid-soluble intermediates; moreover, we had experienced several disappointing results in attempting to oxidize the diol derived from **4** using either a modified Jones procedure[9] or using Pfitzner–Moffatt conditions.[10] In both cases, the low lipid solubility of the products made their isolation troublesome. Oxidation of **6** with pyridinium chlorochromate (PCC)[11] on a millimole scale gave a 91% yield of diketone **7**; however, on a half-mole scale the yield dropped to 56%, a drop which was due primarily to the intractability of the residues that accompany this oxidation procedure. Differentiation of the two ketonic moieties in **7** was achieved through formation of monoketal **8**; however, the use of this procedure was not practical since the isolation of **8** required a chromatographic separation from the diketal **9** and the dione **7**. While investigating alternative oxidations of diol **6**, we serendipitously discovered a way to differentiate the symmetric functionality through the oxidation of diol **6** to monoketone **10** using poly(vinylpyridinium chlorochromate) (PVPCC).[12] The results obtained with the PVPCC oxidation varied with the choice of solvent and temperature: reaction in dichloromethane at ca. 22 °C gave selective monooxidation and complete conversion of **6** to **10** (94%) in 7 days, whereas reaction in toluene at 80 °C resulted in complete consumption of starting material in 1.5 h, and there was obtained a 68% yield of monoketone **10** contaminated with a trace of the dione **7**. These reactions are summarized in Scheme II.

Scheme III. Formation of 13a[a]



[a] (a) $C_6H_5NHNH_3^+Cl^-$, DMF, 95 °C, 3 h; (b) $C_6H_5(CH_3)NNH_3^+Cl^-$, DMF, 95 °C, 2 h; (c) $C_6H_5(CH_3)NNH_3^+Cl^-$, DMF, 95 °C, 45 min; (d) ClCOCOCl, Me_2SO, TEA, −78 °C, ca. 30 min; (e) HOAc, 10 N HCl, 80 °C, 1.5 h.

Formation of the Bicyclic-Fused Indole 13a. It was reported that 9-benzoylbicyclo[3.3.1]nonan-2-one could be converted in 61% yield to 12-benzoyl-6,7,8,9,10,11-hexahydro-6,11-imino-5*H*-cyclooct[*b*]indole by reaction with phenylhydrazine in acetic acid containing sulfuric acid.[13] We found in our investigation of the Fischer indole synthesis that the ketones **8** and **10** were transformed directly into indoles **11a** (76%), **11b** (93%), and **12** (82%) by reaction with the appropriate hydrazine hydrochloride in DMF at about 100 °C. Ketone **13a** was obtained by two methods: (1) hydrolysis of **11b** (99%); (2) oxidation of alcohol **12** with Me_2SO–oxalyl chloride.[14] A small amount of **13a** was detected by TLC analysis of the mixture ob-

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(8) Portmann, R. E.; Ganter, C. *Helv. Chim. Acta* **1973**, *56*, 1991.
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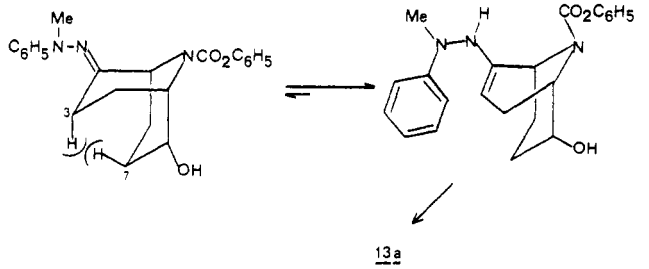
(12) Frechet, J. M. J.; Warnock, J.; Farrall, M. J. *J. Org. Chem.* **1978**, *43*, 2618.
(13) Calvert, B. J.; Hobson, J. D. *J. Chem. Soc.* **1964**, 5378.
(14) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

Scheme IV



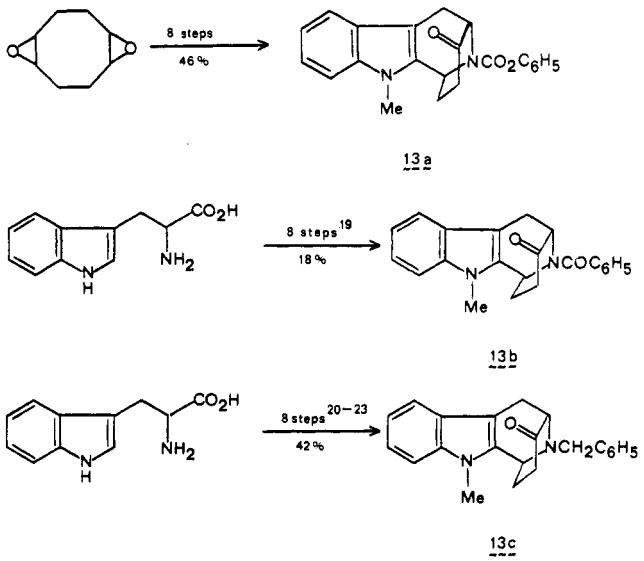
13a

tained by reacting diketone 7 with *N*-methyl-*N*-phenylhydrazine hydrochloride in DMF at 100 °C, but there were so many byproducts in the mixture that we did not attempt to determine a yield by product isolation. These reactions are summarized in Scheme III.

The ease of indole formation in these foregoing cases merits additional comment. In no case were we able to detect or isolate an intermediate hydrazone, and indole formation was observed by thin-layer, chromatography to occur within 20 min at room temperature. By its ease, this DMF procedure rivals the procedure whereby equivalent quantities of a ketone and an arylhydrazine are mixed in acetic acid and heated at reflux;[15] furthermore, there is a considerable contrast between the mild conditions of this DMF-based method and more typical conditions of the Fischer synthesis, which require a preformed hydrazone and which typically utilize an acid such as zinc chloride and temperatures of about 150 °C.[16] The relative facility of indole formation in our case is probably a function of the steric interactions that are present in the 9-azabicyclo[3.3.1]nonane system. The 9-azabicyclo[3.3.1]nonane system contains two six-membered rings, which, in principle, can exist optionally in chair–chair, chair–boat, or boat–boat conformations. The bicyclo[3.3.1]nonane system is known from ESR spectroscopy studies to exist in a chair–chair conformation that is somewhat flattened in order to relieve a buttressing interaction of the *endo*-hydrogens at positions 3 and 7.[17] The 9-azabicyclo[3.3.1]-nonane systems also adopt a chair–chair conformation unless there is an endo 3-substituent larger than hydrogen.[18] Once a ketone such as **8** or **10** forms a hydrazone, one expects that the buttressing interaction of the *endo*-hydrogens at carbons 3 and 7 will promote a rapid tautomerization of the C-3 hydrogen, thereby reducing strain by forming a 2,3-double bond (see Scheme IV). The ene–hydrazine intermediate that is formed can then undergo the electrocyclic process of carbon–carbon bond formation that leads ultimately to the observed indole. Thus it appears that, once formed, a 9-azabicyclo[3.3.1]-nonan-2-one hydrazone is particularly prone to giving an ene–hydrazine intermediate, and this feature accounts for both the relatively mild conditions required for indole formation and also for the failure to detect a hydrazone intermediate.

At this point, we can compare and contrast the overall yield and efficiency of our preparation of intermediate **13a** with other preparations of 12-substituted 5-methyl-9-oxohexahydro-6,10-imino-5*H*-cyclooct[*b*]indoles. Ketone **13a** in Scheme III was obtained in eight steps (through **10**) in 46% overall yield by starting with 1,5-cyclooctadiene diepoxide. The literature reports that the 12-benzoyl

Scheme V. Routes to 12-Substituted 5-Methyl-6,10-imino-5*H*-cyclooct[*b*]indoles



13a

13b

13c

compound **13b** was prepared in 18% overall yield in eight steps by starting with *dl*-tryptophan,[19] and the 12-benzyl compound **13c** was obtained in eight steps from *dl*-tryptophan in 27% overall yield.[20,21] During the course of our work it was reported that the yield of a Pictet–Spengler reaction can be considerably improved by the use of an aprotic reaction medium.[22] The application of this result to the synthetic scheme for **13c** leads to a projected 42% overall yield of **13c** from *dl*-tryptophan in eight steps.[23] Therefore, we see that the "Fischer indole" route to **13a** and the "Pictet-Spengler" route to **13c** are about equal in efficiency. Their differentiation was to be revealed in subsequent steps, and it was to take the guise of altered reactivity related to the difference of an *N*-benzyl group in **13c** and a carbophenoxy group in **13a** (Scheme V).

We also attempted to apply the Gassman synthesis of indoles[7] to the azabicyclononane system. We actually investigated this approach first, and only after repeated failures did we go on to the more classical Fischer synthesis. An α-thiolated carbonyl substrate was required for the Gassman synthesis, and preparing such a precursor was the essence of the problem in our case. Repeated attempts at condensing the enolate of the azabicyclononane **8** (deprotonation with lithium diisopropylamide) with benzene sulfenyl chloride, diphenyl disulfide, phenyl benzenethiosulfonate, and dimethyl disulfide failed to give any detectable amount of an α-thiolated substitution product.[24] In all cases, the starting material **8** was recovered in high yield. A control experiment with a deuterium oxide quench of the enolate gave back **8**, whose mass spectrum indicated a composition of more than 50% of the monodeuterio species.

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(17) Caldararu, H.; Moraru, M. *J. Am. Chem. Soc.* **1974**, *96*, 149.
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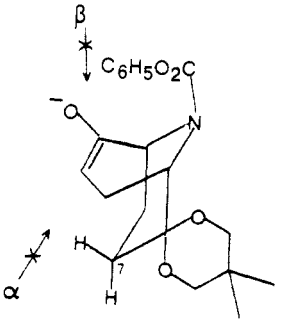
(20) (a) Yoneda, N. *Chem. Pharm. Bull.* **1965**, *13*, 622. (b) *Ibid.* **1965**, *13*, 1231.
(21) Mashimo, K.; Sato, Y. *Tetrahedron Lett.* **1969**, 901.
(22) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; Di Pierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.
(23) The calculation of this yield for **13c** is a composite from the following sources: footnote 15 in ref 22; the yield for *N*-methyltryptophan methyl ester in ref 20a; the yield of the Dieckman condensation quoted in the Experimental Section of ref 20b; the yield for hydrolysis–decarboxylation of 5-methyl-8-(carbomethoxy)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole in ref 21.
(24) For successful examples of α-thiolation of enolates see: Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.

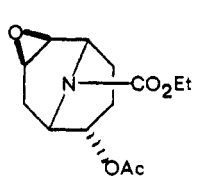
The unreactivity of the enolate of 8 toward bulky electrophiles can be explained by conformational analysis. Examination of I shows that the endo hydrogen at carbon



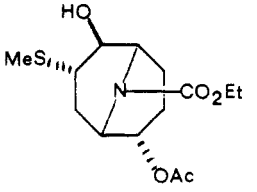
I

7 is stationed under the α face of the enolate. Blockade of the β face is provided by the bulky carbophenoxy group. The stationing of the carbophenoxy group over the enolate ring rather than the ketal-bearing ring is favored by the diminished steric interactions arising out of the ring flattening due to the sp^2 hybrization of carbons 2 and 3. N-9 must take on sp^3 character in order to have the carbophenoxy group cover the enolate. It is known from NMR spectroscopy studies that the energy barrier for rotation about the urethane amide bond is substantially less than that for amides;[25-28] therefore, the degree of double bond character of the nitrogen to carbonyl bond in urethanes is substantially less than the 40% figure that has been estimated for amides.[29] Thus, the unreactivity of the enolate of 8 toward bulky electrophiles is a function of the simultaneous blocking of its α face by the *endo*-hydrogen at carbon 7 and the blocking of its β face by the carbophenoxy group.

Because of these difficulties with enolate unreactivity we decided to explore a different way of introducing an appropriate thio substituent at the 3-position of the azabicyclonane system. Reaction of the β-epoxide 14[8] with



14

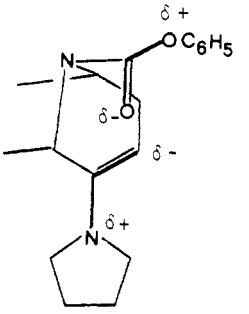


15

methanethiol absorbed on alumina[30] failed to give the desired product 15. Reaction of epoxide 14 with sodium methylmercaptide in ethanol led to cleavage of the acetate without substitution of the mercaptide. In both cases the substitution by methyl mercaptan was unsuccessful because the nucleophile would have to approach from the α face, which is blocked by the *endo*-hydrogen at carbon 7 (see I). This line of experimentation was deemed fruitless, and it was abandoned in favor of the Fischer synthesis.

Introduction of Carbons 20 and 21. In a partial synthesis of ajmaline, Mashimo and Sato showed that the pyrrolidine enamine of **13c** reacted with chloroacetonitrile to give **16** (65%).[31] In surprising contrast, we found that the pyrrolidine enamine of **13a** did not condense with a number of reactive electrophiles ($ClCH_2CN$, $BrCH_2CO_2CH_3$, CH_3I, and ketene thioacetal monoxide **17**), and upon workup **13a** was recovered unchanged. The lack of reactivity implied by these negative results suggested that more activation was required. Accordingly, we turned to the anionic adaptation of the enamine alkylation procedure.[32] The imine derived from **13a** and cyclohexylamine was deprotonated with lithium diisopropylamide (LDA), and the resulting anion was reacted with **17**. Workup of this reaction afforded the starting ketone **13a**. Since the enamine of the *N*-benzyl **13c** was reactive in giving C-alkylation,[31] these negative results obtained with **13a** are in poignant contrast, and there was, therefore, the suspicion that the unreactivity of the enamine of **13a** was related in a special way to the *N*-carbophenoxy group of **13a**.

Such a case of altered reactivity might be explained by a steric effect, one which in this case might be ascribed to a blockage of the β face of the molecule by the carbophenoxy group. Previously we had argued that the urethane nitrogen can be sp^3 to a substantial extent, and therefore the carbophenoxy group would be capable of covering the reacting face. The approach of an electrophile via the α face is blocked by the indole moiety. The same argument should also apply to an N-12 benzyl group, but in the case of **13c** the enamine was sufficiently reactive to undergo electrophilic substitution. Why then was there such a marked difference in reactivity between the enamines of **13a** and **13c**? We suggest by way of explanation that the carbophenoxy group may preferentially align itself over the enamine moiety so as to achieve an energetically favorable pairing of dipoles (see II).[33]



II

The ketene thioacetal monoxides **17** and **18** appeared to be ideal sources of carbons 20 and 21 of ajmaline. The lithium enolate of **13a** combined with **17** to give adduct **19**. The use of lithium diisopropylamide to generate the enolate gave, instead, the alcohol **12** as a byproduct, a reduction which was probably brought on by transfer of hydride from the diisopropylamide ion.[34] This problem of reduction was overcome by the use of lithium hexamethyldisilazide, and with this change **19** could be prepared on the 75-mmol scale in 80–83% yield. Under similar conditions **18** did not condense with the lithium enolate of **13a**, and thus we were denied a facile incorporation of

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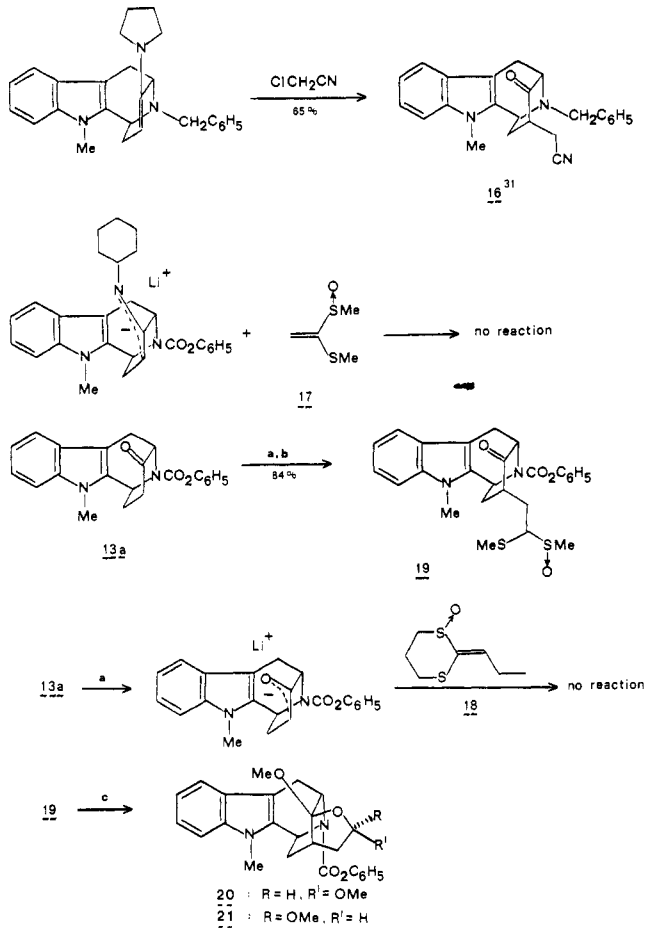
(32) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1971; pp 580–582.
(33) A cyclohexene double bond is known to be deactivated by a quasi-axial carbonyl group. See (a) Kugatova-Shemyakina, G. P.; Ovchinnikov, Y. A. *Tetrahedron* **1962**, *18*, 697. (b) Kugatova-Shemyakin, G. P.; Nikolaev, G. M.; Andreev, V. M. *Ibid.* **1967**, *23*, 2721.
(34) For other examples of ketone reduction by lithium diisopropylamide see: Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

Scheme VI. Introduction of Carbons 20 and 21[a]



[a] (a) $[(CH_3)_3Si]_2N$ Li, THF, 25 °C, 5 min; (b) 17, 25 °C, 20 min; (c) 3% methanolic HCl.

the 20-ethyl group of ajmaline. Either steric hinderance to approach of the reagent or deprotonation of the reagent by the enolate could account for this lack of reaction. Treatment of **19** with methanolic HCl gave a mixture of acetals **20** and **21**. The assignment of these two as C-21 epimers rather than as C-15 epimers was based upon the subsequent covalent linking of C-21 with the nitrogen to give a quinuclidine substructure. Prolonged treatment of **19** with methanolic HCl gave one isomer, **20**, in 88% yield. This assignment of **20** as the more thermodynamically stable isomer came from examination of molecular models, which showed **20** to be less sterically hindered than **21**. (Scheme VI).

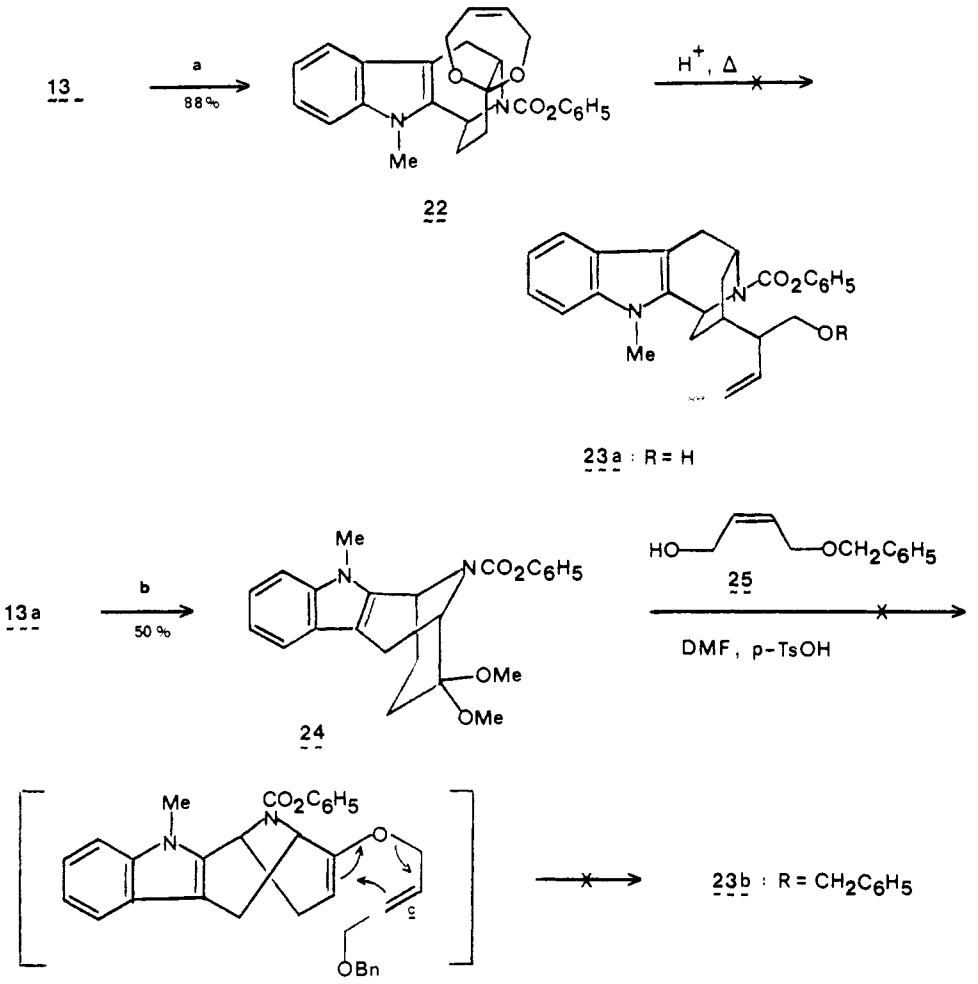
Because of the failure that we experienced in attempting to condense the ethyl-substituted ketene dithioacetal **18** with the enolate **13a**, we were faced with a situation that would require a number of additional steps to effect the introduction of the C-20 ethyl substituent and therefore decided to investigate an alternative to the ketene dithioacetal strategy before going further with the intermediate **19**. We chose to examine the Claisen rearrangement as a way of introducing at C-15 the four carbons that would comprise carbons 18–21. The ketal **22** was obtained in 88% yield from **13a** and *cis*-2-butene-1,4-diol. Heating **22** in DMF with a trace of *p*-toluenesulfonic acid up to about 150 °C or heating in propionic acid at temperatures up to 200 °C failed to produce any detectable amount of the desired rearrangement product **23a**. In all cases the starting material was recovered, and the only other material that was produced was very polar by TLC analysis. We interpret the reluctance of **22** to undergo a Claisen rearrangement in terms of the tendency of its cyclic ketal to remain closed, and thus providing a high energy of activation for the formation of the enol ether intermediate that must necessarily precede the Claisen rearrangement. To circumvent this problem, we investigated another approach to the Claisen rearrangement. The dimethyl ketal **24** was heated in DMF with butenyl carbinol **25** in the presence of acid. The hope was that under these conditions there would be an acid-catalyzed exchange in the ketal function to give a mixed methyl 4′-(benzyloxy)-2′-butenyl ketal, which, in the ideal case, could lose the elements of methanol under protic catalysis and thereby provide an intermediate with the potential to undergo the desired Claisen rearrangement to give **23b**. This approach did not succeed any better than did our attempts with the cyclic ketal **22**. We abandoned the Claisen approach after these negative results and concentrated on continuing the synthesis with the dithioacetal monoxide **19**. The Claisen rearrangment chemistry is shown in Scheme VII.

Introduction of C-17. Advancing the intermediate **19** further toward the ajmaline skeleton required a formal homologation to an intermediate having C-17 in the aldehyde oxidation state. We had already achieved this type of homologation by condensation of the lithiated phosphonate of **26** (R = *n*-Bu) with **13a** followed by treatment of the isolated 1,2-adduct with potassium *tert*-butoxide to give enol ether **27** in 37% overall yield[35] (Scheme VIII). Hydrolysis of the tetrahydrofuryl adduct **20** with lithium hydroxide gave the amine **28** (87%), which was then converted to quinuclidinol **29a** in 90% yield. Acylation of **29a** with pivalic anhydride gave a mixture of *O*-pivalates **29b** (92%). This result was in accord with the chemistry of ajmaline[36] where one obtains O-acylation at the 21-hydroxyl rather than N-acylation, which could have resulted if the quinuclidinol had opened to a secondary amine under acylation conditions. Condensation of this mixture **29b** with lithiated **26** (R = Et), followed by treatment of the product of this reaction with potassium *tert*-butoxide gave the THP–enol ether **30a** (34% from **29b**). The NMR spectrum of the 1,2-addition product from **29b** and phosphonate **26** showed the absence of a resonance for the pivalate group, thereby indicating that this group had been cleaved by nucleophilic attack of lithiated phosphonate **26**. Acetylation of **30a** gave the *O*-acetate **30b**, which upon acidic hydrolysis afforded a mixture of C-16 epimeric aldehydes **31** and **32** in 87% yield. The NMR spectrum of this mixture in deuteriochloroform contained the aldehyde protons at δ 9.86 and 9.43 in a ratio of 2:3, respectively. The lower field resonance was assigned to the α-formyl isomer **31**, and the higher field resonance was assigned to the β-formyl isomer **32** on the basis of the resonances reported for **33** (δ 9.8) and **34** (δ 9.5).[5] Reaction of this mixture of **31** and **32** with a mixture of acetic acid, acetic anhydride, and hydrochloric acid and then working up the mixture with ammonium hydroxide[37] gave a complex mixture from which we were unable to isolate anything that could be assigned to the desired cyclization product **35**.

Because of the esthetically unappealing and inefficient series of acylation, deacylation, and reacylation reactions that accompanied the progression of **29a** to **30b**, we examined the use of a silyl blocking group on the C-21 hydroxyl. We were able to obtain the *O*-*tert*-butyldimethylsilyl compound **29c** in only 30% yield together with

(35) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.
(36) Robinson, R. *Angew. Chem.* **1957**, *69*, 40.
(37) Bartlett, M. F.; Lambert, B. F.; Werblood, H. M.; Taylor, W. I. *J. Am. Chem. Soc.* **1963**, *85*, 475.

Scheme VII. Attempted Introduction of C-20 and C-21 by Claisen Rearrangement[a]



[a] (a) *cis*-2-Butene-1,4-diol, *p*-TsOH, toluene, reflux, 3 h; (b) CH_3OH, $HC(OCH_3)_3$, H_2SO_4, room temperature, 16 h.

approximately 60% of an unidentified decomposition product. Given the low efficiency of this reaction, we chose not to investigate the aldehyde homologation using the phosphonate reagent **26**, and we opted instead to explore another strategy for putting in C-17 and for linking it with C-7. Reaction of **29c** with lithiated trimethylsilyldithiane[38] gave **36** in 80% yield. Attempted cyclization of **36** to the ajmal structure **37** by using trifluoroacetic acid/triethylsilane[39] at room temperature for 24 h was uneventful, and starting material was recovered essentially quantitatively upon workup.

At this point we decided to abandon this entire line of synthetic strategy for preparing ajmaline. Further continuation would have required several additional steps to introduce the C-20 ethyl group. We are currently investigating a more converging synthetic approach to ajmaline.

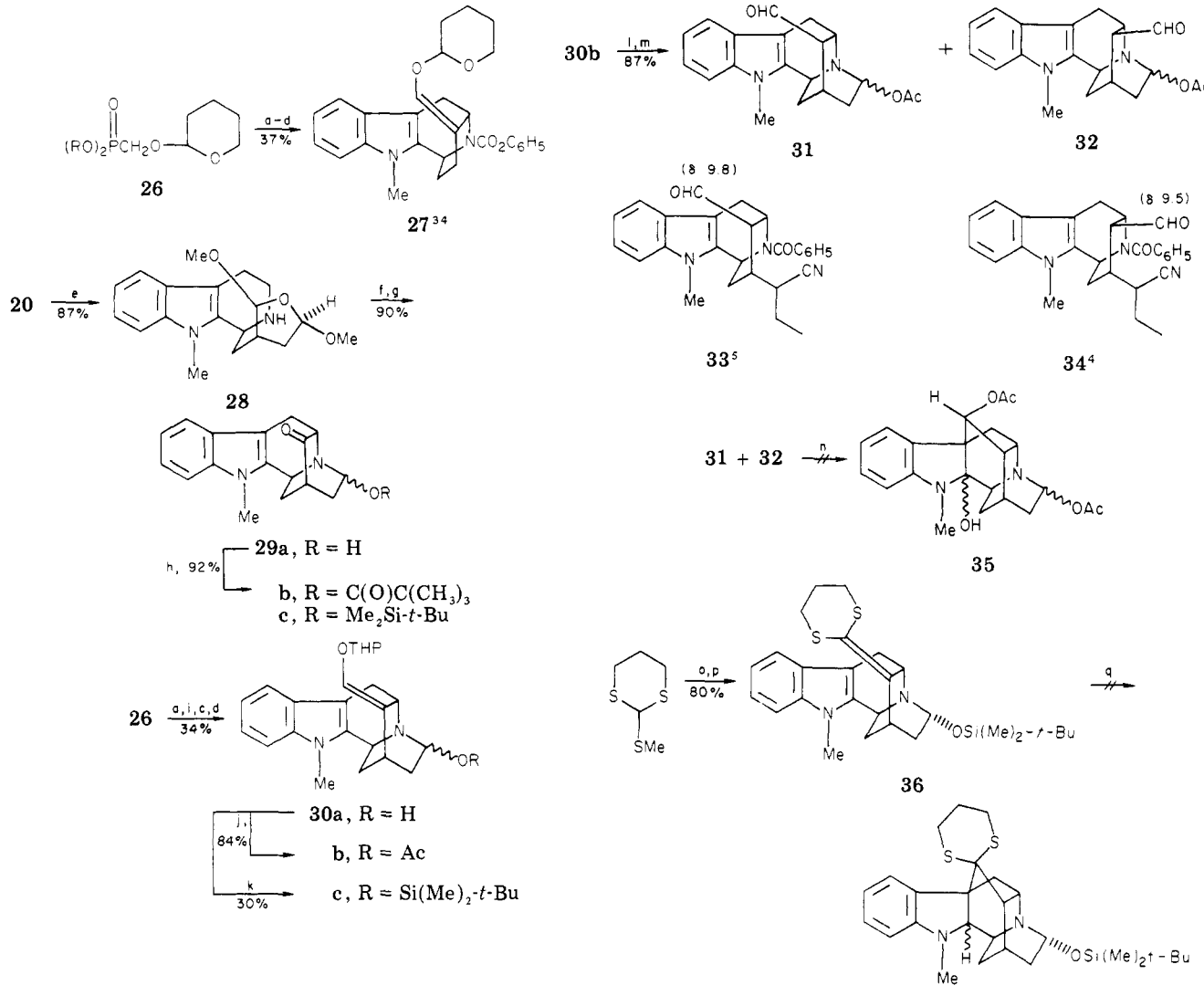
Experimental Section

Melting points (uncorrected) were determined on a Fisher-Johns apparatus. Infrared spectra were obtained by using a Perkin-Elmer 237 grating instrument. Proton NMR spectra were obtained by using a Varian A-60A, a Varian HA-100, or a Bruker WM-300 spectrometer on solutions of ca. 10% (v/v) containing 1% tetramethylsilane as an internal standard. Carbon NMR spectra were determined at 22.62 MHz in rotating 10-mm tubes on a Bruker WH-90 operating in the pulse Fourier transform mode. The pulse width was 5 μs (15 μs = 90°). The sample temperature was maintained at 305 K. The repetition rate for noise-decoupled spectra was 0.7 s, and the free induction decays (6000–9000 accumulations) were stored in 8192 points. An 0.8-Hz line-broadening function was applied before zero filling to 16 384 points and Fourier transformation, yielding a digital resolution of 0.783 Hz. Mass spectra were obtained with an Atlaswerke CH-7 instrument. Elemental analyses were performed by the Syntex Analytical Services Department and by A. Bernhardt, Mulheim-Ruhr.

***N*-Methyl-2,6-diacetoxy-9-azabicyclo[3.3.1]nonane (4).** The method given is an extension of the method of Portmann and Ganter.[8] In three equal portions, *cis,cis*-1,5-cyclooctadiene diepoxide (130 g, 0.928 mol) was heated overnight with 40% aqueous methylamine (390 mL, 3.32 mol) and methanol (300 mL) in a glass pressure vessel at 85 °C. The reaction mixtures were combined and concentrated. The remaining traces of water were removed by azeotropic distillation with toluene (300 mL). After removal of the solvent, the mixture of diols was dissolved in pyridine (250 mL). Acetic anhydride (200 mL) was added, and the mixture was stirred for 16 h. The solution was concentrated; remaining traces of pyridine were removed by Kugelrohr distillation. The residue was purified by filtration over 1 kg of 80–230-mesh silica gel (eluent ether) to give a yellow oil (217.2 g, 91%), which slowly crystallized. This mixture (212 g, 0.831 mol) was sealed in 21 glass ampules (average content 10 g). Each ampule was heated in a Woods metal bath at 300 ± 5 °C for 15 min. (**Caution**: any unremoved solvent from previous preparations is potentially explosive under these conditions. Care must be taken to completely remove all the solvent.) After cooling, the contents of the ampules were recombined and recrystallized from hexane (200 mL) to afford pure **4** as white prisms (141.4 g). The residue was purified by column

(38) Seebach, D.; Kolb, M.; Grobel, B. *Chem. Ber.* **1973**, *106*, 2277.
(39) For an example of a cationic cyclization using the dithian-2-ylidene function see: Andersen, N. H.; Yamamoto, Yasusi; Denniston, A. D. *Tetrahedron Lett.* **1975**, 4547.

Scheme VIII. Introduction of C-17[a]



[a] (a) $[(CH_3)_2CH]_2Ni$ Li, THF, −78 °C, 5 min; (b) 13a, −100 °C, 30 min; (c) H_2O; (d) KO-*t*-Bu, THF, room temperature, 30 min; (e) LiOH, H_2O, dioxane, room temperature, 20 h; (f) HCl, H_2O, THF, reflux, 30 min; (g) 3 N NaOH, room temperature, 1 h; (h) $[(CH_3)_3CCO]_2O$, DMAP, TEA, THF, room temperature, 30 min; (i) **29b**, −100 °C, 30 min; (j) Ac_2O, DMAP, TEA, THF, room temperature, 30 min; (k) TBDMSCl, imidazole, DMF, room temperature, 5 h; (l) HCl, H_2O, THF, room temperature, 16 h; (m) pH 9 buffer; (n) AcOH, Ac_2O, HCl, room temperature, 18 h; (o) *n*-BuLi, THF, 0 °C, 15 min; (p) **30c**, 0 °C, 1 h; (q) Et_3SiH, TFA.

chromatography over silica gel (250 g) with ether to give, as a white solid, pure **4** (54.9 g). The total yield was 196.3 g (92.6%).

9-(Carbophenoxy)-*endo*,*endo*-2,6-diacetoxy-9-azabicyclo[3.3.1]nonane (5). To a solution of anhydrous lithium iodide (125 g, 1.87 mol) in dry acetone (600 mL) was added the amine **4** (213 g, 0.835 mol). The solution was stirred mechanically until most of the amine had dissolved. The solution was cooled to 0 °C, and a solution of phenyl chloroformate (109.3 mL, 0.88 mol) in acetone (400 mL) was added dropwise over 40 min. After the addition was complete, the reaction was stirred at 25 °C for a further 3.5 h. The solution was concentrated, taken into ethyl acetate (3 L), and washed with water (2 × 400 mL). The combined aqueous washings were extracted with ethyl acetate (2 × 100 mL), and the organic phases were combined, washed with saturated sodium bicarbonate (100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated to give a brown oil which was recrystallized from ethyl acetate (550 mL)/hexane (450 mL) to produce the urethane **5** as off-white prisms, 214 g (71%). An analytical sample was prepared by recrystallization from ethyl acetate/hexane to give white prisms: mp 145–147 °C; IR (KBr) 1735, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.75–2.25 (m, 8 H), 2.09 (s, 6 H), 4.25–4.55 (m, 2 H), 4.9–5.25 (br s, 2 H), 7.05–7.45 (m, 5 H); mass spectrum, *m/e* (relative intensity) 361 (P, 13), 268 (100), 226 (30), 166 (38), 95 (19), 77 (17).

Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88. Found: C, 62.87; H, 6.65; N, 3.69.

9-(Carbophenoxy)-*endo*,*endo*-2,6-dihydroxy-9-azabicyclo[3.3.1]nonane (6). The diacetate **5** (214 g, 0.593 mol) was stirred mechanically as a slurry in hot methanol (1 L). A solution of potassium carbonate (66 g, 0.478 mol) in water (300 mL) was added over 15 min. The heating bath was removed, and stirring at ambient temperature was continued for 2 h. The solution was concentrated to 400 mL, diluted with ethyl acetate (1.5 L), washed with water (300 mL) and brine (200 mL), dried over magnesium sulfate, and concentrated to give the diol **6** as white crystals (161.1 g, 98% yield) which were used directly in the next step. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 143–144 °C; IR (CH_2Cl_2) 3589, 3450, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.3 (m 8 H), 3.1 (s, 2 H), 3.7–4.4 (m, 4 H) 6.95–7.55 (m, 5 H); mass spectrum, *m/e* (relative intensity) 278 (P + 1, 5), 260 (2), 184 (100), 140 (30), 95 (30), 94 (23).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.07; H, 6.94; N, 4.99.

9-(Carbophenoxy)-2,6-dioxo-9-azabicyclo[3.3.1]nonane-2,6-dione (7). The diol **6** (34.7 g, 0.125 mol) was dissolved in 350 mL of chloroform. Celite (70 g) was added, and the solution was

stirred mechanically and cooled to 0 °C. Pyridinium chlorochromate (81 g, 0.376 mol) was added in one portion, the cooling bath was removed, and stirring was continued at 25 °C for 20 h. A further 8 g of oxidizing agent was added, and stirring was continued at 25 °C for 6 h. Ether (500 mL) was added to the reaction and the solution decanted. The residue was washed with ether (2 × 500 mL), and the combined organic phases were concentrated and then filtered through silica (150 g) with ether (1.5 L) as the eluant. Concentration gave a colorless oil, (25.2 g). Recrystallization from ethyl acetate/hexane (1:1, 100 mL) gave the pure diketone **7** as white crystals (6 g). Purification of the residue by column chromatography over silica (400 g) with 25% ethyl acetate/hexane as the eluant produced a further 13.3 g of diketone **7** for a total yield of 19.3 g (56.4%). An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 71–72 °C; IR (KBr) 1725, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.65–2.8 (m, 8 H), 4.8–5.1 (m, 2 H), 7.0–7.55 (m, 5 H); mass spectrum, *m/e* (relative intensity) 273 (P 33), 245 (10), 230 (12), 217 (28), 124 (68), 77 (100).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92, H, 5.53; N, 5.13. Found: C, 65.72; H, 5.52; N, 5.19.

9-(Carbophenoxy)-9-azabicyclo[3.3.1]nonane-2,6-dione Bis(2,2-dimethylpropylene) Ketal (9). 2,2-Dimethylpropanediol (8 g, 76.9 mmol) and *p*-toluenesulfonic acid monohydrate (500 mg, 2.63 mmol) were added to a solution of the diketone **7** (10 g, 36.6 mmol) in toluene (350 mL). The mixture was heated under reflux in a water separator for 3.25 h. It was then cooled, diluted with ethyl acetate (150 mL), washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried over magnesium sulfate, and concentrated to give a white powder, 16.3 g (100%). Recrystallization from cyclohexane afforded 14.06 g of pure **9** (three crops) in 86% yield. An analytical sample was obtained as white platelets by recrystallization from hexane: mp 162–164 °C; IR (KBr) 1748 cm^{-1}; NMR ($CDCl_3$) δ 0.73 and 0.795 (2 s, 6 H), 1.06 and 1.15 (2 s, 6 H), 1.6–2.2 (m, 8 H), 3.25–3.92 (m, 8 H), 4.78–5.02 (2 br m, 2 H), 7.0–7.42 (m, 5 H); mass spectrum, *m/e* (relative intensity) 445 (P, 8), 352 (7), 260 (63), 141 (100), 69 (24), 55 (21).

Anal. Calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14. Found: C, 67.50; H, 7.95; N, 3.08.

9-(Carbophenoxy)-9-azabicyclo[3.3.1]nonane-2,6-dione 2,2-Dimethylpropylene Ketal (8). The diketone **7** (8.0 g, 29.3 mmol) and the diketal **9** (13.04 g, 29.3 mmol) were dissolved in toluene (300 mL). Toluenesulfonic acid monohydrate (1.0 g, 5.26 mmol) was added, and the mixture was heated under reflux for 5 h. The solution was cooled, washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to afford 21 g of a clear oil. The product was separated by column chromatography over silica (600 g; eluant 15% acetone/hexane) to give recovered diketal **9** (4.84 g), product **8** (12.18 g), and diketone **7** (2.94 g). The yield of product was 58%. Based on recovered **7** the yield was 91%. An analytical sample of **8** was obtained by recrystallization from cyclohexane: mp 110–111 °C; IR (KBr) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.82 and 0.95 (2 s, 3 H), 1.08 and 1.15 (2 s, 3 H), 2.02–2.8 (m, 8 H), 3.3–4.1 (m, 4 H), 4.62–4.83 (m, 1 H), 5.0–5.55 (m, 1 H), 7.03–7.55 (m, 5 H); mass spectrum, *m/e* (relative intensity) 359 (P, 2), 180 (3), 141 (100), 128 (16), 69 (22), 55 (62).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 67.07; H, 7.02; N, 3.99.

9-(Carbophenoxy)-6-*endo*-hydroxy-9-azabicyclo[3.3.1]nonan-2-one (10). Poly(vinylpyridinium chlorochromate) (PVPCC)[12] was activated prior to use by being stirred in water for 10 min, after which time it was filtered and air-dried. The diol **6** (15.5 g, 55.96 mmol) was slurried in toluene (200 mL). Activated PVPCC (66 g) was added, and the mixture was rapidly stirred (mechanically) and was heated to maintain an internal temperature of 90 °C for 5 h. The mixture was filtered, and the polymer was washed with ethyl acetate (600 mL). The filtrates were combined, washed with brine (50 mL), dried over magnesium sulfate, and concentrated. Trituration of the residue with ether gave the monoketone **10** as a white powder, 10.6 g (68%).

Stirring 2.35 g (8.5 mmol) of **6**, 19 g of wetted PVPCC, and 100 mL of dichloromethane at room temperature for 7 days followed by filtration and washing with 400 mL of dichloromethane gave 2.2 g (94%) of **10** on evaporation. An analytical sample was obtained by crystallization from ether/hexane: mp 94–96 °C; IR (KBr) 3450, 1725, 1710 cm^{-1}; NMR ($CDCl_3$) 1.2–2.75 (m, 9 H), 3.7–4.1 (m, 1 H), 4.5–4.9 (m, 2 H), 6.95–7.5 (m, 5 H); mass spectrum, *m/e* (relative intensity) 275 (P, 20), 182 (60), 154 (100), 110 (45), 94 (52), 93 (45).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.52; H, 6.23; N, 4.99.

Spiro[12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9,2′:5′,5′-dimethyl-1′,3′-dioxane] (11a). A mixture of 100 mg (0.278 mmol) of the monoketal–ketone **8**, 50 mg (0.347 mmol) of phenylhydrazine hydrochloride and 3 mL of DMF was heated at 95 °C for 3 h. The residue obtained after removal of the DMF under vacuum was taken up in 100 mL of acetate, and this mixture was washed with three 20-mL portions of water and 20 mL of saturated sodium chloride solution, an it was then dried over sodium sulfate. Evaporation of the solvent gave 135 mg of a foam, which was further purified by column chromatography from 100 g silica gel, eluting with 30% acetone–hexane. This gave 91 mg (76%) of product. An analytical sample was obtained through recrystallization from 2-butanone–hexane to give off-white crystals: mp 210–211 °C; IR (KBr) 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.78, 0.91, 1.01, and 1.10 (4 s, 6 H), 1.2–2.4 (m, 4 H), 3–4 (m, 6 H), 5–5.5 (m, 2 H), 6.9–7.6 (m, 9 H), 7.9 and 8.2 (2 s, 1 H).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.52; N, 6.48. Found: C, 72.09; H, 6.65; N 6.39.

Spiro[5-methyl-12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9,2′:5′,5′-dimethyl-1′,3′-dioxane] (11b). The ketone **8** (10.4 g, 28.97 mmol) was dissolved in DMF (50 mL). 1-Methyl-1-phenylhydrazine hydrochloride (5.73 g, 36.15 mmol) was added and the solution stirred and heated at 100 °C for 2 h. The solution was concentrated to about 15 mL, was diluted with ethyl acetate (300 mL), was washed with water (4 × 100 mL) and brine (100 mL), and was dried over magnesium sulfate. Evaporation of the solvent afforded an orange foam (13.8 g), which upon trituration with diisopropyl ether (30 mL) gave pure **11b** (11.2 g). Purification of the residue by column chromatography over silica (50 g; elution with 15% acetone–hexane) gave a further 0.8 g of material. The total yield was 12.0 g (93%) of product. An analytical sample was obtained by recrystallization from ethyl acetate/hexane to give white prisms: mp 203–204 °C; IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.82, 0.92, 1.07, and 1.15 (4 s, 6 H), 1.5–2.7 (m, 4 H), 3.1–4.2 (m, 6 H), 3.51 and 3.66 (2 s, 3 H), 5.2–5.8 (m, 2 H), 7.28–7.95 (m, 5 H); mass spectrum, *m/e* (relative intensity) 446 (P, 25), 305 (21), 141 (100), 64 (29), 55 (24), 43 (57).

Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; M, 6.27. Found: C, 72.60; H, 6.86; N, 6.46.

5-Methyl-9α-hydroxy-12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (12). The ketone–alcohol **10** (28.77 g, 0.105 mol) and 1-methyl-1-phenylhydrazine hydrochloride (18.24 g, 0.115 mol) were dissolved in DMF (250 mL). The solution was stirred and heated at 100 °C for 45 min and then concentrated to approximately 40 mL. The residue was dissolved in ethyl acetate, washed with water (3 × 100 mL) and brine (50 mL), dried over magnesium sulfate, and concentrated. The oily residue was recrystallized from ethyl acetate (40 mL) to afford **12** as off-white crystals (27.4 g). The mother liquor was purified by column chromatography over silica (250 g; eluting with 20% acetone–hexane) to give a further 3.7 g of product. The total yield was 31.1 g (82%). An analytical sample was obtained from ethyl acetate–hexane as white crystals: mp 180–181 °C; IR (KBr) 3425, 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.25–2.25 (m, 5 H), 3.0–3.2 (m, 2 H), 3.58 and 3.61 (2 s, 3 H), 3.8–4.1 (m, 1 H), 5.4–5.6 (m, 1 H), 6.9–7.6 (m, 9 H); mass spectrum, *m/e* (relative intensity) 362 (P, 100), 303 (25), 269 (25), 43 (65).

Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.62; H, 6.16; N, 7.71.

5-Methyl-12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-9-one (13a). The ketal **11a** (6.0 g, 13.45 mmol) was stirred in glacial acetic acid (50 mL). Hydrochloric acid 10 mL, 3 N) was added, and the mixture was stirred and heated at 80 °C for 1.5 h, at which time the solution was clear. The reaction mixture was concentrated to about 1/ mL and diluted with ethyl acetate (300 mL). This solution was washed with water (3 × 50 mL), saturated sodium bicarbonate (50 mL),

and brine (50 mL), dried over sodium sulfate, and concentrated to give an off-white solid. Recrystallization from ethyl acetate–hexane gave pure **13a** as white prisms, 4.55 g (94%). A further 220 mg of **13a** was obtained by column chromatography over silica (100 g; eluting with 20% acetone–hexane). The total yield was 4.77 g (98.5%). An analytic sample was obtained by recrystallization from ethyl acetate–hexane: mp 161–163 °C; IR (KBr) 1725, 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.0–3.5 (m, 6 H), 3.68 (s, 3 H), 5.02–5.2 (m, 1 H), 5.65–5.82 (br s, 1 H), 7.0–7.55 (m, 5 H); mass spectrum, *m/e* (relative intensity) 360 (P, 100), 303 (75), 267 (20), 183 (36), 170 (32), 43 (70).

Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.38; H, 5.62; N, 7.71.

The ketone **13a** was also prepared by dimethyl sulfoxide–oxalyl chloride oxidation[14] of alcohol **12**. A stirred solution of 2.46 g (19.5 mmol) of oxalyl chloride in 25 mL of dichloromethane was cooled to −78 °C. A solution of 7.6 g (97.5 mmol) of dimethyl sulfoxide in 20 mL of dichloromethane was added dropwise over 7 min. After 10 min a solution of 6.78 g (18.7 mmol) of alcohol **12** in 25 mL of dichloromethane and 5 mL of dimethyl sulfoxide was added dropwise over 10 min while the temperature was maintained at −78 °C. After 30 min, 26 mL (19.6 g, 195 mmol) of triethylamine was added over 4 min. The mixture was allowed to warm to room temperature and was poured into 100 mL of water. The aqueous layer was separated and was washed with 100 mL of dichloromethane. The combined dichloromethane extracts were washed with 50 mL of water and 50 mL of saturated sodium chloride solution. After drying (sodium sulfate) and evaporation of the solvent there was obtained 6.18 g (92%) of a yellow foam that was homogeneous by TLC (30% acetone–hexane).

Preparation of Tetrahydrofuryl Adducts 20 and 21. *n*-Butyllithium (1.57 M, 49 mL, 77 mmol) was added via syringe to a solution of hexamethyldisilyzane (16.36 mL, 77 mmol) in THF (100 mL) under argon at 0 °C. After being stirred for 15 min, this solution was added under positive pressure via a cannula to a solution of the ketone **13a** (25.21 g, 70 mmol) in THF (200 mL) under argon at 25 °C. After the addition was complete, the mixture was stirred a further 5 min, and then a solution of the ketene thioacetal monosulfoxide **17**[40] (10 g, 73.5 mmol) in THF (20 mL) was added by syringe. After the mixture was stirred 20 min at 25 °C, saturated ammonium chloride solution (50 mL) was added, and then the mixture was poured onto water (50 mL) and separated. The aqueous layer was washed with ethyl acetate (2 × 200 mL); then the organic phases were combined and washed with 3 *N* hydrochloric acid (2 × 100 mL) and brine (50 mL), dried over magnesium sulfate, and concentrated to a brown oil. The oil was absorbed onto 20 g silica gel, and this silica gel was added on top of a column of 60 g of silica gel. Filtration with 1.5 L of ether removed less polar byproducts. Final elution with 10% methanol/ethyl acetate gave the product **19** as a brown foam: 29.0 g (83.5%); IR (CH_2Cl_2) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.8 (m, 5 H), 1.98–2.38 (5 s, 3 H), 2.57–2.7 (4 s, 3 H), 2.9–3.5 (m, 2 H), 3.63 and 3.72 (2 s, 3 H), 5.05–5.4 (m, 1 H) 5.65–5.9 (m, 1 H), 6.95–7.7 (m, 5 H); mass spectrum, *m/e* (relative intensity) 432 (10), 385 (20), 303 (16), 94 (100), 47 (100), 45 (82).

The adduct **19** (33.7 g, 67.9 mmol) was dissolved in 3% methanolic HCl solution (300 mL) and stirred at 25 °C for 2.5 h. The precipitate was filtered off and was washed with methanol (200 mL) to give pure cyclic adduct **20** (25.45 g) as a white powder. The filtrate was concentrated and then purified by column chromatography over silica (160 g; eluting with 15% acetone–hexane) to afford a further 1.2 g of product. The total yield of product was 26.65 g (87.5%). An analytical sample was obtained from ethyl acetate–hexane as white crystals: mp 222–224 °C; IR (CCl_4) 1715 cm^{-1}; NMR δ 1.7–2.3 (m, 6 H), 3.0–3.2 (m, 2 H), 3.33 (s, 3 H), 3.5 (s, 3 H), 3.61 and 3.63 (2 s, 3 H), 5.05–5.32 (m, 2 H), 5.35–5.6 (m, 1 H), 7.0–7.6 (m, 9 H); mass spectrum, *m/e* (relative intensity) 448 (P, 68), 416 (87), 355 (15), 323 (100), 303 (64), 183 (37).

Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.62; H, 6.29; N, 6.25. Found: C, 69.30; H, 6.32; N, 6.02.

When the reaction mixture was worked up after 20 min, the minor isomer **21** could also be obtained and separated by preparative TLC: oil; IR (CCl_4) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.95 (m, 4 H), 2.25–2.6 (m, 2 H), 4.99, 5.11 (br d, 1 H), 5.55–5.3 (m, 1 H), 5.42–5.6 (m, 1 H), 7.05–7.6 (m, 5 H); mass spectrum, *m/e* (relative intensity) 448 (P 76), 416 (69), 355 (10), 323 (100), 303 (47), 183 (30).

Spiro[5-methyl-12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9,2′:1′,3′-dioxep-5′-ene] (22). A mixture of 100 mg (0.3 mmol) of ketone **13a**, 75 mg (0.9 mmol) of *cis*-2-butene-1,4-diol, 5 mg of *p*-toluenesulfonic acid, and 20 mL of toluene was heated under reflux with separation of water in a Dean–Stark apparatus. After 3 h the contents of the flask were cooled to room temperature and were poured into 50 mL of ethyl acetate. This solution was washed with 10 mL of 5% sodium bicarbonate solution and 10 mL of brine. After the mixture was dried over sodium sulfate, the solvent was removed to give 150 mg of a semisolid, which was purified by filtration through 15 g of silica gel with 50% ethyl acetate–hexane. Evaporation of the filtrate gave 105 mg of a white solid: mp 87–90 °C; 1710 cm^{-1}; NMR ($CDCl_3$) 0.9–2.45 (m, 4 H), 3.05–3.25 (m, 2 H), 3.57 and 3.59 (25, 3 H), 3.85–4.7 (m, 4 H), 4.92–5.10 (m, 1 H), 5.45–5.70 (m, 3 H), 6.9–7.6 (m, 9 H); mass spectrum, *m/e* (relative intensity) 430 (P, 77), 359 (91), 305 (44), 183 (42), 134 (100).

Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.13; H, 6.34; N, 5.92.

5-Methyl-9,9-dimethoxy-12-(carbophenoxy)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (24). A mixture of 200 mg (0.6 mmol) of ketone **13a**, 3 mL of trimethyl orthocarbonate, 250 μL of methanol, and 1 drop of concentrated sulfuric acid was set aside unde an argon atmosphere for 16 h at room temperature. This mixture was diluted with 100 mL of diethyl ether, the resulting solution was washed with 10 mL water and 10 mL brine, and it was then dried over magnesium sulfate. Evaporation of solvent gave 122 mg of a white solid (50%). An analytical sample was prepared by recrystallization from ethyl acetate–hexane to give white prisms: mp 97–99 °C; IR (KBr) 1715 cm^{-1}, 0.9–3.4 (m, 6 H), 3.22, 3.24, 3.27, 3.29 (4 s, 6 H) 3.63 and 3.65 (2 s, 3 H) 4.8–4.96 (m, 1 H), 5.45–5.65 (m, 1 H), 6.9–7.65 (m, 9 H).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.25; N, 6.93.

Preparation of Quinuclidinol 29a. Tetrahydrofuryl adduct **20** (15.0 g, 33.48 mmol) was dissolved in hot dioxane (200 mL). A solution of lithium hydroxide hydrate (6.7 g, 167.5 mmol) in water (200 mL) was added, and the mixture was stirred and heated under reflux for 20 h. The insoluble lithium salts were filtered off, and the filtrate was diluted with water (300 mL) and was extracted with three 250-mL portions of ethyl acetate. The combined organic layers were washed with brine (50 mL), were dried over sodium sulfate, and were concentrated. The residue (14.0 g) was purified by filtration over silica gel (120 g). Elution with ether removed phenol, and then elution with 10% methanol–ethyl acetate gave amine **28** as a white foam: 9.55 g (87); mp 107–110 °C; IR (CH_2Cl_2) 3400 cm^{-1}; NMR ($CDCl_3$) δ 2.4 (m, 6 H), 2.9–3.15 (m, 2 H), 3.32 (s, 3 H)), 3.54 (s, 3 H), 3.60 (s, 3 H), 3.6–4.0 (m, 1 H), 4.1–4.3 (m, 1 H). 5.36 (t, 1 H), 7.0–7.7 (m, 4 H); CNMR ($CDCl_3$) δ 22.14 (t), 29.13 (q, NCH_3), 36.18 (t), 37.87 (t), 38.62 (d), 45.22 (d), 48.11 (q, OCH_3), 48.96 (d), 56.73 (q, OCH_3), 106.14 (d), 106.79 (s), 106.89 (s), 108.74 (d), 118.37 (d), 118.98 (d), 103.31 (s), 121.13 (s), 127.01 (s), 135.21 (s), 137.16 (s); mass spectrum, *m/e* (relative intensity) 328 (P, 59), 327 (43), 296 (16), 183 (100), 43 (74).

A mixture of 4 g (12.2 mmol) of **28**, 15 mL of 3 N HCl, and 15 mL of THF was heated at reflux for 30 min. The solution was cooled in an ice bath, and 15 mL of 3 N sodium hydroxide solution was added with stirring. After 1 h the solid was collected by filtration, and it was washed with water. After the solid was dried, there was obtained 3.07 g (90%) of an off-white powder: mp >300 °C; IR (Nujol) 1710 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.17; H, 6.47; N, 9.82.

Preparation of the Quinuclidine Pivalate 29b. A mixture of 4.0 g (14.2 mmol) of **29a**, 4 mL of pivalic anhydride, 0.4 g of 4-(dimethylamino)pyridine, 10 mL of triethylamine, and 120 mL of THF was heated at reflux for 4 h. After the mixture cooled, 10 mL water was added, and the mixture was stirred for 10 min. The mixture was poured into 300 mL of ethyl acetate, and it was

(40) Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 4711.

washed with 50 mL of 5% sodium bicarbonate solution and 50 mL brine. After the mixture was dried drying (Na_2SO_4), the solvent was removed, and the residue (6.2 g) was chromatographed on 120 g of silica gel (eluting with 25% ethyl acetate–hexane). There were obtained 70 mg of isomer A and 4.7 g of isomer B; total 4.77 g (92%). Isomer A: mp 208–209 °C; IR (KBr) 1725 (br) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.53 (t), 27.18 (q), 29.29 (q), 33.09 (t), 36.41 (t), 38.95 (s), 39.63 (d), 43.56 (d), 62.32 (d), 81.50 (d), 104.82 (s), 108.87 (d), 118.63 (d), 119.41 (d), 121.68 (d), 126.75 (s), 136.83 (s), 137.81 (s), 176.53 (s), 219.18 (s); mass spectrum, *m/e* (relative intensity) 366 (P, 28), 337 (30), 253 (30), 236 (21), 211 (43), 183 (100).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65. Found: C, 71.83; H, 7.19; N, 7.64.

Isomer B: mp 239–240 °C; IR (KBr) 1725 (br) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.07 (t), 27.11 (q), 29.39 (q), 32.28 (t), 35.31 (t), 38.88 (s), 40.44 (d), 48.54 (d), 58.52 (d), 81.21 (d), 105.43 (s), 108.91 (d), 118.69 (d), 119.41 (d), 121.72 (d), 126.79 (s), 136.38 (s), 177.14 (s), 220.15 (s).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65. Found: C, 71.86; H, 6.75; N, 7.64.

Preparation of *O*-(*tert*-Butyldimethylsilyl)quinuclidine 29c. To a stirred suspension of 1.2 g (4.3 mmol) of **29a** in 20 mL of DMF was added 1.4 g (20.6 mmol) of imidazole. After the contents were in solution, 1.3 g (8.6 mmol) of *tert*-butyldimethylsilyl chloride was added, and the mixture was stirred at room temperature for 5 h. The mixture was poured into 150 mL of water and was extracted with three 150-mL portions of ethyl acetate. The analysis using 30% acetone–hexane showed mainly two components: one with R_f = 0.5 and one that remained at the application point. After evaporation of the solvent, the residue was filtered through 30 g of silica gel with diethyl ether. Evaporation of the filtrate gave **29c**: 0.47 g (30%); mp 182.5–184.5 °C; IR (CH_2Cl_2) 1715 cm^{-1}; NMR ($CDCl_3$) δ (0.13 (s, 3 H), 0.14 (s, 3 H), 0.91 (s, 9 H), 1.86–1.97 (m, 2 H), 2.29 (q, J_a = 8.8 Hz, J_b = 12.0 Hz, 1 H), 2.37–2.48 (m, 2 H), 2.84 (q, J_a = 5.1 Hz, J_b = 15.5 Hz, 1 H), 3.29 (q, J_a = 1.4 Hz, J_b = 15.5 Hz), 3.60 (s, 3 H), 4.07 (d, J = 5, 1 Hz, 1 H), 4.28 (q, J_a = 1.4 Hz, J_b = 8.8 Hz, 1 H), 4.87 (q, J_a = 6.0 Hz, J_b = 7.5 Hz, 1 H), 4.87 (q, J_a = 6.0 Hz, J_b = 7.5 Hz, 1 H), 7.08 (o, J_a = 7.0 Hz, J_b = 7.5 Hz, J_c = 1.3 Hz, 1 H), 7.18 (o, J_a = 7.0 Hz, J_b = 7.5 Hz, Jc = 1.2 Hz, 1 H), 7.25 (o, J_a = 7.5 Hz, J_b = 1.2 Hz, J_c = 0.9 Hz, 1 H), 7.48 (o, J_a = 7.0 Hz, J_b = 1.3 Hz, J_c = 1.0 Hz, 1 H).

Anal. Calcd for $C_{23}H_{32}N_2O_2S$: C, 69.65; H, 8.13; N, 7.06; Si, 7.08. Found: C, 69.55; H, 7.95; N, 7.14; Si, 7.19.

Preparation of THP Enol Ether 30a and Acetate 30b. To a solution of lithium diisopropylamide prepared from 1.53 mL of (10.9 mmol) diisopropylamine, 30 mL of THF, and 6.96 mL of 1.57 M *n*-butyllithium (10.9 mmol) cooled to −78 °C in a dry ice–methanol bath was added 2.55 mL (10.9 mmol) of phosphonate **26**.[35] After 15 min at −78 °C, liquid nitrogen was added to the bath until the temperature of the contents of the flask reached −100 °C. A solution of ketone **29b** in 15 mL of THF was added dropwise over 20 min while the temperature was held at −100 °C through periodic addition of liquid nitrogen. After 30 min at −100 °C the TLC of an aliquot showed no **29b** remaining. The mixture was poured into 200 mL of ethyl acetate, and this solution was washed with 50 mL of water and 50 mL of brine. After being dried over sodium sulfate, the solvent was removed to give 2.7 g of a foam. The NMR spectrum of this material did not contain absorptions for a pivalate.

The residue was dissolved in 10 mL of THF, 4 g of potassium *tert*-butoxide was added, and this mixture was set aside for 30 min, at which time it was poured into 100 mL of ethyl acetate. This solution was washed with 15 mL of water and 15 mL of brine and then was dried over sodium sulfate. After evaporation of solvent there was obtained 1.6 g of a residue, which was purified by chromatography from 70 g of silica gel (eluting with 50% ethyl acetate–hexane). There was obtained **30a**: 0.35 g (34%); mp 240–265 °C gradual decomposition; NMR ($CDCl_3$) δ 0.8–2.5 (m, 11 H), 2.6–5 (m, 12 H, including a three-proton at δ 3.6), 5.9–6.35 (m, 1 H), 6.9–7.75 (m, 4 H).

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.66; H, 7.36; N, 7.32.

A mixture of 0.28 g (0.74 mmol) of **30a**, 30 mg of 4-(dimethylamino)pyridine, 1 mL of triethylamine, 0.5 mL of acetic anhydride, and 10 mL of THF was set aside at room temperature for 30 min, at which time it was diluted with 100 mL ethyl acetate and then was washed with 30 mL of 5% sodium bicarbonate and 30 mL of brine. Evaporation gave a residue which was filtered through 10 g of silica gel with diethyl ether. Evaporation of the filtrate gave the product: 0.26 g (84%); mp 110–116 °C; IR (KBr) 1725 cm^{-1}; NMR ($CDCl_3$) δ (inter alia) 1.3–2.1 (m, 6 H), 2.15 and 2.17 (2 s, 3 H, CH_3CO), 3.63 and 3.67 (2 s, 3 H, NCH_3), 7.05–7.7 (m, 4 H).

Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.06; H, 7.16; N, 6.63. Found: C, 71.21; H, 7.09; N, 6.53.

Hydrolysis of 30b. A solution of 1 g (2.37 mmol) of THP enol ether **30b** in 40 mL of THF was purged of oxygen by passing argon through it for 10 min. Ten mL milliliters of 1 N hydrochloric acid was added, and the argon was bubbled through for an additional 10 min. The solution (under argon) was set aside at room temperature for 16 h, at which time it was poured into 400 mL of pH 9.0 buffer. This mixture was extracted with four 125-mL portions of diethyl ether. After the mixture was dried over sodium sulfate, the extract was evaporated to give 695 mg of a mixture of **31** and **32** as a foam: 87%; indefinite melting point; IR (CH_2Cl_2) 1730, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.9–3.3 (m, 9 H), 2.17 (s, 3 H), 3.65 and 3.70 (2 s, 3 H) 4.45–4.75 (m, 1 H), 5.6–6.2 (m, 1 H), 6.95–7.7 (m, 4 H), 9.33 and 9.77 (2 br s, 1 H).

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.51; N, 8.29.

Preparation of Ketene Dithioketal 36. To a solution of 0.3 g (1.56 mmol) 2-(trimethylsilyl)-1,3-dithiane[38] in 4 mL of THF at 0 °C under argon was added 1 mL of 1.57 M *n*-butyllithium in hexane (1.57 mmol). After this solution was stirred at 0 °C for 15 min, a solution of 0.36 g (0.91 mmol) of ketone **29c** in 4 mL of THF was added, and this mixture was stirred at 0 °C for 1 h. The mixture was poured into 100 mL of ethyl acetate, and this solution was washed with 30 mL of brine and was dried with magnesium sulfate. After evaporation of the solvent there was obtained 0.36 g of off-white crystals (80%). An analytical sample was recrystallized from ethyl acetate to give white crystals, mp 226–228 °C.

Anal. Calcd for $C_{27}H_{38}N_2OS_2Si$: C, 65.01; H, 7.68; N, 5.62; S, 12.86; Si, 5.63. Found: C, 65.16; H, 7.57; N, 5.69; S, 13.04; Si, 5.79.

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