Analogues of the Iboga Alkaloids. Synthesis and Reactions of (±)-15-Oxo-20-deethylcoronaridine Derivatives

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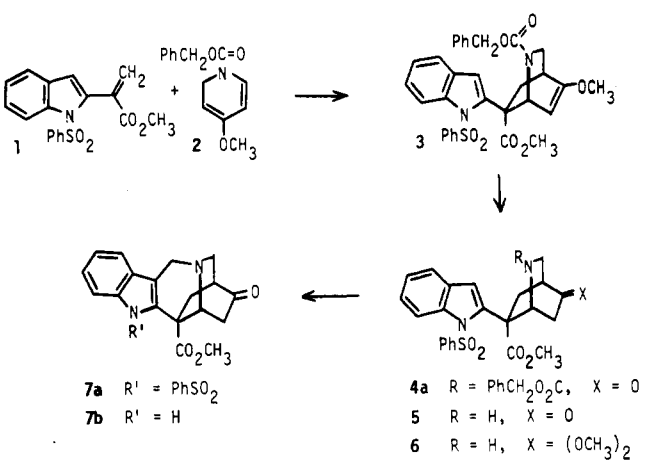
The Diels–Alder adduct of methyl α-methylene-1-(phenylsulfonyl)-1*H*-indole-2-acetate and 1-[(benzyloxy)-carbonyl]-4-methoxy-1,2-dihydropyridine is utilized as the starting material for synthesis of 15-oxo-20-deethyl analogues of the iboga alkaloids, specifically (±)-20-deethyl-15-oxo-5-norcoronaridine (**7b**), (±)-20-deethyl-15-oxocoronaridine (**13**), and (±)-6,7-seco-20-deethyl-15-oxocoronaridine (**27**). Studies on the generation of the corresponding *N*-phenylsulfonyl-protected enolates demonstrate that fragmentation of the isoquinuclidinone ring to give enaminones occurs partially in the case of (±)-20-deethyl-15-oxocoronaridine and nearly completely in the case of (±)-6,7-seco-20-deethyl-15-oxocoronaridine but not in the case of (±)-20-deethyl-15-oxo-5-norcoronaridine. The ease of fragmentation is correlated with the relative strain in the ketone and the fragment enaminone as estimated by MMPI calculations.

The Diels–Alder reaction of indole-2-acrylates and 1,2-dihydropyridines provides a highly efficient route for the formation of 6-indolyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate esters. This structure constitutes a substantial portion of the iboga alkaloid skeleton. This cycloaddition reaction has served as the basis for syntheses of (±)-20-deethylcatharanthine[1] and (±)-catharanthine.[2] In this paper, we describe the use of 1-carbobenzoxy-4-methoxy-1,2-dihydropyridine in the Diels–Alder reaction. The methyl enol ether function incorporated in this way permits the conversion of the adducts to 15-oxo-20-deethyl analogues of the iboga skeleton. Specifically, we report synthesis of 20-deethyl-15-oxo-5-norcoronaridine (**7b**), 20-deethyl-15-oxocoronaridine (**13**), and 6,7-seco-20-deethyl-15-oxocoronaridine (**27**). The reactivity of these compounds is discussed, particularly regarding the formation and reactions of the *N*-phenylsulfonyl-protected C15–C20 enolates.

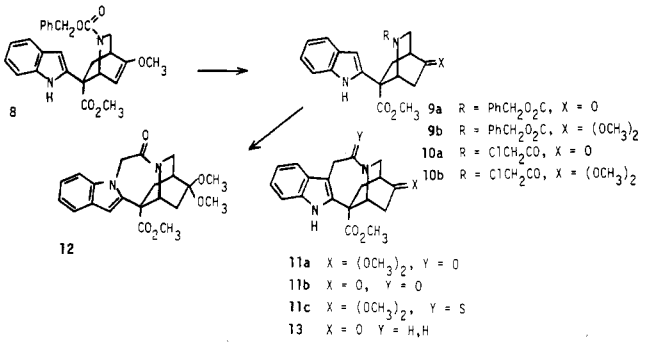
1-(Alkoxycarbonyl)-4-methoxy-1,2-dihydropyridines are readily prepared from 4-methoxypyridine by the Fowler method[3] as reported by Raucher and Macdonald.[4] We used the (benzyloxy)carbonyl derivative to facilitate deacylation at nitrogen. As expected from frontier orbital concepts, the 4-methoxy substituent is a favorable one, and the Diels–Alder reaction took place smoothly at 70 °C over 72 h to give **3** in 50–60% yield (Scheme I). Ketone **5** was prepared from **3** by two alternative routes. Reaction of **3** with trimethylsilyl iodide[5] led to cleavage of both the (benzyloxy)carbonyl group and the methyl vinyl ether, yielding keto amine **5** directly. A two-step approach in which the ketone **4a** was generated by hydrolysis of the enol ether function and the (benzyloxy)carbonyl then removed by transfer hydrogenolysis was more convenient.[6] The noriboga skeleton was established by cyclization of **5** with formaldehyde, giving **7a** in 58% overall yield from **3**. Reductive removal of the benzenesulfonyl group with sodium amalgam[7] gave **7b** in 58% yield. The high-resolution (360-MHz) NMR spectrum was entirely consistent with the expected structure, and all four AB-type methylene quartets are readily assigned (see Table I).

Two routes were explored for introduction of the two-carbon tryptamine bridge found in the iboga structure. The first uses chloroacetamide photocyclization[8] and parallels the method used earlier to synthesize (±)-15-deethylcatharanthine.[1] Chloroacetamide **10a** proved to be an unsatisfactory photocyclization substrate, perhaps because of competing photochemistry at the carbonyl group. Photolysis of the corresponding ketal **10b** proceeded smoothly, affording the pentacyclic lactam **11a** in 69% yield. In addition, a smaller amount (14%) of the N-alkylation product **12** was isolated. Reductive removal of the carbonyl of **11a** was accomplished via the thiolactam

Scheme I



Scheme II



(1) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382. Marazano, C.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 37.
(2) Marazano, C.; LeGoff, M.-T.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389.
(3) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.
(4) Raucher, S.; Macdonald, J. E. *Synth. Commun.* **1980**, *10*, 325.
(5) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.
(6) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.
(7) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.
(8) Sundberg, R. J. *Org. Photochem.* **1983**, *6*, 121.

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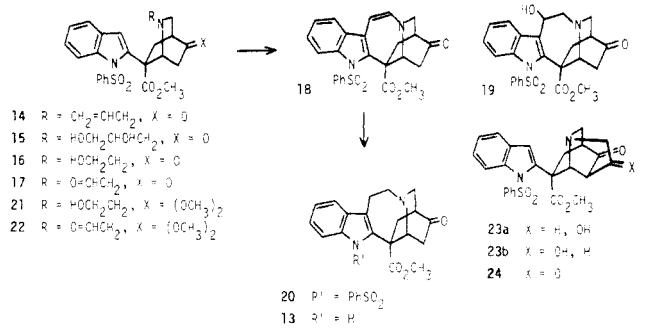
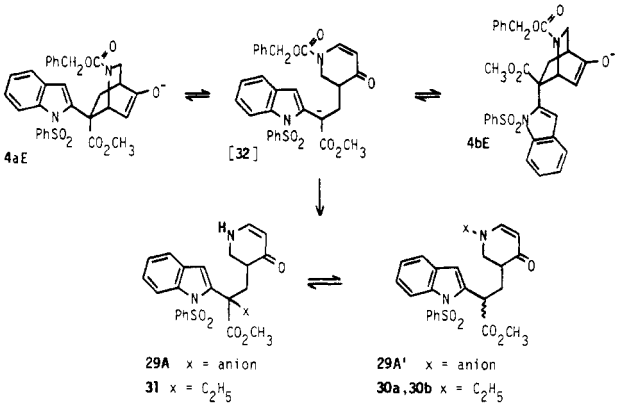
‡Abstracted in part from the M.S. Thesis of A.M.F., Dec 1985.

0022-3263/87/1952-3151$01.50/0

Scheme III



Scheme IV

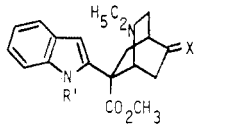


11c.[9] The overall yield of **13** from **11a** is 12%. The dione **11b** was also prepared by hydrolysis of **11a** (Scheme II).

The conceptual basis of the alternative route was the introduction at the amine nitrogen of a two-carbon fragment incorporating a potential electrophile, followed by cyclization involving C3 of the indole ring. Of the various previous approaches to the iboga skeleton,[10] only the Rosemund synthesis of (±)-20-deethylibogamine, in which a PPA-induced Friedel–Crafts acylation closes the indole 3–N_b bridge, utilizes this reaction pattern.[11] We decided to use aldehyde **17** as the key intermediate. Allylation of **5** gave **14** in good yield. It was hydroxylated by osmium tetroxide and then cleaved by periodate.[12] The best results were obtained when 4 equiv of sodium metaperiodate was used and the reaction run at 0 °C for 40 min.[13] A better route to **17** proceeded via the alcohol **16**, which could be prepared from **5** by alkylation using either iodoethanol or ethylene oxide. Swern oxidation[14] of **16** provided the rather unstable **17** in almost quantitative yield. The cyclization of **17** was investigated under a number of conditions (Scheme III). The best results were obtained when **17** was allowed to react with excess BF_3·OEt_2 at 60 °C for 40 min. The enamine **18** was the principal product. It was converted to **20** by sodium cyanoborohydride reduction. Two minor products, **23a** and **23b**, were also observed. Use of $TiCl_4$ as the cyclization reagent afforded a mixture of **18** and the presumed intermediate **19**. Dehydration of **19** to **18** could be accomplished with *p*-toluenesulfonic acid. The enamine **18** was identified on the basis of characteristic vinyl peaks at 5.91 and 6.56 ppm.[15] Reductive desulfonylation of **20** gave (±)-20-deethyl-15-oxocoronaridine (**13**). Using the BF_3·OEt_2 cyclization method, the overall yield from alcohol **16** was 44%. The compound obtained by this route was identical by spectroscopic and TLC comparison with the material obtained by the photochemical route and was also spectroscopically identical (NMR, IR) with material prepared by Kuehne and coworkers by an entirely different route.[16,17]

Alkylation of ketal **6** by either ethylene oxide or iodoethanol gave the alcohol **21**. Swern oxidation gave the ketal **22** in good overall yield. Cyclization with either $TiCl_4$ or BF_3·OEt_2 led to mixtures **23a** and **23b**, the minor products observed in the cyclization of **17**. The structures of **23a** and **23b** were postulated on the basis of the NMR spectra and mechanistic plausibility. The epimeric relationship between the two compounds was established by oxidation of both to the same dione **24** by Swern's reagent.[18] The mechanistic basis of the dichotomy in cyclization of **22** as compared with **17** may reflect formation of an enol ether from **22** under the cyclization conditions. The enol ether may then react more rapidly with the aldehyde than does the indole 3-position.

The seco analogue **27** was prepared beginning with ethylation of **6** with ethyl iodide. The reaction afforded **25** in 76% yield. The product **25** was N-desulfonylated to **26** in 94% yield when treated with sodium amalgam in methanol. A fair yield (36%) of **27** was obtained by deketalization, performed by treating **26** first with $TiCl_4$ and then quenching the solution with aqueous sodium carbonate.[18] Alternatively, **28** could be obtained by alkylation of **5** with ethyl iodide in 80% yield. However, the desulfonylation of **28** was very poor, giving 10% or less of **27** under a variety of conditions.



25 R' = $PhSO_2$, X = $(OCH_3)_2$
26 R' = H, X = $(OCH_3)_2$
27 R' = H, X = O
28 R' = $PhSO_2$, X = O

The ketones **4a**, **7a**, **20**, and **28** are potential precursors of the corresponding C20 ethylated structure found in the natural iboga alkaloids. It was therefore of interest to study the feasibility of alkylation of the enolates. As the

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(10) A compilation of synthetic approaches to catharanthine is given in: *Synform* **1984**, *2*, 45; *Chem. Abstr.* **1984**, *101*, 7487b. Subsequent work: Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913. Imanishi, T.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1985**, *33*, 4202. Imanishi, T.; Yagi, N.; Shin, H.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 4052. Szantay, C.; Keve, T.; Bölcskei, H.; Acs, T. *Tetrahedron Lett.* **1983**, *24*, 5539. Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236. Huffman, J. W.; Shamugasundaram, G.; Sawdaye, R.; Raveendranath, P. C.; Desai, R. C. *J. Org. Chem.* **1985**, *50*, 1460. Kuehne, M. E.; Reider, P. J. *J. Org. Chem.* **1985**, *50*, 1464.

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(12) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

(13) Bobbitt, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967**, *32*, 2225. Careful control of the reaction conditions was necessary to avoid oxidation of the glycol to the *N*-formyl derivative.

(14) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(15) Nagata, W.; Hirai, S.; Kawata, K.; Okumura, T. *J. Am. Chem. Soc.* **1967**, *89*, 5046.

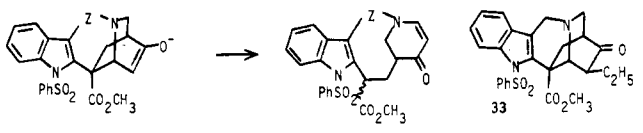
(16) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913.

(17) We thank Professor Kuehne for providing comparison spectra.

(18) The stereochemistry of compounds **23a** and **23b** was assigned on the basis of proton–proton coupling constants. The carbinol proton at C5 is well resolved in both isomers. In **23a** it appears as a doublet of doublets, J = 7.0, 3.5 Hz, which is consistent with a value of about 90° for the dihedral angle between the C(5)H–C(6)H protons and the absence of a C(5)H–C(6)H coupling. This is consistent with the relationship in a molecular model of **23a**. In the other isomer **23b**, the carbinol proton appears as a triplet of doublets with coupling constants of 7.0 and 2.0 Hz. The appearance of a C(5)H–C(6)H coupling is in accord with a molecular model of **23b** that indicates the C(5)H–C(6)H dihedral angle is about 20°.

(19) Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336.

Scheme V



7aE Z = $-CH_2-$
20E Z = $-CH_2CH_2-$
28E Z = -H C_2H_5-

[34] Z = $-CH_2-$
35a,35b Z = $-CH_2CH_2-$
30a,30b Z = -H C_2H_5-

study developed, it became apparent that simple enolate alkylation was not an efficient process. The enolates were generated with 1.3 equiv of LDA or 2.2 equiv of sodium (hexamethyldisilyl)amide (HMDSA) in THF. The enolate solutions were then allowed to react with ethyl iodide at various temperatures.

When the lithium enolate of **4a** (**4aE**) was generated in the presence of 1 equiv of HMPA at −78 °C and then treated with 5 equiv of ethyl iodide and allowed to warm to room temperature, a small amount of ethylated material was found, but the main product was **4b**, the C16 epimer of **4a** (35%). When the sodium enolate was generated with 2.2 equiv of HMDSA anion at −20 °C followed by reaction with ethyl iodide, the two products were the diastereomeric fragmentation products **30a** and **30b** (Scheme IV). These structures were subsequently confirmed by formation from **28** as will be described below. A mixture of **4a** and **4b** was also recovered. When the enolate formation was done with HMDSA at −60 °C, a different compound, **31**, was formed. The structure was assigned on the basis of the upfield appearance of the ethyl signals (implying C-alkylation) and the absence of a signal for the proton at C16, which is distinct in **30** and related structures. In addition, a mixture of **4a** and **4b** was also obtained. In general the material balance in these reactions was poor.

The isolation of the epimeric mixture **4a**–**4b** indicates that **4aE** undergoes a reversible fragmentation via [**32**]. The isolation of **30a**, **30b**, and **31** must result from cleavage of the (benzyloxy)carbonyl group. This is most likely to have occurred via the fragmented intermediate [**32**]. The apparent influence of temperature on N- vs. C-alkylation of **29A**–**29A′** was not pursued.

When **7aE**, the enolate of **7a**, was generated with LDA and reaction with ethyl iodide attempted at 25 °C, only recovered ketone **7a** was found. Use of HMDSA at −30 °C also returned starting material (44%), but some of the C-ethylated material **33** was formed (~10%) under these conditions. The fragmentation product [**34**] was not observed in any of the trials with **7a**.

When **20** was treated with LDA (1.5 equiv, 0 °C, for 6 h) followed by ethyl iodide (10 equiv), the major product was **35a**,**35b** (3:1 ratio), the result of fragmentation (53% yield). When HMDSA was used (2.2 equiv, −10 °C, 2 h), no starting material was recovered and a mixture of both epimers **35a** and **35b** (1:1) of the fragmentation product was found (48% yield).

When **28** was reacted with LDA (1.5 equiv, −30 °C, 6 h) followed by ethyl iodide (10 equiv), the fragmentation product **30a** was obtained in 87% yield along with a small amount of starting material (6%). Fragmentation of this enolate also occurred at −78 °C (Scheme V).

These results indicate a high degree of susceptibility of the 15,20-enolates in the iboga system toward fragmentation. Such fragmentation has been noted before. Kuehne found that the silyl enol ether of **13** was converted to a fragmented enaminone by tetrabutylammonium fluoride in aqueous THF.[16] Andriamialisoa, Langlois, and Langlois observed acid-catalyzed fragmentation of 15-oxocoronaridine to the C20 ethyl derivative of **35** in trifluoroacetic acid at 60 °C.[20] Although the conditions in the preparative experiments were not directly comparable, they clearly indicate the ease of fragmentation to be in the order **7aE** < **20E** < **28E**. To pursue this point, **7a**, **20**, and **28** were treated with LDA (1.3 equiv) at −25 °C and aliquots were quenched at 2-h intervals. HPLC analyses of the products showed nearly complete (~90%) fragmentation of **28E** after 4 h, ~50% fragmentation of **20E**, and no fragmentation of **7aE**. The compositions of the reaction mixtures were not further changed over 22 h, suggesting that equilibria had been established. To pursue the relationship further, we used the MMPI molecular mechanics program[21] to estimate the relative heats of formation and strain of the cyclic ketones **7a**, **20**, and **28** relative to the fragmented enaminones [**34**], **35**, and **30**. The calculations were done on the desulfonylated structures (H for $PhSO_2$). The strain energy, resonance energy, and heat of formation calculated for the most stable geometry found for each structure are given in Table II. The results are in qualitative accord with the experimental observations. Fragmentation is found to be unfavorable for **7a** but approximately (within 1 kcal) energy neutral for **20** and **28**. In each case, the calculation assigns a resonance energy of about 10 kcal to the enaminone system. The fragmentation of **7a** is disfavored relative to **20** and **28** because considerably less strain is released by fragmentation.

Experimental Section

1-[(Benzyloxy)carbonyl]-4-methoxy-1,2-dihydropyridine (2). To a solution of 4-methoxypyridine (1.39 g, 0.013 mol) in dry methanol (25 mL) cooled to −78 °C under nitrogen was added sodium borohydride (0.54 g, 1.1 equiv), and the mixture was stirred at −78 °C for 15 min. A solution of benzyl chloroformate (2.04 mL, 1.1 equiv) was added dropwise and the reaction mixture stirred for a further 15 min at −78 °C. Triethylamine was added, and after being stirred for 15 min, the reaction mixture was poured into ice-cold 0.5 M sodium bicarbonate (30 mL). The resulting solution was extracted with ether. The combined ether extracts were washed with dilute ammonium hydroxide, dried (potassium carbonate), and evaporated to give a pale yellow oil: 3.12 g, 85%; ^1H NMR ($CDCl_3$) 7.43 (s, 5 H), 6.85 (d, 1 H), 5.23 (s, 2 H), 5.04 (d, 1 H), 4.75 (d, 1 H), 4.44 (s, 2 H), 3.56 ppm (s, 3 H).

Methyl 2-[(Benzyloxy)carbonyl]-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-8-methoxy-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylate (3). Methyl α-methylene-1-(phenylsulfonyl)-1*H*-indole-2-acetate[7] (3.07 g, 0.01 mol) was powdered and stirred with 1-[(benzyloxy)carbonyl]-4-methoxy-1,2-dihydropyridine (6.64 g, 3 equiv) in dry xylene under nitrogen at 68–70 °C. Reaction progress was monitored by TLC. After 3 days, TLC showed no remaining acrylate and one major and one minor new spot. The red oil was dissolved in dichloromethane, washed repeatedly with 2% HCl and then water, dried, and evaporated to give an oily orange foam. The mixture was separated on silica gel (4:3:1 dichloromethane–hexane–ether). The major component was isolated as a white foam, which was crystallized from ethyl acetate–hexane to give pure **3**: 2.88 g, 55%; mp 171–172 °C. Anal. Calcd for $C_{32}H_{30}O_7N_2S$: C, 65.52; H, 5.12; N, 4.78. Found: C, 65.28; H, 5.19; N, 4.75.

The minor component was isolated as a yellow oil (0.83 g) and was identified by NMR as the enaminone[22] from hydrolysis of the vinyl ether group in the dihydropyridine: ^1H NMR ($CDCl_3$) 7.86 (d, 1 H), 7.40 (s, 5 H), 5.32 (d, 1 H), 5.21 (s, 2 H), 4.02 (t, 2 H), 2.51 ppm (t, 2 H).

(20) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1981**, *15*, 245.
(21) The MS-DOS-based MM program supplied by Serena Software, Bloomington, IN, was used. Geometries were input for five or six different structures that appeared likely from molecular models to represent the most stable conformations. The input typically *did not* converge to the same minimum energy. The lowest energy found is cited.
(22) Haider, A.; Cornuz, G.; Wyler, H. *Helv. Chim. Acta* **1975**, *58*, 1287.

Table I. ^{1}H NMR Spectral Assignments[a]

compd	3	14	17	20	21	CO_2Me	indole 3-H	other
3[b]	3.03 d 3.18 dt J_{AB} = 10	2.78 m	2.02 dd 3.24 dt J_{AB} = 13	5.50 d J = 6.5	5.00 d J = 6.5	3.60	7.00	PhCH_2 5.05 d, 5.18 d J_{AB} = 13
4a[b]	3.36 dd 3.7[c] J_{AB} = 12	2.6[c]	2.30 dd 3.60 dt J_{AB} = 14.5	2.73 dt 2.6[c] J_{AB} = 18	5.2[c]	3.67	6.9	PhCH_2 5.08 d, 5.25 d J_{AB} = 13
4b[b]	4.03 dd *c* J_{AB} = 12	*c*	2.31 2.68 J = 14	2.88 2.7[c] J = 18	5.35 m	3.50	6.77	PhCH_2 5.11 d, 5.25 d J_{AB} = 13
5	2.98 dd 3.16 dt J_{AB} = 11	2.48[c]	2.31 dd 3.58 dt J_{AB} = 14	2.51 dd[c] 2.78 dd J_{AB} = 18	4.00 t	3.69	6.86	
6	2.47 dd 2.98 dt J_{AB} = 11	2.12 br s	2.35 dd 3.28 d[c] J_{AB} = 15	2.02 dd 2.27 d J = 15	3.7[c]	3.66	6.94	$(OCH_3)_2$ 3.22 3.27
7a	2.78 d 3.52[c] J_{AB} = 10	2.41 m	2.20 dd 3.17 dt J_{AB} = 15	2.61 dd 2.70 d J_{AB} = 18	3.40	3.55		CH_2(6) 3.86 d 4.29 d J_{AB} = 17
7b	2.84 d 3.41 dt J_{AB} = 11	2.37	2.24 dd 2.53 dt J_{AB} = 14.5	2.63 dd 2.75 dd J_{AB} = 18	3.68	3.83		CH_2(6) 3.85 d 4.27 d J_{AB} = 16
8	3.13[c] 3.18[c]	2.79 m	2.13 dd J = 13, 2 3.18[c]	5.10 dd J = 7, 2	5.68 d J = 7	3.54	6.43	OCH_3 3.59 PhCH_2 5.05
9a	3.46 d J = 12 3.65[c]	2.73 m	3.27 dt J = 16 2.64 dd J = 16, 3	2.47 d J = 19 2.75[c]	5.43	3.67	6.52	PhCH_2 5.02, 4.97 J_{AB} = 11
9b	3.54[c] 3.30[c]	2.35 m	2.19 dd J = 14, 2 2.13 dd J = 14, 4	3.56 dt J = 18 2.03 d J = 18	5.10	3.65	6.48	$(OCH_3)_2$ 3.20 d, 3.19 d PhCH_2 5.09, 4.97 J = 13 J_{AB}
10a	3.63 d 2.72[c] J_{AB} = 10	2.89 m	3.30 dt 2.68 J_{AB} = 15	2.52 d 2.86[c] J_{AB} = 18	5.81 br s	3.70	6.51	COCH_2Cl 3.86
10b	3.73 dt 2.18[c] J_{AB} = 10	2.45 br s	3.25[c] 2.27 dd J_{AB} = 14	2.12 dd 1.95 dd J_{AB} = 15	5.49 br s	3.67	6.48	$(OCH_3)_2$ 3.20, 3.22 CH_2CO 3.88 d, 3.79 d J_{AB} = 13
11a	3.75 dd 3.42 d J_{AB} = 13	2.36 m	2.96 dm 2.49 dd J_{AB} = 14	2.12 dd 1.64 dd J_{AB} = 15	4.21 br s	3.78		$(OCH_3)_2$ 3.18, 3.25 CH_2(6) 3.75 d, 4.05 d J_{AB} = 16
11b[d]	3.40 d 3.81 dd J_{AB} = 12.5	2.6 m	1.79 dd 3.06 dm J_{AB} = 14.5	2.34 dd 2.98 dd J_{AB} = 19	5.09 t	3.64		CH_2(6) 3.57 d, 4.30 d J_{AB} = 15
11c	2.48 3.78[c] J_{AB} = 13	2.47 m	2.96[c] 1.67 dd J_{AB} = 14	2.55 dd 2.20 dd J_{AB} = 15	5.11 br s	3.88		$(OCH_3)_2$ 3.20, 3.26 CH_2(6) 4.29, 4.51
12	3.46 dd 3.81 dd J_{AB} = 12.5	2.35[c]	1.66 dd 3.2[c] J_{AB} = 14.5	2.17 dd 2.38[c] J_{AB} = 14.5	4.79 t	3.75	6.50	CH_2(6) 4.97, 5.11 J_{AB} = 14.5
13[f]	2.28 d[c] 3.12 d J_{AB} = 10	2.55 m	2.96 dt 3.22 J_{AB} = 14	2.28 d[c] 2.68 dd J_{AB} = 18	4.23 dm	3.78		CH_2CH_2 3.07 m 3.22 m 3.34 m 3.53 m
14	2.55 d 3.15 dd J_{AB} = 11	2.52 m	2.22 d *c* J_{AB} = 14.5	2.26 d 2.80 dd J_{AB} = 19.5	3.77 m	3.67	6.87	$CH_2CH{=}CH_2$ 3.42 m 5.16 d 5.22 d 5.83 m
15[e]	3.22 dd[c] *c* J_{AB} = 11	2.56 m	2.28 dd *c* J_{AB} = 14.5	2.35 d J_{AB} = 19.5	3.74	3.67	6.77	
16[f]	2.55 dd[c] 3.22 dd J_{AB} = 11	2.55 m	2.26 dd 3.50 dm J_{AB} = 14.5	2.35 dd 2.78 dm[c] J_{AB} = 20	3.74	3.68	6.84	CH_2CH_2OH 2.78 m 3.05 m, 3.60 3.60

Table I (Continued)

compd	3	14	17	20	21	CO_2Me	indole 3-H	other
17	2.70 d 3.36 dd J_{AB} = 10	2.57 m	2.36 dd 3.44 dm[c] J_{AB} = 14.5	2.44 d 2.78 dd J_{AB} = 19	3.82 m	3.67	6.82	$CH_2CH{=}O$ 3.43 dd 3.59 d J_{AB} = 16
18	3.25 dd 3.92 d J_{AB} = 11	2.38 m	1.74 dd 3.74 dm[c] J_{AB} = 14.5	2.45 dd 2.86 dd J_{AB} = 20	3.05 m	3.77		CH=CH 5.91 d 6.56 d J = 7
19	*c*	2.50 m	2.66 dd 3.28 d[c] J_{AB} = 14.5	2.57 dd 2.87 d[c] J_{AB} = 18	5.08 d	3.64		$CHOHCH_2$ 5.38 d 3.85 d 2.85 dd
20	2.78 d[f] *c* J_{AB} = 10	2.50 m	2.62 dd[f] *c* J_{AB} = 14	2.55 dd[f] *c* J_{AB} = 18	4.33	3.63		CH_2CH_2[c,f] 2.73 td 2.98 dd 3.3–4.5 m 3.6 m
21	2.59 dt 2.67 dd J_{AB} = 10.5	2.17	2.36 dd 3.07[c] J_{AB} = 15	2.11 dd 2.32 d J_{AB} = 15	3.58 m	3.65	6.93	CH_2CH_2OH 2.74 m 3.43 m $(OCH_3)_2$ 3.17, 3.20
22	2.58 dt 2.87 dd J_{AB} = 10	2.16 m	2.36 dd[c] 2.98 dm J = 14	2.06 dd 2.38 d J = 15	3.67 d J = 4	3.60	7.14[c]	CH_2CHO 3.27 d, J = 18 3.37 dd, J = 18, 2 9.44 br s $(OCH_3)_2$ 3.15, 3.24
23a	2.43 dt[c] 3.07 d J_{AB} = 12.5	2.39 m[c]	2.28 dd 3.34 dt J_{AB} = 15	2.75 d $J_{20,21}$ = 2	3.98 d $J_{20,21}$ = 2	3.61	7.58[c]	$CHOHCH_2$ 3.12 dd 3.23 dd[c] J_{AB} = 14.0 4.36 dd J = 3.5, 7
23b	2.85 dt[c] 3.14 d J_{AB} = 12.5	2.44 m	2.22 dd 3.40 dm J_{AB} = 14.5	2.95 dd J = 7, 3	3.69 d J = 3	3.63	7.40[c]	$CHOHCH_2$ 3.48 dd 2.85[c] J_{AB} = 14.0 4.76 dt J = 7, 7, 2
24	2.78 dm 3.37[c] J_{AB} = 12.5	2.55 m	2.42 dd 3.46 dm J_{AB} = 14.5	3.37	4.30 d J = 3	3.67	7.50[c]	O CCH_2 3.17 d J_{AB} = 18
25	3.14[c] *c* J_{AB} = 12	*c*	3.14 dm J = 14	*c*	3.53 br s	3.60	7.02	CH_2CH_3 0.98 t, J = 7 $(OCH_3)_2$ 3.16, 3.25
26	2.63 dm 3.21[c] J_{AB} = 11	2.18 m	1.95 dd 2.96 dm J_{AB} = 14	1.91 dd 2.12 dd J_{AB} = 15	3.42 m	3.85	6.10	CH_2CH_3 1.20 t, J = 7 2.68 q
27	2.73[c] 3.51 dd J_{AB} = 10.8	2.56 m	2.22 dd[c] 3.16 dm J_{AB} = 14.5	2.18 d[c] 2.80 dd J_{AB} = 19.5	3.83 t	3.80	6.14	CH_2CH_3 1.22 t 2.73 m[c]
28	2.51 dm[c] 3.19 dd J_{AB} = 11	2.50 m[c]	2.20 dd 3.43 dm J_{AB} = 14	2.23 dd 2.78 dd[c] J_{AB} = 18	3.72 m	3.64	6.82	CH_2CH_3 1.08 t, J = 7 2.70 m 2.78 m
30a[f]	3.48 dd J = 14, 6 3.20[c]	2.40 m	2.67 m 1.90 m	4.92 d J = 7	7.00 d J = 7	3.66	6.70	CH_2CH_3 1.21 t, J = 7 3.26 q C(16)H 4.78 dd J = 9, 6
30b[g]	3.54 dd J = 14, 6	2.38 m	2.38 m 2.03 m	4.94 d	7.00 d	3.58	6.74	CH_2CH_3 1.25 t, J = 7 3.25 q
31[f]	3.25 t 3.57 dm J = 13	2.70 m	2.48 dd J = 15, 4 1.92[c]	5.07 J = 7	7.17 t J = 7	3.92	*c*	CH_2CH_3 0.92 t, J = 7 1.97 m, 1.20 m
33	3.38 dm 2.74 J_{AB} = 10	2.40[c]	3.16 d 2.15 dd J_{AB} = 14	2.40[c]	3.28 br s	3.54 s		CH_2CH_3 0.93 t, J = 7 1.70 m, 1.98 m $C(5)H_2$ 4.22, 3.84 J_{AB} = 17

Table I (Continued)

compd	3	14	17	20	21	CO_2Me	indole 3-H	other
35a	3.64[c] 3.21[c]	1.74 dm	2.54 m 2.26 dm J = 13	4.85 d[c] J = 7	7.07 d J = 7	3.55 s		C(16)H 4.88 dd J = 14, 5 3.45 m, C(5)H 3.15,[c] C(6)H

[a] Alkaloid numbering. Unless otherwise noted spectra refer to $CDCl_3$ solutions at 350 MHz. Values are given in parts per million. Coupling constants are in hertz. [b] The room-temperature spectrum shows a ~3:1 ratio of two rotamers. The peaks reported are for the major rotamer. [c] Overlaps another peak. [d] In Me_2SO. [e] Isolated as a mixture of two diasteremomers in 2:1 ratio. Peaks reported are for the major diastereomer. [f] Assignments confirmed by decoupling. [g] Peaks assigned from mixture of **30a** and **30b**.

Table II. Output of MMPI Calculation[a]

	7a	[34]	20	35	28	30
strain	46.9	38.7	54.8	38.6	48.4	33.5
resonance	52.5	62.8	52.4	62.9	52.5	62.9
ΔH_f	-71.0	-64.1	-68.9	-70.0	-83.4	-83.2

[a] Energies in kilocalories/mole.

Methyl 2-[(Benzyloxy)carbonyl]-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (4a). A solution of compound **3** (800 mg, 1.37 mmol) in a 1:1 mixture of THF and 10% aqueous HCl (60 mL) was stirred at 25 °C for 45 min. The solution was poured into 20% aqueous sodium carbonate solution (25 mL) and extracted with ethyl acetate. The extract was dried and evaporated to give **4a** (742 mg, 95%) as a pure white foam. A sample crystallized from ethyl acetate–hexane melted at 162–164 °C. Anal. Calcd for $C_{31}H_{28}N_2O_7S$: C, 65.02; H, 4.93; N, 4.89. Found: C, 64.93; H, 4.96; N, 4.87.

Methyl 8-Oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (5). A. From 4a by Transfer Hydrogenolysis. To a solution of compound **4a** (500 mg, 0.87 mmol) in methanol–water (9:1, 80 mL) was added 10% palladium–carbon (500 mg) followed by cyclohexadiene (0.83 mL, 8.76 mmol) and trifluoroacetic acid (0.20 mL, 2.66 mmol). The mixture was stirred at 25 °C for 1 h, filtered, and concentrated under vacuum to a small volume. A solution of 20% aqueous sodium carbonate (30 mL) was then added, and the solution was extracted with methylene chloride. The extract was washed with brine, dried, and concentrated to give a foam, which was purified by flash chromatography (ethyl acetate), affording pure compound **5**, 352 mg, 92%. A sample recrystallized from ethyl–acetate hexane melted at 178–180 °C. Anal. Calcd for $C_{23}H_{22}N_2O_5S$; C, 63.00; H, 5.06; N, 6.39. Found: C, 62.89; H, 5.12; N, 6.33.

B. Directly from 3 by Reaction with Trimethylsilyl Iodide. A solution of **3** (200 mg, 0.34 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C and treated with a solution of 300 mg of Me_3SiI in 1 mL of dichloromethane. After the solution was stirred for 50 min, the ice bath was removed and 3 × 20 mg portions of Me_3SiI were added at 30-min intervals. After a total of 4 h, TLC showed most of the starting material to have been consumed. A solution of 0.3 N HCl in methanol (4 mL) was added, and the solution was stirred for 1 h at room temperature. The reaction mixture was diluted with ether (100 mL) and extracted with cold 10% HCl. The aqueous extract was basified (pH 12) with cold 10% NaOH and extracted several times with ethyl acetate. The extract was dried and evaporated to give the keto amine **5** as a white foam, 127 mg, 85%.

Methyl 8,8-Dimethoxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (6). Compound **6** was obtained from **3** in 90% yield following procedure A above for the obtaining **5** from carbamate **4a** except that anhydrous methanol was used as the solvent.

5-Nor-20-deethyl-15-oxocoronaridine (7b). To a solution of the keto amine **5** (225 mg, 0.21 mmol) in acetonitrile (50 mL) was added *p*-toluenesulfonic acid (300 mg) followed by a solution of THF containing approximately 15 mg of formaldehyde (generated by pyrolysis of paraformaldehyde). After the solution was stirred for 3 h at room temperature, TLC showed no remaining starting material. An extractive workup for the amine gave **7a** as an orange glass (168 mg, 73%), which was used without further purification in the reaction with sodium amalgam. A solution of compound **7a** (20 mg) in methanol (8 mL) was treated successively at intervals of 2 h with a total of 600 mg of disodium hydrogen phosphate and 240 mg of 6% sodium amalgam. After a total reaction time of 6 h, the cloudy gray solution was decanted from mercury and poured into water. The solution was extracted with dichloromethane, dried, and evaporated to give a white foam (15 mg). This was eluted through a short silica gel column (6:2:1 dichloromethane–ether–ethanol) to give a white crystalline solid (8 mg, 58%), which was recrystallized from ethyl acetate–hexane: mp 192–193 °C dec; mass spectrum, *m/e* 310, 278, 214, 154. Anal. Calcd for $C_{18}H_{18}N_2O \cdot {}^1/_3H_2O$: C, 68.34; H, 5.95; N, 8.85. Found: C, 68.45; H, 5.98; N, 8.83.

Methyl 2-[(Benzyloxy)carbonyl]-6-*exo*-indol-2-yl-8-methoxy-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylate (8). A solution of **3** (0.8 g) in methanol (300 mL) was treated at three successive 2-h intervals with a total of 24 g of disodium hydrogen phosphate and 9.6 g of 6% sodium amalgam. After a total reaction time of 6 h, the cloudy white solution was poured into water, decanted from mercury, and extracted with dichloromethane. The extracts were dried and evaporated to give the desulfonylated carbamate **8** (0.58 g, 95%) as a pure white solid. The analytical sample was recrystallized from ethyl acetate–hexane: mp 173–174 °C; mass spectrum, *m/e* 447, 446, 445, 387, 311, 245, 200, 110, 91. Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.64; H, 5.87; N, 6.27. Found: C, 69.82; H, 5.87; N, 6.22.

Methyl 2-[(Benzyloxy)carbonyl]-6-*exo*-indol-2-yl-8-oxo-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (9a). The carbamate **8** (100 mg) was dissolved in a 1:5 water–methanol solution (30 mL) by refluxing the solution for 5 min. A few drops of the concentrated H_2SO_4 were added to acidify the solution, and the mixture was stirred at room temperature. The solution was made progressively more aqueous by addition of water, and the reaction was monitored by TLC. After 6 h and at a 1:1 ratio of water–methanol (60 mL), TLC showed mainly the ketone **9a** and a trace of the ketal **9b**. The solution was neutralized with 10% NaOH and extracted with dichloromethane. The extracts were dried and evaporated to give a bright pink foam, which was purified on silica gel (1:1:1 dichloromethane–ether–hexane). The ketone **9a** was isolated as a foam (80 mg, 82%) and crystallized from ethyl acetate–hexane to afford a white crystalline solid: mp 131–132 °C; mass spectrum, *m/e* 432, 400, 373, 231, 201, 91. Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.59; H, 5.66; N, 6.38.

Methyl 2-[(Benzyloxy)carbonyl]-6-*exo*-indol-2-yl-8,8-dimethoxy-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (9b). The carbamate **8** (600 mg) was dissolved in methanol (50 mL) by refluxing the solution for a few minutes. A few drops of concentrated H_2SO_4 were added to make the solution acidic. The resulting bright yellow solution was stirred for 1.5 h, after which TLC indicated that no starting material remained. The pink solution was reduced in volume in vacuo. The resulting solution was made alkaline (pH 10) with 10% NaOH and partitioned between dichloromethane and water. The dichloromethane extract was dried and evaporated to give a pink foam. Purification by flash chromatography on silica gel (1:1:1 dichloromethane–ether–hexane) gave ketal **9b** as a white solid: 408 mg, 60%; mass spectrum, *m/e* 478, 446, 432, 311, 245, 201, 91. The analytical sample was prepared by recrystallization from ethyl acetate–

hexane; mp 143–145 °C. Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85; Found: C, 67.64; H, 6.34; N, 5.78.

Methyl 2-(Chloroacetyl)-6-*exo*-indol-2-yl-8,8-dimethoxy-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (10b). To a solution of the ketal **9b** (0.35 g) in dry methanol (35 mL) was added palladium black (0.26 g) followed by trifluoroacetic acid (0.17 g, 2 equiv) and then cyclohexadiene (0.70 g). The solution was stirred at room temperature for about 10 min until the palladium became more flocculent in appearance. The solution was filtered and cooled to 0 °C, and a pH 9 buffer solution consisting of 0.39 g of tris(hydroxymethyl)aminomethane hydrochloride and 4.28 g of tris(hydroxymethyl)aminomethane dissolved in 15 mL of water was added. With the rapidly stirring mixture kept at 5–10 °C, a solution of 2.5 g of chloroacetic anhydride (20 equiv) in 5 mL of THF was added over a period of 0.5 h. After the mixture was stirred at room temperature for 2 h, the volume of solvent was reduced, and the resulting solution was partitioned between dichloromethane and water, dried, and evaporated to give an off-white foam (300 mg). This was purified by eluting through a short gravity silica gel column (4:3:2:1 dichloromethane–hexane–ether–ethanol) to give the chloroacetamide **10b** as a white solid: 202 mg, 62%; mass spectrum, *m/e* 420, 388, 374, 201. Recrystallization from dichloromethane afforded the analytical sample, mp 189–190 °C dec. Anal. Calcd for $C_{21}H_{25}N_2O_5Cl$: C, 59.91; H, 5.99; N, 6.68. Found: C, 59.76; H, 6.04; N, 6.63.

(±)-20-Deethyl-15,15-dimethoxy-5-oxocoronaridine (11a). A solution of chloroacetamide **10b** (260 mg) in methanol–water (2:1, 270 mL) containing sodium bicarbonate (750 mg) was photolyzed under nitrogen with a 450-W Hanovia mercury lamp in a quartz immersion well equipped with a Vycor filter sleeve. After 20 min, the methanol was evaporated off, and the remaining solution was partitioned between dichloromethane and water. The dichloromethane layer was dried and evaporated to give a foam, which after flash chromatography (ethyl acetate) afforded **11a** (164 mg, 69%) and **12** (34 mg, 14%). A sample of **11a** crystallized from methanol melted at 278–280 °C. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.28. Found: C, 65.50; H, 6.32, N, 7.27. A sample of **12** recrystallized from methanol melted at 210–212 °C. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.28. Found: C, 65.57; H, 6.32; N, 7.27.

(±)-20-Deethyl-5,15-dioxocoronaridine (11b). A solution of compound **11a** (100 mg, 0.26 mmol) in a mixture of THF and 10% aqueous HCl (1:2, 20 mL) was stirred at 25 °C for 2 h. The solution was made alkaline with sodium carbonate and extracted with ethyl acetate. The extract was dried, filtered, and evaporated to give 68 mg (78%) of a white solid, which was identified as **11b** by NMR.

(±)-20-Deethyl-15-oxocoronaridine (13). To a solution of the lactam **11a** (30 mg, 0.08 mmol) in dry toluene (3 mL) was added Lawesson's reagent (16 mg, 0.5 equiv), and the mixture was refluxed for 1 h. TLC showed no remaining starting material, and the toluene was removed on a rotary evaporator. The resulting crude green solid was purified by flash chromatography on silica gel (1:1:1 dichloromethane–ether–hexane) to give thiolactam **11c** as a white solid (13 mg, 42%). This material was reduced without further purification. The thiolactam **11c** (50 mg) was dissolved in dichloromethane (5 mL). This solution was added by syringe to a dry flask containing trimethyloxonium tetrafluoroborate (approximately 50 mg) under nitrogen. After 1 h, TLC showed that all of **11c** had been consumed. The solvent was evaporated to give a yellow solid residue, which was dissolved in dry methanol (12 mL) to give a cloudy yellow solution. This was cooled to 0 °C, and sodium cyanoborohydride (20 mg, 2.5 equiv) was added in small portions. The solution instantly became clear. After 1 h, 10% HCl (2 mL) was added and the solution stirred for a few minutes. After being cooled to 0 °C, the solution was made basic (pH 10) with 10% NaOH and extracted with ether to give a pale green glass (23 mg). This was purified by flash chromatography on silica gel to give **13** as an amorphous white solid: 13 mg, 32%; mass spectrum, *m/e* 324, 228, 214, 154, 123.

Methyl 2-Allyl-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (14). To a solution of compound **5** (300 mg, 0.68 mmol) in acetonitrile (10 mL) containing anhydrous potassium carbonate (450 mg) was added a solution of allyl bromide (0.35 mL, 4.11 mmol) in acetonitrile (0.5 mL). The resulting mixture was stirred at 25 °C under nitrogen, and after 6 h the solvent was removed under reduced pressure. The residue was taken up in methylene chloride, washed twice with brine, dried, and evaporated to give a white foam, which after purification by flash chromatography (1:1 ethyl acetate–hexane) afforded 310 mg (93% yield) of pure compound **14**. A sample recrystallized from ethyl acetate–hexane melted at 181–182 °C. Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85. Found: C, 65.15; H, 5.55; N, 5.79.

Methyl 2-(2,3-Dihydroxypropyl)-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (15). A solution of compound **14** (170 mg, 0.36 mmol) in THF (8 mL) and distilled water (5 mL) at room temperature was treated first with 0.7 mL (0.1 equiv) of a solution of osmium tetroxide in *tert*-butyl alcohol (250 mg in 20 mL of *tert*-butyl alcohol containing 0.1 mL of *tert*-butyl hydroperoxide) and then with 4-methylmorpholine *N*-oxide (50 mg, 0.43 mmol). The resulting solution was allowed to react at room temperature for 6 h. A slurry of sodium dithionite (300 mg in 10 mL of water) and 300 mg of Florisil was added, and the mixture was stirred for 30 min. The filtered solution was saturated with sodium chloride and extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to give a foam, which was eluted through a flash silica gel column (4:1 ethyl acetate–hexane) to give **15** (160 mg, 88%) as a diastereomeric mixture. A sample of **15** recrystallized from ethyl acetate melted at 204–206 °C. Anal. Calcd for $C_{26}H_{28}N_2O_7S$: C, 60.93; H, 5.51; N, 5.46. Found: C, 60.76; H, 5.56; N, 5.43.

Methyl 2-(2-Hydroxyethyl)-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (16). Method A. A solution of amine **5** (400 mg, 0.91 mmol) and 2-iodoethanol (470 mg, 2.74 mmol) in acetonitrile (20 mL) containing potassium carbonate (378 mg) was stirred under nitrogen at 60 °C for 20 h. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to give a crude product, which was purified by flash chromatography (ethyl acetate), affording the alcohol **16** (380 mg, 86%) as a colorless foam. A sample recrystallized from acetone–methanol melted at 190–192 °C. Anal. Calcd for $C_{25}H_{26}N_2O_6S$: C, 62.23; H, 5.43; N, 5.81. Found: C, 62.20; H, 5.49; N, 5.76.

Method B. A solution of amine **5** (100 mg, 0.23 mmol) in tetrahydrofuran–methanol (9:1, 8 mL) was treated with an excess of ethylene oxide. The mixture was stirred at 25 °C for 3 days, poured into a 10% sodium carbonate solution, and extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to give a white foam, which after chromatographic purification afforded the alcohol **16**, 77 mg, 70%.

Methyl 2-(Formylmethyl)-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (17). Method A. Periodate Cleavage of 15. A solution of **15** (90 mg, 0.17 mmol) in THF (10 mL) was treated with aqueous 0.1 N sodium metaperiodate (7 mL, 0.7 mmol) at 0 °C for 40 min. The reaction mixture was made alkaline with sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated to give 80 mg of a solid, which was identified as **17** by proton NMR.

Method B. Swern Oxidation of 16. To a solution of oxalyl chloride (65 μL, 0.75 mmol) in methylene chloride (15 mL) was added a solution of Me_2SO (110 μL, 1.5 mmol) in methylene chloride (2 mL). The reaction mixture was stirred at −60 °C for 10 min, and then a solution of alcohol **16** (300 mg, 0.62 mmol) in methylene chloride (3 mL) was slowly added; stirring was continued for an additional 15 min. Triethylamine (433 μL, 3.1 mmol) was added and the reaction mixture stirred for 5 min and then allowed to warm at room temperature. Water was added, and the aqueous layer was extracted with methylene chloride. The organic layer was washed with brine and dried. The filtered solution was concentrated, affording 295 mg of a white foam, which was identified as the aldehyde **17** by proton NMR. The product was used in the following reaction without further purification.

(±)-20-Deethyl-1-(phenylsulfonyl)-15-oxocoronaridine (20). Method A. Cyclization with Titanium Tetrachloride. To a solution of aldehyde **17** (295 mg) in methylene chloride (30 mL) was added a solution of 4 equiv of titanium tetrachloride

in methylene chloride (1 mL). The mixture was stirred under nitrogen at 25 °C for 6 h and then poured into 10% aqueous sodium carbonate solution. The aqueous layer was extracted with methylene chloride, and the organic layer was washed with brine, dried, and filtered through Celite under suction. Evaporation under reduced pressure gave a crude reaction mixture, which after flash chromatography with a short silica gel column (1:1 ethyl acetate–hexane) afforded 30 mg of enamine **18** and 75 mg of the alcohol **19**: mass spectrum, *m/e* 479, 462, 354, 339, 321, 167, 149, 141. A solution of alcohol **19** (75 mg, 0.16 mmol) in benzene containing *p*-toluenesulfonic acid monohydrate (33 mg, 0.17 mmol) was heated at 60 °C for 30 min. The mixture was poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was dried, filtered, and evaporated to give the enamine **18** (63 mg). The combined samples of enamine **18** (93 mg) obtained in the above reactions were dissolved in a mixture of THF (3 mL) and pH 5 acetic acid–sodium acetate buffer solution (6 mL), and then sodium cyanoborohydride (50 mg) was added. After the resultant mixture was stirred at 25 °C for 4 h, a solution of 20% sodium carbonate was added until the pH was basic. The mixture was extracted with ethyl acetate, and the extract was filtered and evaporated to give a glass, which after purification by flash chromatography afforded 85 mg of compound **21** (overall yield from alcohol **16** is 29%). A sample recrystallized from ethyl acetate–hexane melted at 226–228 °C. Anal. Calcd for $C_{25}H_{24}N_2O_5S$: C, 64.64; H, 5.21; N, 6.03. Found: C, 64.50; H, 5.27; N, 5.97.

Method B. Cyclization with Boron Trifluoride Etherate. A solution of aldehyde **17** (255 mg), obtained from 260 mg of alcohol **16**, as described above, was dissolved in boron trifluoride diethyl etherate (6 mL) and stirred at 65 °C for 40 min under nitrogen. The mixture was slowly poured into 20% aqueous sodium carbonate solution (100 mL) and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated to give a crude reaction mixture of which the main component was the enamine **18** along with traces of compounds **23a** and **23b**, as inferred by TLC and proton NMR. The crude reaction mixture was subjected to reduction with sodium cyanoborohydride under the same conditions described above, affording after purification compound **20** (110 mg, 44% from the alcohol **16**) and small amounts of **23a** (15 mg, 6%) and **23b** (10 mg, 4%).

(±)-20-Deethyl-15-oxocoronaridine (13). A solution of **20** (25 mg, 0.05 mmol) in anhydrous methanol (25 mL) was treated at three 2-h intervals with disodium hydrogen phosphate (250 mg each addition) and 5% sodium amalgam (150 mg each addition). The reaction mixture was decanted from mercury, poured into water, and extracted with methylene chloride. The extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give a crude reaction mixture, which after purification by flash chromatography (1:1 ethyl acetate–hexane) afforded (±)-20-deethyl-15-oxocoronaridine (14 mg, 81%). The material as determined by NMR and TLC was identical with a sample prepared by the photochemical route.

Methyl 2-(Formylmethyl)-8,8-dimethoxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (22). Compound **21** was obtained from amine **6** (88% yield) under the same conditions described in method A for the preparation of **16** from amine **5**: mass spectrum, *m/e* 528, 479, 387, 355, 339, 168, 154, 100, 77. A sample recrystallized from ether melted at 156–158 °C. Aldehyde **22** (47 mg) was obtained from alcohol **21** (50 mg) by the same conditions described for the preparation of **17** from alcohol **16** and was used in the following reaction without further purification.

Methyl 5-Hydroxy-10-oxo-8-*endo*-[1-(phenylsulfonyl)indol-2-yl]-3-azatricyclo[4.3.1.$0^{3,7}$]decane-8-*exo*-carboxylate (23a, 23b). Method A. To a solution of aldehyde **22** (47 mg) in methylene chloride (8 mL) was added a solution of 4 equiv of titanium tetrachloride in methylene chloride (0.5 mL). The mixture was stirred under nitrogen at 25 °C for 1.5 h, poured into 10% sodium carbonate solution, and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated to give a crude reaction mixture, which after flash chromatography (1:1 ethyl acetate–hexane) afforded the epimeric cyclization products **23a** (4.6 mg, 10%) and **23b** (11.5 mg, 25%).

Method B. A solution of aldehyde **22** (197 mg) obtained from alcohol **21** (200 mg), as described above, was dissolved in boron trifluoride diethyl etherate (1 mL) and stirred at 65 °C for 20 min under nitrogen. The reaction mixture was slowly poured into 20% sodium carbonate solution (30 mL) and extracted with methylene chloride. The combined organic layers were washed with brine, dried, and evaporated to give a mixture of **23a** (20 mg, 11%) and **23b** (50 mg, 28%).

Methyl 2,5-Dioxo-8-*endo*-[1-(phenylsulfonyl)indol-2-yl]-3-azatricyclo[4.3.1.$0^{3,7}$]decane-8-*exo*-carboxylate (24). A solution of alcohol **23a** (35 mg, 0.07 mmol) was oxidized with Swern's reagent as described for conversion of **16** to **17** to give the dione **24** (25 mg, 71%) after flash chromatography (1:2 ethyl acetate–hexane). Following the same procedure, **24** was obtained from alcohol **23b** in 75% yield. A sample of **24** crystalline from ethyl acetate–hexane melted at 262–264 °C. Anal. Calcd for $C_{25}H_{22}N_2O_6S$: C, 62.75; H, 4.63; N, 5.85. Found: C, 62.59; H, 4.66; N, 5.79.

(±)-6,7-Seco-20-deethyl-15-oxocoronaridine (27). A solution of amine **6** (250 mg, 0.52 mmol) and iodoethane (0.4 mL, 5.16 mmol) in acetonitrile containing potassium carbonate (215 mg, 1.55 mmol) was stirred under nitrogen for 3 h. The mixture was poured into water and extracted with ethyl acetate to give a foam, which after purification by flash chromatography (1:3 ethyl acetate–hexane) afforded pure compound **25** (200 mg, 76%). A solution of compound **25** (100 mg, 0.20 mmo) in anhydrous methanol (80 mL) was treated successively at two 2-h intervals with disodium hydrogen phosphate (1 g each addition) and 5% sodium amalgam (600 mg each addition). After a total reaction time of 4 h, the mixture was decanted from mercury, poured into water and extracted with methylene chloride. The extract was dried and evaporated to give a solid, which after purification by flash chromatography (1:1 ethyl acetate–hexane) afforded pure compound **26** (68 mg, 94%). To a solution of compound **26** (70 mg, 0.19 mmol) in methylene chloride (10 μL), cooled at 0 °C, was added a solution of titanium chloride (41 μL, 0.38 mmol) in methylene chloride (0.7 mL). The mixture was stirred at 0 °C for 5 min, poured into 20% aqueous sodium carbonate solution, and extracted with methylene chloride. Purification by flash chromatography (1:1 ethyl acetate–hexane) afforded pure compound **27**, 22 mg, 36%. A sample of **27** crystallized from hexane melted at 132–134 °C. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.82; H, 6.83; N, 8.50.

Methyl 2-Ethyl-8-oxo-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (28). Compound **28** was obtained in 80% yield from amine **5** following the above described procedure for the preparation of **25** from amine **6**. A sample of **28** crystallized from ethyl acetate–hexane melted at 204–206 °C. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00. Found: C, 64.15; H, 5.70; N, 5.87.

Attempted Alkylation of 4aE. A. Using Lithium Diisopropylamide. A solution of **4a** (230 mg, 0.40 mmol) in THF was treated with LDA (1.3 equiv) and HMPA (1 equiv) at −78 °C. The solution was maintained at this temperature for 30 min. Ethyl iodide (5 equiv) was added, and the solution was allowed to warm to room temperature. The product mixture obtained by extraction was fractionated and by chromatography gave small amounts of incompletely separated materials that had incorporated ethyl groups. The main fraction (35% recovery) was **4b**.

B. Using Sodium Hexamethyldisilylamide. A solution of **4a** (100 mg, 0.18 mmol) in THF was treated with 2.2 equiv of NaHMDSA at 0 °C. After the mixture was stirred at 0 °C for 15 min, the solution temperature was lowered to −78 °C and ethyl iodide (9 equiv) was added. The solution was held at −20 °C for 8 h and the product extracted and separated by chromatography. Diastereomeric compounds **30a** and **30b** (18%) were obtained as an inseparable mixture. A mixture of **4a**–**4b** was also recovered. When the reaction was repeated with the exception that the alkylation solution was maintained at −60 °C for 7 h, the main product was **31**; a 1:1 mixture of **4a** and **4b** was also recovered. When the addition of ethyl iodide was omitted and the solution was quenched after 24 h at −20 °C, a 2:1 mixture of **4a** and **4b** was recovered (20%).

Methyl α-[(1-Ethyl-4-oxo-1,2,3,4-tetrahydropyrid-3-yl)-methyl]-1-(phenylsulfonyl)indole-2-acetate (30). To a stirred solution of diisopropylamine (48, μL, 0.34 mmol) in THF (4 mL) at −30 °C was added 160 μL (0.25 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After the resultant mixture was stirred

for 15 min, a solution of ketone **28** (80 mg, 0.17 mmol) in THF (2 mL) was introduced, and the mixture was stirred under nitrogen an additional 10 min. Ethyl iodide (137 μL, 1.70 mmol) was added and the resulting mixture stirred at −30 °C for 6 h, after which saturated aqueous ammonium chloride was added. The mixture was diluted with ethyl acetate, the organic layer separated, and the aqueous phase extracted with ethyl acetate. The crude reaction mixture was separated by flash chromatography (1:1–3:1 ethyl acetate–hexane), affording 70 mg of compound **30a** (87%) and 5 mg of starting material.

(±)-1-(Phenylsulfonyl)-5-nor-15-oxocoronaridine (33). A stirred solution of **7a** (50 mg, 0.11 mmol) and sodium hexamethyldisilazide (240 μL of α 1 M solution in THF, 0.24 mmol) in THF (2 mL) was stirred at 0 °C for 15 min. The mixture was cooled at −30 °C, and ethyl iodide (88 mL, 1.11 mmol) was added. Stirring was maintained for 14 h, at which time saturated aqueous ammonium chloride was introduced and the mixture allowed to warm to room temperature. The solution was partitioned between water and ethyl acetate. The separation of the reaction mixture by flash chromatography (1:4–1:1 ethyl acetate–hexane) afforded 6 mg (11%) of **33** and 22 mg (44%) of the starting material **7a**.

(±)-16-Carbomethoxy-20-deethyl-1-(phenylsulfonyl)-15-oxo-20,21-didehydrocleavamine (35a, 35b). A. Using Lithium Diisopropylamide. To a stirred solution of diisopropylamine (15 μL, 0.11 mmol) in THF (2 mL) at 0 °C was added 60 μL (0.10 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After the resultant mixture was stirred for 15 min, a solution of ketone **20** (30 mg, 0.07 mmol) in THF (1 mL) was added and the mixture stirred under nitrogen for 10 min. Ethyl iodide (52 μL, 0.65 mmol) was added and the resulting mixture stirred at 0 °C for 6 h, after which saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate. Separation of the reaction mixture by flash chromatography (1:1–3:1 ethyl acetate–hexane) afforded 13 mg of starting material and 16 mg (53%) of compound **35a,35b** as a 3:1 mixture.

B. Using Sodium Hexamethyldisilylamide. A stirred solution of compound **20** (40 mg, 0.09 mmol) and NaHMDSA (0.18 mL of a 1 M solution in THF, 0.19 mmol) in THF (2 mL) was stirred at 0 °C for 15 min. The mixture was cooled at −78 °C, and ethyl iodide (69 μL, 0.86) was added. The temperature was raised to −10 °C, and stirring was maintained for 2 h. After addition of a saturated solution of ammonium chloride, the mixture was extracted with ethyl acetate. Separation by flash chromatography (3:1 ethyl acetate–hexane) afforded 19 mg (48%) of **35a,35b** as a 1:1 mixture.

Direct Comparison of Fragmentation of 7a, 20, and 28. A solution of each ketone in THF at −25 °C was treated with 1.3 equiv of LDA. Aliquots were removed at 2-h intervals, quenched in aqueous acetonitrile, and analyzed on a C-18 reversed-phase column using aqueous acetonitrile. The ratios of materials are shown:

time	7a:[34]	20:35	28:30
2	100:0	44:56	19:81
4	100:0	50:50	10:90
6	100:0	49:51	10:90
10	100:0	52:48	12:88
22	100:0	46:54	9:91

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Water-Catalyzed Amide Hydrolysis in Dilute Aqueous Carbohydrate Solutions

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Rates and thermodynamic activation parameters were determined for the water-catalyzed hydrolysis of the activated amide bond in three 1-acyl-1,2,4-triazoles of different hydrophobicity by using dilute aqueous solutions of simple carbohydrates as the reaction medium. The solutions show thermodynamically almost ideal behavior. It appears that the kinetic medium effects, and, in particular, the changes in $\Delta^{\ddagger}S^{\ominus}$, are largely determined by carbohydrate-induced alterations in the three-dimensional hydrogen-bond network of water. The specific hydration model for carbohydrates, developed by Franks and his associates, appears to provide a key to the understanding of the carbohydrate medium effects on the hydrolytic model reaction.

In recent years there has been much effort expended to understand the effect of aqueous reaction media on chemical reactivity.[1-3] The approach usually involves perturbation of the aqueous medium by the addition of (non)electrolytes and an analysis of the response of rates and thermodynamic activation parameters in terms of initial state and transition state solvation. However, the addition of small amounts of the additive has usually drastic consequences and leads to the introduction of new intermolecular interactions involving the additive as one component and the initial state and/or transition state as the other component. Furthermore, relatively hydrophobic additives tend to form clusters even in dilute solutions.[4,5] All these specific effects are extremely difficult to separate from effects arising from a perturbation of the motional, spatial, or orientational correlations in the hydrogen-bond network of water as induced by the additive. These difficulties pertain to both "typically aqueous" (TA) and "typically nonaqueous" (TNA) solutions.[6]

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