Synthesis and Structure of Some 3-Aza[5]- and 3-Aza[6](1,7)naphthalenophanes

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Abstract: The synthesis of the naphthalenophanes **1–5** and single-crystal X-ray diffraction studies of **1** and **5** are reported. These compounds, which have the smallest 1,7-naphthalene bridges reported to date and also one of the most highly distorted naphthalene rings in the case of **1**, are prepared from the reactions of **6** and **7**, obtained in 6 steps from **8** and **9**, respectively, with cyanogen bromide or methyl chloroformate or phenyl chloroformate.

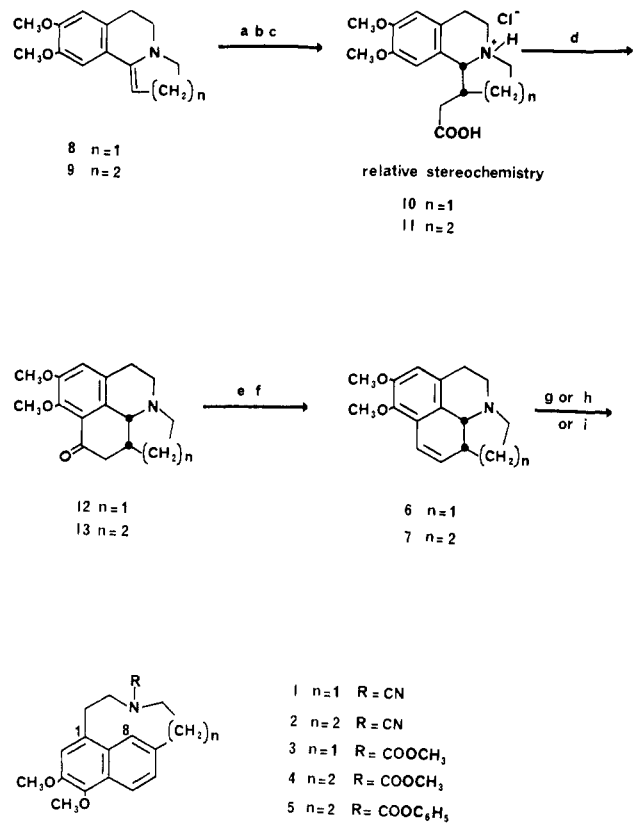
That a benzene ring may be nonplanar has been highlighted by the synthesis[1] and recent[1d,e] single-crystal X-ray structure determinations of [6]paracyclophane derivatives, and a [5]-metacyclophane.[1f] Since fused aromatic systems have greater flexibility than benzene, the synthesis of aromatic-ring-distorted naphthalenophanes[2] may not be difficult.[3] Furthermore, the incorporation of a heteroatom, in particular nitrogen, within the methylene bridge may provide scope for the development of new synthetic routes to strained bridged-aromatic systems. In support of these views, we report an efficient synthesis of the 3-aza[5]- and 3-aza[6](1,7)naphthalenophane derivatives **1–5** and associated X-ray structural studies. Compounds **1** and **3** have the smallest 1,7-naphthalene bridge[4] and, apparently, one of the most highly distorted naphthalene rings[5,6] reported to date.

Crucial to our synthetic strategy was the cyanogen bromide[7] and chloroformate ester mediated[8] rupture of the central carbon–nitrogen bridge of **6** and **7** (Scheme I). It was hoped that this fission would be accompanied by an elimination reaction leading directly to the desired naphthalenophanes.

Our approach began with alkylation of the readily accessible enamines **8**[9] and **9**[10,11a] with ethyl bromoacetate to afford, after some further elaboration, the amino acid salts **10** and **11**. The relative configuration of the methine hydrogen atoms of **10** and **11**, fixed in the sodium borohydride reduction of the iminium salt precursors, was assigned as cis by analogy with closely related[11b] derivatives. Intramolecular acylation[12] of these latter compounds furnished the ketones **12** and **13** which were subjected to a reduction–elimination reaction sequence[12] to give the respective naphthalenophane progenitors **6** and **7**.

Reaction of **6** and **7** with cyanogen bromide gave, in turn, the cyanamides **1** and **2**. The urethanes **3** and **4** were also obtained from **6** and **7**, respectively, when methyl chloroformate was used in place of cyanogen bromide. Similarly the urethane **5** was obtained from the reaction of **7** with phenyl chloroformate. Whereas the yields of the six-atom bridged naphthalene derivatives from these ring-fission reactions were high, those of the five-atom bridged derivatives were only moderate due to other competing cleavage reactions: the bromide **14** and the chloride **15** were also isolated from the reaction of **6** with cyanogen bromide and methyl chloroformate, respectively.

Comparison of the ^1H NMR spectra of **1** and **2** showed the chemical shifts of corresponding naphthalene protons to be very similar and to fall within the expected range for aromatic protons, while coupling patterns were consistent with the designated substitution. Comparison of the ultraviolet spectra of these compounds, however, showed significant red-shifts (up to 10 nm) with decreasing bridge length consistent with[13] naphthalene-ring nonplanarity in **1**. This nonplanarity was unequivocally confirmed, not only in **1** but also in **5**, by single-crystal X-ray structure determinations and is quite remarkable in **1**. The molecular



[a] $BrCH_2CO_2Et$. [b] $NaBH_4$, 0–20 °C. [c] 1 M HCl, 20 °C. [d] H_2SO_4–20% SO_3. [e] $NaBH_4$, 20 °C. [f] 0.1 M HCl, Δ. [g] BrCN, K_2CO_3, $CHCl_3$, 20 °C. [h] CH_3OCOCl, K_2CO_3, $CHCl_3$. [i] C_6H_5OCOCl, K_2CO_3, $CHCl_3$.

structures of **1** and **5** are shown in Figures 1 and 2, the non-hydrogen atom positional co-ordinates in Table I, interatomic dis-

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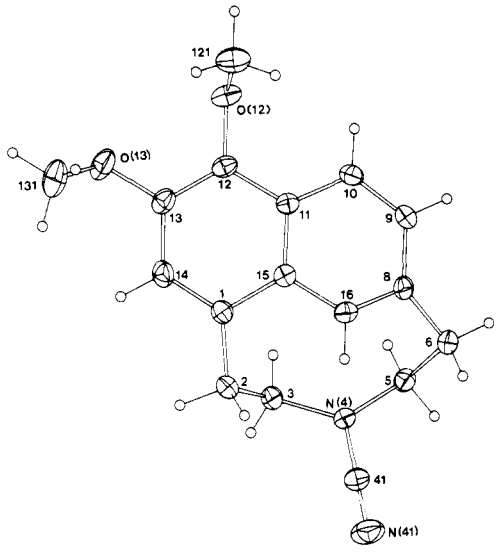

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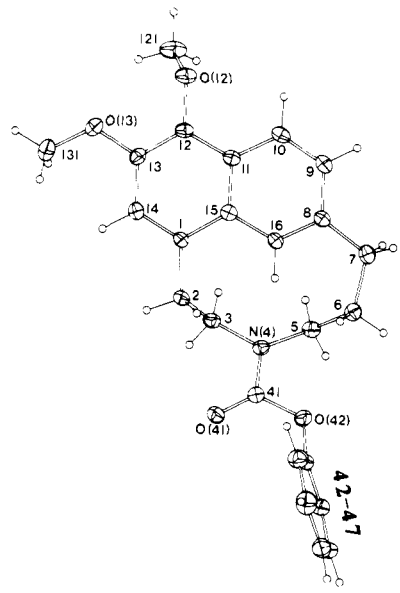

5

Figure 1. Molecular projections of **1** and **5** normal to the naphthalene plane; 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have an arbitrary radius of 0.1 Å. Crystallographic labeling is shown.

Table I. Positional Parameters, and Their Estimated Standard Deviations in Parentheses, of the Non-Hydrogen Atoms of **1** and **5**

atom	*x* (1)	*y* (1)	*z* (1)	*x* (5)	*y* (5)	*z* (5)
C(1)	0.5045 (2)	0.3421 (2)	0.6776 (3)	0.4010 (2)	0.8262 (4)	−0.1609 (3)
C(2)	0.6150 (2)	0.4356 (2)	0.8363 (3)	0.4823 (2)	0.8462 (4)	−0.3012 (4)
C(3)	0.7316 (2)	0.3724 (3)	0.8738 (3)	0.5601 (2)	0.9228 (4)	−0.2548 (4)
N(4)	0.8293 (1)	0.4294 (2)	0.7777 (2)	0.6561 (2)	0.8186 (3)	−0.2561 (3)
C(5)	0.8744 (2)	0.3409 (2)	0.6453 (3)	0.6982 (2)	0.7909 (4)	−0.1056 (4)
C(6)	0.8339 (2)	0.3594 (3)	0.4267 (3)	0.7198 (2)	0.6216 (4)	−0.0408 (4)
C(7)				0.6584 (2)	0.5913 (4)	0.1265 (4)
C(8)	0.6948 (2)	0.3067 (2)	0.3569 (3)	0.5510 (2)	0.6328 (3)	0.1313 (4)
C(9)	0.6290 (2)	0.1715 (2)	0.2440 (3)	0.4786 (3)	0.6368 (4)	0.2767 (4)
C(10)	0.5079 (2)	0.1139 (2)	0.2384 (3)	0.3829 (2)	0.6842 (4)	0.2754 (4)
C(11)	0.4531 (2)	0.1756 (2)	0.3707 (3)	0.3516 (2)	0.7441 (3)	0.1290 (4)
C(12)	0.3400 (2)	0.1072 (2)	0.4074 (3)	0.2542 (2)	0.8092 (4)	0.1185 (4)
O(12)	0.2645 (1)	−0.0148 (1)	0.2835 (2)	0.1822 (2)	0.7940 (3)	0.2553 (3)
C(121)	0.1801 (2)	0.0128 (3)	0.1177 (4)	0.1407 (3)	0.9320 (5)	0.3524 (5)
C(13)	0.3121 (2)	0.1553 (2)	0.5724 (3)	0.2317 (2)	0.8802 (4)	−0.0234 (4)
O(13)	0.2046 (1)	0.0821 (2)	0.6102 (3)	0.1355 (2)	0.9402 (3)	−0.0210 (3)
C(131)	0.1246 (3)	0.1674 (3)	0.6416 (5)	0.1101 (3)	1.0529 (5)	−0.1401 (5)
C(14)	0.3992 (2)	0.2655 (2)	0.7145 (4)	0.3057 (2)	0.8929 (4)	−0.1611 (4)
C(15)	0.5241 (2)	0.3056 (2)	0.4932 (3)	0.4232 (2)	0.7469 (3)	−0.0161 (4)
C(16)	0.6331 (2)	0.3787 (2)	0.4549 (3)	0.5199 (2)	0.6774 (3)	−0.0112 (4)
C(41)	0.8915 (2)	0.5655 (2)	0.8324 (3)	0.7103 (2)	0.7761 (4)	−0.4071 (4)
N(41)	0.9461 (2)	0.6842 2)	0.8777 (4)			
O(41)				0.6853 (2)	0.8071 (3)	−0.5378 (3)
O(42)				0.8004 (2)	0.6906 (3)	−0.3956 (3)
C(42)				0.8588 (2)	0.6100 (4)	−0.5380 (4)
C(43)				0.8341 (3)	0.4876 (5)	−0.6017 (5)
C(44)				0.8985 (3)	0.4027 (5)	−0.7346 (5)
C(45)				0.9846 (3)	0.4436 (5)	−0.7980 (5)
C(46)				1.0070 (3)	0.5671 (5)	−0.7332 (5)
C(47)				0.9442 (3)	0.6519 (4)	−0.6027 (4)

tances in Table II, bond angles in Table III, and medium-ring torsion angles in Table IV.

Apart from the usual shortening of the α-bonds of the naphthalene rings of **1** and **5**,[5] the bond lengths of these compounds,

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(6) For a review of crystal structures of naphthalene-derived cyclophanes containing a nonplanar naphthalene ring see: Keehn, P. M. In "Cyclophanes"; Keehn, P. M. Rosenfeld, S. M. Eds.; Academic Press: New York, 1983; Vol. I, Chapter 3.

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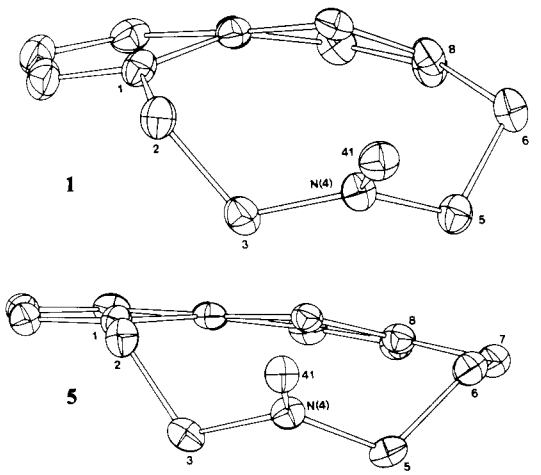

Figure 2. Projections of the ring skeletons of **1** and **5** down the central bond of the naphthalene ring. Some crystallographic numbers are shown.

Table II. Interatomic Distances (Å) for **1** and **5** with Their Estimated Standard Deviations in Parentheses

atoms	1	5
C(1)–C(2)	1.520 (3)	1.508 (4)
C(1)–C(14)	1.369 (4)	1.375 (4)
C(1)–C(15)	1.418 (3)	1.420 (4)
C(2)–C(3)	1.556 (5)	1.558 (5)
C(3)–N(4)	1.486 (4)	1.480 (4)
N(4)–C(5)	1.477 (3)	1.484 (4)
N(4)–C(41)	1.317 (3)	1.343 (4)
C(41)–N(41)	1.149 (3)	
C(5)–C(6)	1.547 (3)	1.549 (5)
C(6)–C(7)		1.531 (4)
C(6)–C(8)	1.502 (5)	
C(7)–C(8)		1.511 (5)
C(8)–C(9)	1.413 (3)	1.416 (4)
C(8)–C(16)	1.359 (4)	1.359 (5)
C(9)–C(10)	1.368 (4)	1.360 (5)
C(10)–C(11)	1.415 (4)	1.420 (5)
C(11)–C(12)	1.418 (4)	1.419 (5)
C(11)–C(15)	1.416 (2)	1.416 (4)
C(12)–C(13)	1.365 (4)	1.371 (5)
C(12)–O(12)	1.381 (2)	1.395 (4)
O(12)–C(121)	1.411 (3)	1.419 (5)
C(13)–C(14)	1.414 (3)	1.412 (4)
C(13)–O(13)	1.382 (4)	1.373 (4)
O(13)–C(131)	1.399 (4)	1.412 (5)
C(15)–C(16)	1.398 (4)	1.405 (4)
C(41)–O(41)		1.211 (4)
C(41)–O(42)		1.372 (4)
O(42)–C(42)		1.404 (4)
C(42)–C(43)		1.366 (6)
C(42)–C(47)		1.371 (5)
C(43)–C(44)		1.395 (5)
C(44)–C(45)		1.375 (7)
C(45)–C(46)		1.361 (7)
C(46)–C(47)		1.373 (5)

as expected,[6] do not deviate dramatically from normal values. Rather, the distortion of the molecular geometries of these compounds is manifested in deviations of bond and torsion angles from normal values. Thus, for example, the torsion angles defined by C-8, C-16, C-15, and C-1 (crystallographic numbering) in **1** and **5** deviate by 40° and 16.4°, respectively, from 180°.

Deviations from the least-squares planes defined by the naphthalene-ring carbon atoms of **1** and **5** are most pronounced for those ring atoms nearest the bridge (Table V). Most notably C-8 is lifted above this least-squares plane in **1** by 0.317 Å whereas C-1–C and C-7–C are pushed below the plane by 0.691 and 0.771 Å, respectively. This pattern of deformation is reproduced by **5**, albeit to a lesser extent, and in both structures reduces unfavorable transannular interactions between H-8 and atoms of the bridge which would otherwise be extreme. Transannular interactions still remain significant in these compounds, however; from the crystal structures of **1** and **5**, for example, the calculated distances between the nitrogen atom and H-8 are 2.35 and 2.23 Å, which are each less[14] than the sum of the van der Waals radii of nitrogen

Table III. Interatomic Bond Angles (deg) of **1** and **5** with Their Estimated Standard Deviations in Parentheses

atom	1	5
C(2)–C(1)–C(14)	123.4 (2)	122.6 (3)
C(2)–C(1)–C(15)	117.0 (2)	119.3 (3)
C(14)–C(1)–C(15)	117.7 (2)	117.8 (3)
C(1)–C(2)–C(3)	113.2 (2)	116.1 (3)
C(2)–C(3)–N(4)	117.9 (2)	116.5 (3)
C(3)–N(4)–C(5)	125.0 (2)	122.3 (2)
C(3)–N(4)–C(41)	117.8 (2)	115.2 (3)
C(5)–N(4)–C(41)	116.7 (2)	121.2 (2)
N(4)–C(41)–N(41)	179.0 (3)	
N(4)–C(5)–C(6)	115.3 (2)	117.7 (3)
C(5)–C(6)–C(7)		116.3 (2)
C(5)–C(6)–C(8)	107.5 (2)	
C(6)–C(7)–C(8)		113.8 (3)
C(6)–C(8)–C(9)	125.3 (2)	
C(6)–C(8)–C(16)	114.3 (2)	
C(7)–C(8)–C(9)		124.6 (3)
C(7)–C(8)–C(16)		118.7 (3)
C(9)–C(8)–C(16)	117.9 (2)	116.6 (3)
C(8)–C(9)–C(10)	120.7 (2)	122.2 (3)
C(9)–C(10)–C(11)	120.4 (2)	120.7 (3)
C(10)–C(11)–C(12)	124.6 (2)	125.0 (3)
C(10)–C(11)–C(15)	117.3 (2)	117.8 (3)
C(12)–C(11)–C(15)	117.5 (2)	117.2 (3)
C(11)–C(12)–C(13)	119.9 (2)	120.9 (3)
C(11)–C(12)–O(12)	119.1 (2)	117.8 (3)
C(13)–C(12)–O(12)	120.8 (2)	121.3 (3)
C(12)–O(12)–C(121)	114.6 (2)	114.7 (3)
C(12)–C(13)–C(14)	120.4 (2)	120.4 (3)
C(12)–C(13)–O(13)	118.8 (2)	116.5 (3)
C(14)–C(13)–O(13)	120.3 (2)	123.0 (3)
C(13)–O(13)–C(131)	115.2 (2)	118.4 (3)
C(1)–C(14)–C(13)	121.1 (3)	121.3 (3)
C(1)–C(15)–C(11)	120.6 (2)	122.1 (3)
C(1)–C(15)–C(16)	118.8 (1)	119.5 (3)
C(11)–C(15)–C(16)	118.7 (2)	118.4 (3)
C(8)–C(16)–C(15)	120.6 (2)	123.5 (3)
N(4)–C(41)–O(41)		126.0 (3)
N(4)–C(41)–O(42)		110.8 (3)
O(41)–C(41)–O(42)		123.2 (3)
C(41)–O(42)–C(42)		117.7 (3)
O(42)–C(42)–C(43)		120.8 (3)
O(42)–C(42)–C(47)		117.4 (3)
C(43)–C(42)–C(47)		121.6 (3)
C(42)–C(43)–C(44)		118.6 (4)
C(43)–C(44)–C(45)		119.7 (4)
C(44)–C(45)–C(46)		120.5 (4)
C(45)–C(46)–C(47)		120.4 (4)
C(46)–C(47)–C(42)		119.2 (4)

Table IV. Medium-Ring Torsion Angles (deg) of **1** and **5** (Atoms Are Denoted by Number Only)

atoms	angle (1)	angle (5)
15–1–2–3	−54.2	−53.8
1–2–3–4	97.8	108.4
2–3–4–5	−122.8	−119.2
3–4–5–6	108.2	118.6
4–5–6–7		−112.8
4–5–6–8	−64.2	
5–6–7–8		57.3
5–6–8–16	59.7	
6–7–8–16		5.9
6–8–16–15	−143.8	
7–8–16–15		−167.3
8–16–15–1	140.0	163.6
16–15–1–2	−12.4	−5.1

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Table V. Deviations from the Least-Squares Planes Defined by the Naphthalene-Ring Carbon Atoms of **1** and **5** (σ, 0.209, 0.087 Å respectively)[a]

defining atoms	**1** deviation (Å)	**5** deviation (Å)
C-1	-0.138	0.055
C-2	-0.265	0.110
C-3	-0.018	0.007
C-4	0.147	-0.067
C-4a	0.173	-0.069
C-5	-0.029	0.010
C-6	-0.287	0.120
C-7	-0.130	0.054
C-8	0.317	-0.139
C-8a	0.229	-0.081
other atoms		
C-1-C	-0.691	0.251
C-7-C	-0.771	0.257

[a] Defining atom numbering based on that for **1** and **5** in Scheme I.

and hydrogen by 0.40 and 0.52 Å, respectively. The chemical consequences of the proximity of the nitrogen atom to the naphthalene ring and of the aromatic-ring distortion in these strained (1,7)naphthalenophanes, and in other related compounds, will be reported in due course.

Experimental Section

General Procedures. Melting points were determined on a Yanagimoto Seisakusho micro-melting point apparatus and are uncorrected. Microanalyses were carried out by AMDEL Microanalytical Service, Melbourne. Preparative thin-layer chromatography (TLC) and column chromatography were carried out with Merk silica gel GF_{254}. Analytical TLC was done on Merk precoated silica gel $60F_{254}$ plates (thickness 0.25 mm). Mixtures of developing solvents were made up by volume. Infrared and ultraviolet spectra were recorded on a Beckman IR-33 spectrometer and a Cary 17 spectrophotometer, respectively. Mass spectra were determined on a VG MM 70 70F mass spectrometer operating at 70 eV with a source temperature of 200 °C (direct insertion); peak intensities (in brackets) are expressed as a percentage of the base peak. ^{1}H nuclear magnetic resonance spectra were recorded at 100 MHz with a Varian FT XL 100 spectrometer and a JEOL JNM-4H-100 spectrometer and at 270 or 300 MHz with a Bruker HX-270 or a Bruker CXP-300 spectrometer, respectively, using tetramethylsilane as internal standard.

8,9-Dimethoxy-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (8). To a solution of 8,9-dimethoxy-2,3,5,6-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoquinolinium chloride[15] (6.0 g, 22.4 mmol) in methanol (20 mL) and water (50 mL) was added 20% potassium hydroxide solution (20 mL). The precipitate which formed was collected by filtration, washed with water (5 mL), and dried in a vacuum at 30 °C for 6 h to afford **8**[9] (4.20 g, 80%) as colorless granules: mp 99–100 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.00 (s, 1 H), 6.58 (s, 1 H), 5.22 (m, 1 H), 3.86 (s, 6 H), 3.30–3.00 (m, 2 H), 2.02 (s, 4 H), 2.67–2.35 (m, 2 H); mass spectrum, *m/e* 231 (M^+, 62%, accurate mass calculated for $C_{14}H_{17}NO_2$ 231.1258, found 231.1258), 230 (100), 229 (33).

Ethyl 2-[8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinol-1-yl]ethanoate (16). To **8** (7.79 g, 33.7 mmol) was added ethyl bromoacetate (7.5 mL, 67.4 mmol), and this mixture was allowed to stand at room temperature for 30 h. The resulting gum was washed with diethyl ether and then dissolved in ethanol (50 mL) and cooled to 0 °C. Sodium borohydride (3.0 g) was added portionwise and the mixture stirred for 1 h at 20 °C. The solvent was evaporated, water (20 mL) was added to the residue, and the resulting solution extracted with chloroform (3 × 30 mL). The residue obtained from evaporation of the dried (Na_2SO_4) organic extracts was subjected to column chromatography (silica, chloroform–3% methanol) to afford **16** (5.52 g, 51%) as a pale yellow gum: R_f 0.25 (chloroform–5% methanol); ^{1}H NMR (100 Hz, $CDCl_3$) δ 6.55 (s, 1 H), 6.48 (s, 1 H), 4.02 (q, J = 7.5 Hz, 2 H), 3.80 (s, 6 H), 3.40–1.45 (m, 12 H), 1.16 (t, J = 7.5 Hz, 3 H); IR (thin film) 1730 cm^{-1}; mass spectrum, *m/e* 319 (M^+, 25%), 318 (M - 1, 35%, accurate mass calculated for $C_{18}H_{24}NO_4$ 318.1705, found 318.1793), 272 (40), 244 (50), 242 (40), 220 (35), 205 (100), 190 (40).

1-(Carboxymethyl)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolinium Chloride (10). A solution of **16** (3.82 g, 12.0 mmol) in 1 M hydrochloric acid (50 mL) was stirred at room temperature for 2 days and then evaporated to dryness. The residue was recrystallized from water–acetone to afford **10** (3.56 g, 91%) as colorless needles: mp 221–223 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 12.1 (br s, exchanged with D_2O, 1 H), 7.22 (s, 1 H), 7.16 (s, 1 H), 5.13 (d, J = 6 Hz, 1 H), 4.10 (s, 6 H), 4.05–1.90 (m, 12 H); IR (Nujol mull) 3300, 2580, 1695 cm^{-1}. Anal. Calcd for $C_{16}H_{22}NO_4Cl$: C, 58.61; H, 6.78; N, 4.27. Found C, 58.60; H, 6.60; N, 4.21.

9,10-Dimethoxy-3,4,6,7-tetrahydro-2*H*-benzo[*a*]quinolizine (9). A solution of 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium chloride[16] (9.36 g, 33.2 mmol) in water (40 mL) was treated with 20% potassium hydroxide solution (40 mL), exactly as described for the preparation of **8**, to afford **9** (7.64 g, 94%) as colorless granules: mp 88–90 °C (lit.[10] mp 88–90 °C).

1-((Ethoxycarbonyl)methyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium Bromide (17). To the finely powdered enamine **9** (7.64 g, 31.1 mmol) was added ethyl bromoacetate (6 mL, 54.1 mmol). The mixture was heated under nitrogen at 120 °C for 0.5 h. The yellow solid which had formed was washed with petroleum ether (bp 40–60 °C) (30 mL) followed by diethyl ether (30 mL) and then recrystallized from ethanol to give **17**[11a,b] (10.90 g, 85%) as yellow prisms: mp 202–203 °C dec; ^{1}H NMR (100 MHz, $CDCl_3$–CD_3OD) δ 7.42 (s, 1 H), 6.95 (s, 1 H), 4.02 (s, 3 H), 3.96 (s, 3 H), 4.50–1.62 (m, 15 H), 1.12 (t, J = 7.5 Hz, 3 H); IR (Nujol mull) 1720, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{26}NO_4Br$: C, 55.34; H, 6.37; Br, 19.38. Found: C, 55.54; H, 6.22; Br, 19.30.

Ethyl 2-[9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizin-1-yl]ethanoate (18). To a stirred solution of **17** (6.23 g, 15.1 mmol) in ethanol (100 mL), cooled to 0 °C, was added sodium borohydride (1.25 g). The mixture was stirred at room temperature for 1 h. The solvent was then evaporated to dryness. Water (20 mL) was added to the residue and the mixture extracted with dichloromethane (3 × 30 mL). Evaporation of the dried (Na_2SO_4) dichloromethane extracts gave **18** (5.00 g, 100%) as a pale yellow oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.64 (s, 1 H), 6.49 (s, 1 H), 3.97 (q, J = 6 Hz, 2 H), 3.79 (s, 6 H), 3.30-1.30 (m, 14 H), 1.15 (t, J = 6 Hz, 3 H); IR (thin film) 1730 cm^{-1}; mass spectrum, *m/e* 333 (M^+, 55%), 332 (M - 1, 100%, accurate mass calculated for $C_{19}H_{26}NO_4$ 332.1862, found 332.1919), 288 (20), 260 (45), 246 (45), 245 (25), 218 (75), 191 (45).

1-(Carboxymethyl)-9,10-dimethoxy-1,2,3,4,5,6,7,11b-octahydrobenzo[*a*]quinolizinium Chloride (11). A solution of the ester **18** (5.00 g, 15.0 mmol) in 1 M hydrochloric acid (100 mL) was stirred at room temperature for 2 days and then evaporated to dryness. The residue was recrystallized from water–acetone to afford **11** (4.82 g, 94%) as colorless needles: mp 225–230 °C dec; ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 10.90 (br s, exchanged with D_2O, 1 H), 7.26 (s, 1 H), 7.19 (s, 1 H), 5.05 (br s, 1 H), 4.20 (s, 3 H), 4.15 (s, 3 H), 4.10–1.05 (m, 14 H); IR (Nujol mull) 3380, 3300, 2600, 2580, 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{24}NO_4Cl$: C, 59.72; H, 7.09; N, 4.10. Found C, 59.31; H, 7.12, N, 4.04.

Preparation of 7,8-Dimethoxy-1,2,5,10,10a,10b-hexahydrobenzo[*de*]-pyrrolo[3,2,1-*ij*]quinolin-9(4*H*)-one (12) and of 8,9-Dimethoxy-2,3,6,11,11a,11b-hexahydro-1*H*-benzo[*de*]pyrido[3,2,1-*ij*]quinolin-10-(5*H*)-one (13). To the amino acid salt **10** (900 mg, 2.75 mmol) was added oleum (80% sulfuric acid–20% free sulfur trioxide) (3 mL), and the mixture was stirred at 20 °C for 10 min and then quenched by the addition of ice (50 g). The solution was basified to pH 11 with a 50% hydroxide solution and extracted with dichloromethane (4 × 100 mL). The residue from the dried (Na_2SO_4) extracts was dissolved in chloroform and filtered through a plug of silica gel to afford, after crystallization from light petroleum (bp 40–60 °C), the ketone **12** (487 mg, 65%); mp 53–54 °C; ^{1}H NMR (100 MHz $CDCl_3$) δ 6.88 (s, 1 H), 3.75 (s, 6 H), 3.40–1.30 (m, 12 H); IR ($CHCl_3$) 1690 cm^{-1}; mass spectrum, *m/e* 273 (M^+, 25%), 272 (M - 1, 100%, accurate mass calculated for $C_{16}H_{18}NO_3$ 272.1286, found 272.1286). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.02; N, 5.13. Found: C, 70.27; H, 7.01; N, 5.13.

Similarly the amino acid salt **11** (1.06 g, 3.11 mmol) was stirred with oleum (3 mL) at 80 °C for 10 min and then worked up as described for the preparation of **12** to give, after recrystallization from chloroform–light petroleum (bp 40–60 °C)–diethyl ether, the ketone **13** (642 mg, 72%): mp 140–141 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.77 (s, 1 H), 4.22 (d, J = 4 Hz, 1 H), 3.77 (s, 6 H), 3.40–2.20 (m, 9 H), 1.80–1.00 (m, 4 H); IR ($CHCl_3$) 1690 cm^{-1}; mass spectrum, *m/e* 287 (M^+, 35%), 286 (M - 1, 100%; exact mass calculated for $C_{17}H_{20}NO_3$ 286.1443, found 286.1438). Anal. Calcd for $C_{17}H_{21}NO_3$; C, 71.04; H, 7.38; N, 4.87. Found: C, 70.89; H, 7.58; N, 4.84.

Preparation of 7,8-Dimethoxy-1,2,4,5,10a,10b-hexahydrobenzo[*de*]-pyrrolo[3,2,1-*ij*]quinoline (6) and 8,9-Dimethoxy-2,3,5,6,11a,11b-hexa-

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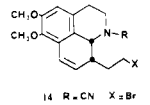
hydro-1*H*-benzo[*de*]pyrido[3,2,1-*ij*]quinoline (7). To a stirred solution of **12** (487 mg, 1.78 mmol) in ethanol (40 mL) was added portionwise sodium borohydride (600 mg) at 0 °C. The solution was stirred for 1 h at 20 °C and evaporated to dryness. To the residue was added water (10 mL), and the resulting solution was adjusted to pH 1 by the addition of 1 M hydrochloric acid. The stirred solution was refluxed for 1.5 h and then cooled and basified to pH 11 by the addition of 20% potassium hydroxide. The mixture was extracted with dichloromethane (3 × 50 mL). The residue from the dried (Na_2SO_4) extracts was dissolved in chloroform and filtered through a plug of silica gel to afford **6** (309 mg, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.63 (d, J = 10 Hz, 1 H), 6.45 (s, 1 H), 5.96 (dd, J = 10, 2 Hz, 1 H), 4.16 (d, J= 9 Hz, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.60–3.30 (m, 1 H), 3.10–2.30 (m, 6 H), 2.30–1.85 (m, 1 H), 1.70–1.20 (m, 1 H); IR (thin film) 1630 cm^{-1}; mass spectrum, m/e 257 (M$^+$, 40%), 256 (M − 1, 100%, accurate mass calculated for $C_{16}H_{18}NO_2$ 256.1337, found 256.1333).

In the same manner **13** (1.42 g, 4.93 mmol) was reduced with sodium borohydride (490 mg) and the resulting alcohol treated with hydrochloric acid. The crude reaction product was extracted with boiling light petroleum (bp 40–60 °C). Evaporation of the light petroleum extracts gave **7** (1.27 g, 95%) as a colorless solid. Recrystallization from light petroleum (bp 40–60 °C) gave **7** as needles: mp 88–89 °C; ^{1}H NMR (100 MHz $CDCl_3$) δ 6.65 (d, J = 10 Hz, 1 H), 6.44 (s, 1 H), 5.98 (dd, J = 10, 4 Hz, 1 H), 4.26 (d, J = 8 Hz, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.35–2.20 (m, 7 H), 1.80–1.40 (m, 4 H); IR (thin film) 1635 cm^{-1}; mass spectrum, m/e 271 (M$^+$, 30%), 270 (M − 1, 100%, accurate mass calculated for $C_{17}H_{20}NO_2$ 270.1494, found 270.1490). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.23; H, 7.82; N, 5.16. Found: C, 74.96; H, 7.91; N, 5.16.

Reaction of 6 and 7 with Cyanogen Bromide. To a stirred solution of **6** (300 mg, 1.17 mmol) in dry ethanol–free chloroform (30 mL) was added anhydrous potassium carbonate (1.61 g) followed by cyanogen bromide (245 mg). The mixture was stirred at 20 °C for 15 h and then filtered. The filtrate was evaporated and the residue subjected to preparative TLC (silica gel; chloroform) to afford two fractions.

Fraction 1 (R_f 0.65) gave, after crystallization from diethyl ether, the **3-aza[5](1,7)naphthalenophane**, 9,10-dimethoxy-1,2,4,5-tetrahydro-6,8-etheno-3*H*-3-benzazonine-3-carbonitrile (**1**) (204 mg, 62%), as colorless prisms: mp 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 1.3 Hz, 1 H), 7.84 (d, J = 8.3 Hz, 1 H), 7.10 (dd, J = 8.3, 1.3 Hz, 1 H), 6.82 (s, 1 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 4.03 (dd, J = 14.6, 6.8 Hz, 1 H), 3.95 (dd, J = 15.7, 8.1 Hz, 1 H), 3.85 (dt, J = 14.0, 2.5 Hz, 1 H), 3.25 (ddd, J = 14.6, 12.0, 2.8 Hz, 1 H), 2.80 (dd, J = 16.1, 6.8 Hz, 1 H), 2.58 (dt, J = 14.4, 1.9 Hz, 1 H), 1.70 (ddd, J = 14.2, 12.0, 1.9 Hz, 1 H), 1.34 (dd, J = 14.7, 8.1 Hz, 1 H); IR ($CHCl_3$) 2220 cm^{-1}; UV (MeOH) λ_{max} 224 nm (log ϵ 4.36), 254 (4.66), 305 (3.66), 313 (3.64), 353 (3.37); mass spectrum, m/e 282 (M$^+$, 100%, accurate mass calculated for $C_{17}H_{18}N_2O_2$ 282.1376, found 282.1372), 281 (30), 267 (25), 251 (60), 228 (40), 227 (25), 214 (25), 213 (60), 197 (25), 141 (20). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.44; N, 9.92. Found: C, 72.42; H, 6.32; N, 9.95.

Fraction 2 (R_f 0.85) gave 9-(2-bromoethyl)-5,6-dimethoxy-2,3,9,9a-tetrahydro-1*H*-benzo[*de*]quinoline-1-carbonitrile (**14**) (80 mg, 19%) as a pale yellow gum: ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.78 (d, J = 10 Hz, 1 H), 6.48 (s, 1 H), 6.11 (dd, J = 10, 6 Hz, 1 H), 4.44 (d, J = 6 Hz, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 4.00–3.15 (m, 5 H), 2.95–2.60 (m, 2 H), 2.30–1.50 (m, 2 H); IR (thin film) 2220 cm^{-1}; mass spectrum, m/e 364 (M$^+$, 25%, accurate mass calculated for $C_{17}H_{19}NO_2{}^{81}Br$ 364.0610, found 364.0678), 362 (45), 309 (65), 307 (65), 201 (35), 107 (30), 105 (25), 85 (60), 83 (100).



14 R = CN X = Br
15 R = $COOCH_3$ X = Cl

Reaction of **7** (270 mg, 0.995 mmol) with cyanogen bromide (522 mg, 4.93 mmol) for 48 h at 20 °C by means of the method described for the preparation of **1** gave, after preparative TLC (silica gel; chloroform) (R_f 0.30) and crystallization from ethyl acetate–light petroleum (bp 40–60 °C), the **3-aza[6](1,7)naphthalenophane**, 10,11-dimethoxy-1,4,5,6-tetrahydro-7,9-etheno-3-benzazecine-3(2*H*)-carbonitrile (**2**) (264 mg, 90%) as colorless needles: mp 135–136 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.91 (d, J = 8 Hz, 1 H), 7.23 (d, J = 8 Hz, 1 H), 6.94 (s, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 3.80–2.00 (m, 10 Hz); IR ($CHCl_3$) 2220 cm^{-1}; UV (MeOH) λ_{max} 222 nm (4.34), 242 (4.76), 298 (3.70), 343 (3.46); mass spectrum, m/e 296 (M$^+$, 80%, accurate mass calculated for $C_{18}H_{20}N_2O_2$ 296.1525, found 296.1519), 295 (25), 281 (15), 227 (100), 214 (55). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.82; N, 9.45. Found: C, 72.75; H, 6.69; N, 9.39.

Reaction of 6 with Methyl Chloroformate. To a stirred solution of **6** (261 mg, 1.01 mmol) in dry ethanol–free chloroform (30 mL) was added anhydrous potassium carbonate (1.40 g) followed by methyl chloroformate (2.32 mL). The mixture was refluxed for 1 h, stirred at 20 °C for 18 h, and then filtered. The residue obtained from evaporation of the filtrate was subjected to preparative TLC (silica gel; chloroform) to afford two fractions.

Fraction 1 (R_f 0.35) gave, after crystallization from diethyl ether–light petroleum (bp 40–60 °C), the **3-aza[5](1,7)naphthalenophane**, methyl 9,10-dimethoxy-1,2,4,5-tetrahydro-6,8-etheno-3*H*-benzazonine-3-carboxylate (**3**) (214 mg, 67%), mp 110–111 °C: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.88 (br s, 1 H), 7.75 (d, J = (3.67), Hz, 1 H), 7.00 (br d, J = 8 Hz, 1 H), 6.70 (s, 1 H), 4.30–1.00 (m, 8 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H); IR (film) 1700 cm^{-1}; UV (MeOH) λ_{max} 225 nm (log ϵ 4.39), 254 (4.67), 305 (3.69), 313 (3.67), 353 (3.56); mass spectrum, m/e 315 (M$^+$, 90%, accurate mass calculated for $C_{18}H_{21}NO_4$ 315.1470, found 315.1505), 300 (100), 284 (20), 228 (25), 227 (15), 213 (60), 197 (20), 83 (35). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.54; H, 6.72; N, 4.44. Found: C, 68.83; H, 6.85; N, 4.30.

Fraction 2 (R_f 0.65) gave methyl 9-(2-chloroethyl)-5,6-dimethoxy-2,3,9,9a-tetrahydro-1*H*-benzo[*de*]quinoline-1-carboxylate (**15**) (104 mg, 30%) as a colorless gum: ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.78 (d, J = 10 Hz, 1 H), 6.50 (s, 1 H), 6.07 (dd, J = 10, 7 Hz, 1 H), 4.88 (d, J = 7 Hz, 1 H), 4.60–4.30 (m, 1 H), 3.96–3.80 (m, 1 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.55–3.30 (m, 2 H), 3.05–2.45 (m, 3 H), 1.95–1.45 (m, 2 H); IR (film) 1710 cm^{-1}; mass spectrum, m/e 353 (15%), 351 (M$^+$, 50%, accurate mass calculated for $C_{18}H_{22}NO_4{}^{35}Cl$ 351.1263, found 351.1211), 365 (45), 363 (100).

Reaction of 7 with Methyl Chloroformate and with Phenyl Chloroformate. To a stirred solution of **7** (1.385 g, 5.103 mmol) in dry ethanol–free chloroform (50 mL) was added anhydrous potassium carbonate (6.90 g) followed by methyl chloroformate (11.6 mL). The mixture was refluxed for 4 h, stirred at room temperature for 36 h, and then filtered. The residue obtained from evaporation of the filtrate was subjected to column chromatography on silica with chloroform as the eluant to afford, after recrystallization from diethyl ether–light petroleum (bp 40–60 °C), the 3-aza[6](1,7)naphthalenophane, methyl 10,11-dimethoxy-1,4,5,6-tetrahydro-7,9-etheno-3-benzazecine-3(2*H*)-carboxylate (**4**) (1.443 g, 86%) (R_f 0.25, silica gel, chloroform), as colorless prisms: mp 130–131 °C; ^{1}H NMR (100 MHz, $(CCl_2D)_2$, 140 °C) δ 7.94 (d, J = 2 Hz, 1 H), 7.88 (d, J = 10 Hz, 1 H), 7.19 (dd, J= 10, 2 Hz, 1 H), 6.89 (s, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.37–2.79 (m, 8 H), 2.49–2.20 (m, 2 H); IR (thin film) 1700 cm^{-1}; UV (MeOH) λ_{max} 222 nm (log ϵ 4.41), 241 (4.80), 268 (3.65), 278 (3.78), 290 (3.75), 337 (3.48), 343 (3.45); mass spectrum, m/e 329 (M$^+$, 50% accurate mass calculated for $C_{19}H_{23}NO_4$ 329.1625, found 329.1623), 227 (100), 102 (35), 83 (15). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.27; H, 7.05; N, 4.25. Found: C, 69.34; H, 7.02; N, 4.24.

To a stirred solution of **7** (300 mg, 1.11 mmol) in dry ethanol–free chloroform (30 mL) was added anhydrous potassium carbonate (1.53 g) followed by phenyl chloroformate (2.80 mL), and the mixture was refluxed for 5 h and then stirred at room temperature for 12 h. The mixture was filtered and the filtrate evaporated. The residue was treated with 5% potassium carbonate solution (30 mL) and extracted with chloroform (4 × 30 mL). The dried (Na_2SO_4) chloroform extracts were evaporated, and the residue was subjected to preparative TLC (silica gel, chloroform) to afford (R_f 0.25) the 3-aza[6](1,7)naphthalenophane, phenyl 10,11-dimethoxy-1,4,5,6-tetrahydro-7,9-etheno-3-benzazecine-3-(2*H*)-carboxylate (**5**) (387 mg, 89%), as a colorless solid. Recrystallization from dichloromethane–light petroleum (bp 40–60 °C) gave **5** as prisms: mp 146–147 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.92 (d, J = 6 Hz, 1 H), 7.45–7.05 (m, 6 H), 6.95 (s, 1 H), 4.50–2.00 (m, 10 H), 3.94 (s, 3 H), 3.90 (s, 3 H); IR (film) 1720 cm^{-1}; UV (MeOH) λ_{max} 240 nm (log ϵ 4.78), 289 (3.75), 300 (3.72), 336 (3.44), 343 (3.42); mass spectrum, m/e 391 (M$^+$, 95%), accurate mass calculated for $C_{24}H_{25}NO_4$ 391.1783, found 391.1778), 376 (15), 297 (15), 241 (20), 227 (95), 107 (20), 77 (20). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.62; H, 6.45; N, 3.58. Found: C, 73.57; H, 6.19; N, 3.71.

Crystallography of 1 and 5. Crystal data of **1**: $C_{17}H_{18}N_2O_2$, M_r 282.3, triclinic, space group $P\bar{1}$ (C_i^1, No. 2), a = 11.468 (3) Å b = 9.579 (3) Å, c = 7.133 (2) Å, α = 94.70 (2)°, β = 104.59 (2)°, γ = 102.47 (2)°, U = 732.6 (4) Å^3, D_m = 1.29 (1), D_c = 1.28 g cm^{-3} (Z = 2), F(000) = 300, T = 295 K, μ(Mo) = 0.92 cm^{-1}. Crystal data of **5**: $C_{24}H_{25}NO_4$, M_r 391.5, triclinic, space group $P\bar{1}$ (C_i^1, No. 2), a = 14.531 (5) Å, b = 8.800 (3) Å, c = 8.251 (3) Å, α = 87.90 (3)°, β = 77.95 (3)°, γ = 76.68 (3)°, U = 1004 (1) Å^3, D_m = 1.29 (1), D_c = 1.30 g cm^{-3} (Z = 2), F(000) = 416, T = 295 K, μ(Mo) = 0.95 cm^{-1}.

Structure Determinations. Unique data sets were measured with a Syntex $P2_1$ four-circle diffractometer in conventional $2\theta/\theta$ scan mode, the $2\theta_{max}$ limit being 50° (**1**), 45° (**5**) (monochromatic Mo Kα radiation,

$\lambda = 0.7106_9$ Å). Of the 2600 independent reflections obtained for **1**, 1812 with $I > 3\sigma(I)$ were used in the full-matrix least-squares refinement without absorption correction, and after solution of the structure by direct methods. In the case of **5**, of 2628 independent reflections, 1999 with $I > 3\sigma(I)$ were similarly treated. Thermal parameter treatment was isotropic (constrained) for hydrogen atoms and anisotropic for the other atoms; $(x,y,z)_H$ were constrained at idealized values in **5** and refined for the non-metal hydrogens in **1**. Residuals at convergence were $R = 0.041$, $R' = 0.051$ for **1** and $R = 0.044$, $R' = 0.053$ for **5**, reflection weights being $[\sigma^2F_o) + 0.0003(F_o)^2]^{-1}$. Neutral complex scattering factors were used.[17] Computation was performed with the X-RAY 76 program system.[18]

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Supplementary Material Available: Listing of structure factor amplitudes for **1** and **5**, and Tables S1–S4 listing non-hydrogen atom thermal parameters and hydrogen atom parameters for **1** and **5** (18 pages). Ordering information is given on any current masthead page.

Application of [2,3] Sigmatropic (Wittig) Rearrangements in Synthesis. The Synthesis of (+)-Prelog–Djerassi Lactone

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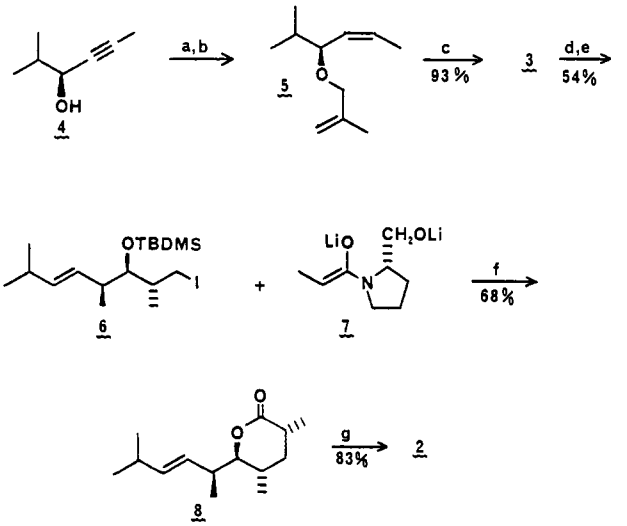
Abstract: The [2,3] sigmatropic (Wittig) rearrangement has been used as a key step in the synthesis of (+)-Prelog–Djerassi lactonic aldehyde. This reaction was used to control the relative and absolute configuration of two of the four chiral centers of the lactone. The remaining centers were introduced by a stereoselective hydroboration and an asymmetric alkylation of a prolinol amide enolate. The synthesis is short, efficient, and amendable to analogue synthesis. The final lactone is obtained in essentially 100% epimeric and optical purity.

Chirality transfer via [3,3] sigmatropic rearrangements of allylic alcohols is a powerful method for absolute control of chirality during carbon–carbon bond-forming reactions.[1] It has recently been demonstrated that [2,3] sigmatropic (Wittig) rearrangements also proceed with essentially complete chirality transfer and a high degree of diastereoselectivity.[2] Since the resulting products contain functionality which may be manipulated into more complex products, this reaction should also provide a powerful method for the construction of complex molecules.[3] Herein we demonstrate the use of the [2,3] sigmatropic rearrangement in the synthesis of the Prelog–Djerassi lactonic aldehyde.

The Prelog–Djerassi lactonic acid, **1**, a degradation product of narbormycin and methylmycin,[4] has been prepared by many groups.[5] The lactonic aldehyde, **2**, a key intermediate in the syntheses of the macrolide antibiotics, 6-deoxyerythronolide B and narbomycin, has been prepared from the acid in two steps.[6] Our strategy for the synthesis of these compounds was to use the high diastereoselectivity of the [2,3] Wittig rearrangement to control

Scheme I



a: H_2, Pd/$BaSO_4$. b: NaH, $CH_2{=}CH(CH_3)CH_2Cl$, THF reflux. c: *n*-BuLi/*t*-BuOK, −78 → 0 °C. d: TBDMSCl, imidazole, DMF. e: $(C_6H_{11})_2BH$ then I_2/NaOMe. f: HCl, THF, 25 °C, 24 h. g: O_3, $(CH_3)_2S$. (yields are of isolated product)

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