Total Syntheses of (±)-Crinine and (±)-Buphanisine

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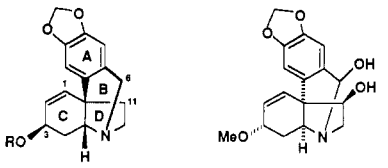
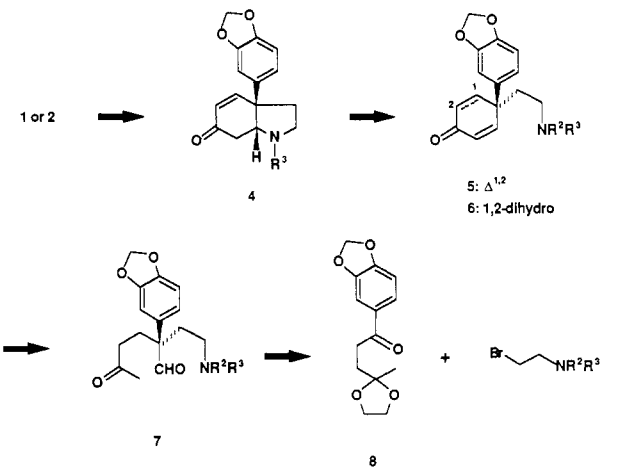
Concise total syntheses of the Amaryllidaceae alkaloids (±)-crinine (**1**) and (±)-buphanisine (**2**) have been achieved. The overall strategy features the novel application of a general protocol for elaboration of a quaternary carbon at a carbonyl center to effect the facile construction of the key intermediate 4,4-disubstituted cyclohexenone **12** from the monoprotected 1,4-dione **8**. Transformation of **12** into dienone **14** was readily accomplished by sequential α'-bromination and dehydrobromination; subsequent removal of the *N*-(allyloxy)carbonyl protecting group was accompanied by spontaneous cyclization to give exclusively the *cis*-hydroindolenone **15**. Hydride reduction of **15** afforded a mixture of epimeric allylic alcohols **25** and **26**; inversion of the hydroxyl function in **26** via the mesylate **27** to give the requisite **25** proceeded without event. N-Debenzylation of **25** followed by insertion of the bridging methylene group onto **30** by a Pictet–Spengler reaction afforded (±)-crinine (**1**). Alternatively, treatment of a mixture of **25** and **26** with methanesulfonyl chloride followed by methanolysis of the resulting epimeric mesylates afforded **28** which was converted into (±)-buphanisine (**2**) by sequential N-debenzylation and Pictet–Spengler cyclization. An attempt to effect the highly diastereoselective formation of hydroindolenone **23** from enantiomerically pure **22** was unsuccessful.

Introduction

The 5,10-ethanophenanthridine ring system is a structural element that characterizes one of the main skeletal subgroups of the Amaryllidaceae family of alkaloids.[2] Although the bases crinine (**1**)[3,4] and haemanthidine (**3**)[5] have been proven to be popular targets for the development and application of new synthetic methods and strategies in this arena, buphanisine (**2**), the methyl ether of crinine, has not been the object of such efforts. In previous accounts from these laboratories,[6] we have set forth a general strategy for the total synthesis of members of several classes of the alkaloids of the *Amaryllidaceae* family. The salient feature of the approach entails the practical application of a general method for the construction of quaternary carbon atoms bearing differentially functionalized alkyl appendages at the carbonyl carbon of a ketone (eq 1).[7] By subsequent application of a sequence of logical disconnections, the challenge posed by the syntheses of **1** and **2** may be simplified as adumbrated in retrosynthetic fashion in Scheme I. In the key step of this plan, the carbonyl function of the monoprotected 1,4-dione **8** is elaborated in a single chemical operation to the highly functionalized intermediate **7**, which is then cyclized directly into the 4,4-disubstituted cyclohexenone **6**. Subsequent transformation of **6** into the targeted alkaloids **1** and **2** via **5** and **4** would then be achieved in a straightforward manner according to protocols previously estab-



Scheme I



$$\text{R}^1\text{R}^2\text{C=O} \xrightarrow{\text{Step 1}} \text{R}^1\text{R}^2\text{C(R}^3\text{)(NR}^4\text{Li)} \xrightarrow[\text{Step 2}]{\text{El}^+} \text{R}^1\text{R}^2\text{C(COR}^3\text{)(El)} \qquad (1)$$

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(2) For reviews of the chemistry of the *Amaryllidaceae* alkaloids, see: (a) Fuganti, C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, pp 83–164. (b) Tsuda, Y. *Heterocyles* **1978**, *10*, 555. (c) Grundon, M. F. In *Specialist Periodical Reports*, The *Alkaloids*; The Chemical Society: London, 1983; Vol. 13, pp 187–195. See also: Vols. 1–12. (d) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic Press: New York; 1987; Vol. 30, pp 251–376.

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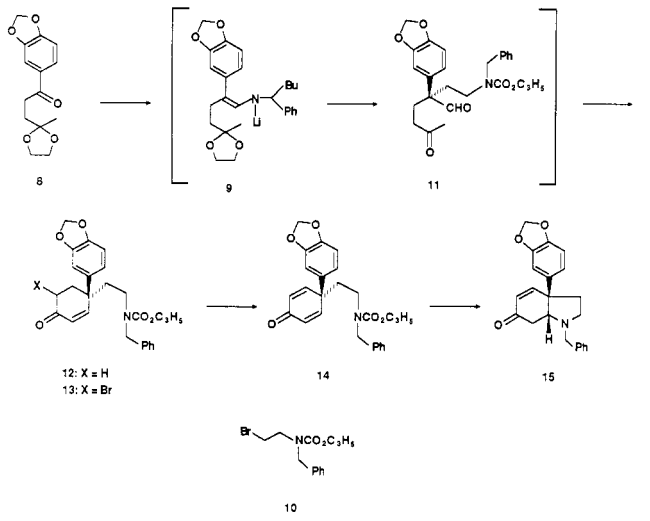
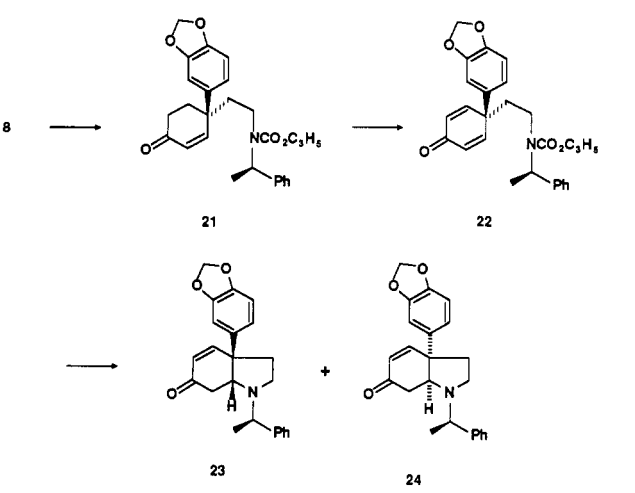
Scheme II



Scheme III

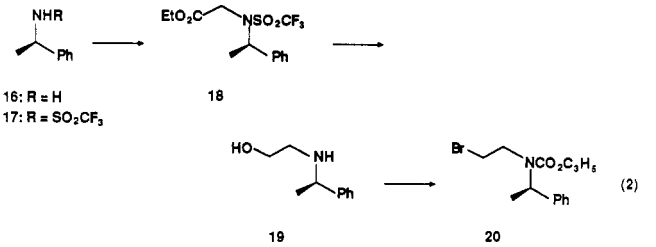


lished in closely related systems.[6d] We now disclose the full details of our efforts in this area that culminated in facile total syntheses of (±)-crinine (1) and (±)-buphanisine (2).[8]

As depicted above, the opening move in this undertaking involved construction of the 4,4-disubstituted cyclohexenone **12** by application of the method outlined in eq 1. The only significant issue at the outset regarded the selection of two protecting groups for the nitrogen atom resident in the electrophilic partner that would be utilized in step 2 of the construction; on the basis of prior experience,[6] *N*-benzyl and *N*-(allyloxy)carbonyl groups seemed eminently suitable. Thus, olefination of the monoprotected 1,4-dione **8**, which was available in two simple steps from piperonal,[6c,d] with diethyl (benzylideneamino)lithiomethylphosphonate followed by regioselective addition of *n*-butyllithium to the intermediate 2-aza diene afforded the metallo enamine **9** in situ, thereby completing step 1 of the homologation sequence.[7] Alkylation of **9** with allyl benzyl(2-bromoethyl)carbamate (**10**), which was prepared in two steps [(a) 48% aqueous HBr, (b) C_3H_5OCOCl, K_2CO_3, Et_2O/H_2O; 85%] from commercially available *N*-benzylethanolamine, and subsequent workup with aqueous acid provided the crude δ-keto aldehyde **11**. When **11** was treated with pyrrolidinium acetate in aqueous methanol, cycloaldolization with concomitant dehydration ensued to deliver the key intermediate cyclohexenone **12** in 71% overall yield from **8**.

The next stage of the synthesis required the preparation of cyclohexadienone **14**, which was conveniently achieved in 70–80% overall yield by selective α′-monobromination of **12** with phenyltrimethylammonium perbromide (PTAB) followed by dehydrobromination of the mixture of diastereoisomeric bromo enones **13** thus produced by exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at reflux. After removal of the *N*-(allyloxy)carbonyl protecting group from **14** by using catalytic amounts of $PdPh_3P$ in the presence of triphenylphosphine and 2-ethylhexanoic acid,[9] spontaneous cyclization of the intermediate secondary amine via 1,4-addition to the enone moiety ensued to provide *cis*-hydroindolenone **15** as the sole product in 87% yield (Scheme II).

Recognizing that the prochiral cyclohexadienone **14** underwent cyclization to provide hydroindolenone **15** in racemic form, it occurred to us that it might be feasible to effect an asymmetric synthesis of both crinine (**1**) and buphanisine (**2**). The essential question at this juncture was whether the presence of a stereogenic carbon on the *N*-alkyl protecting group could confer a significant level of asymmetric induction upon the Michael addition that formed the pyrrolidine ring. In order to test this intriguing hypothesis, the optically pure alkylating agent **20** was prepared from (*R*)-α-phenylethylamine (**16**) by following a protocol featuring triflamides that was previously developed by Hendrickson.[10] Thus, alkylation of triflamide **17** with ethyl bromoacetate in the presence of K_2CO_3 provided **18**, which was reduced with lithium aluminium hydride to give amino alcohol **19** (eq 2). Reaction of **19**



(2)

with 48% aqueous hydrobromic acid followed by treatment of the crude salt thus obtained with allyl chloroformate under modified Schotten–Baumann conditions afforded the requisite alkylating agent **20** in 78% overall yield from **16**.

Monoprotected dione **8** was then converted into a mixture of diastereomeric cyclohexenones **21** (ca. 1:1) in 51% overall yield by a sequence of reactions identical with those previously described for the preparation of **12**, with the obvious exception that metallo enamine **9** was alkylated with **20** (Scheme III). Subsequent bromination of **21** with PTAB followed by base-induced (DBU) dehydrobromination of the resulting α′-bromocyclohexenones afforded optically pure cyclohexadienone **22** in 63% yield. Palladium(0)-catalyzed cleavage[9] of the *N*-(allyloxy)carbonyl protecting group generated an intermediate amino cyclohexadienone that underwent cyclization to provide an inseparable mixture (1.4:1 by ^1H NMR) of diastereomeric hydroindolenones **23** and **24**. Unfortunately, efforts to enhance this ratio in favor of one of the diastereomers by acid-catalyzed equilibration were unsuccessful. Although one might envisage that the placement of other chiral auxiliaries on the nitrogen atom could lead to improved

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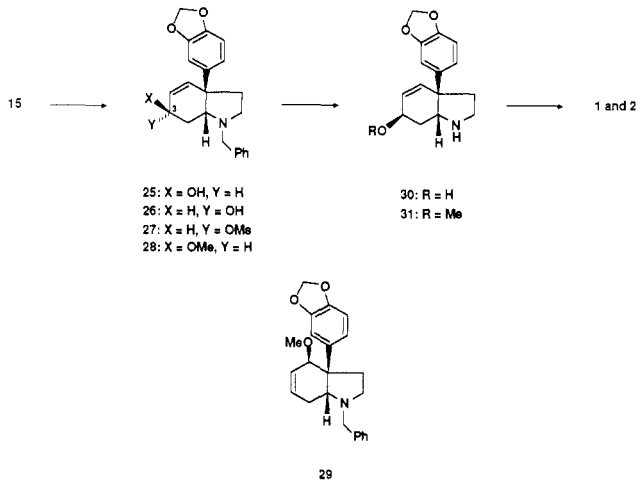
Scheme IV



asymmetric induction in this cyclization, no further possibilities were examined.

Returning to the central task at hand, attention was focused upon the remaining steps required to complete the transformation of hydroindolenone **15** into (±)-crinine (**1**) and (±)-buphanisine (**2**). Despite numerous efforts, it was not possible to define suitable conditions for effecting the highly stereoselective 1,2-reduction of the enone moiety present in **15** to give the allylic alcohol **25**, which possesses the hydroxyl group at C(3) in the requisite β-orientation. The hydride reduction of **15** afforded mixtures of **25** and **26**, the latter generally being the major component although the ratios of the two varied significantly according to the hydride reagent employed. For example, when **15** was treated with diisobutylaluminum hydride (DIBAL), a mixture of **25** and **26** (1:10) was obtained, whereas reduction of **15** with lithium aluminum hydride or sodium borohydride under a variety of conditions provided mixtures of **25** and **26** that ranged in composition from 1:1.6 to 2.3. Interestingly, reaction of **15** with alane in THF gave a mixture of **25** and **26**, in which the former possessing the correct β-configuration at C(3) was slightly preferred (1.3–1.5:1).

Since extensive experimentation did not yield a satisfactory technique for achieving the highly stereoselective reduction of **15** to give **25**, efforts were redirected toward development of a tactic to invert the configuration at C(3) of the undesired alcohol **26**. Although the Mitsunobu protocol[11] had been recently exploited for effecting the inversion of a related alcohol in a synthesis of elwesine (dihydrocrinine),[4l] subjection of **26** to these and similar conditions afforded mixtures of products. Attempts to exploit solvolytic pathways were also unavailing as dissolution of the unstable allylic mesylate **27**, which was prepared by treating **26** with methanesulfonic anhydride in the presence of triethylamine, in 2% aqueous sodium bicarbonate gave a mixture (ca. 1:1) of **25** and **26**. The problem was ultimately resolved by allowing **27** to react with cesium acetate in DMF[12] followed by saponification of the intermediate allylic acetates with methanolic potassium carbonate. This procedure furnished **25** in 75% overall yield together with lesser amounts (<10%) of starting alcohol **26**. Inasmuch as mesylate **27** appeared by TLC to have been formed quantitatively, production of the acetate derivative of **26** was presumably a consequence of a competing S_N1 process (Scheme IV).

The task of accessing an intermediate suitable for the total synthesis of (±)-buphanisine (**2**) proved to be a simpler one. Namely, methanolysis (MeOH, K_2CO_3) of the allylic mesylates that were obtained upon treatment of a mixture of **25** and **26** with methanesulfonic anhydride furnished the desired allylic ether **28** in 75% yield. Although none of the allylic ether epimeric with **28** at C(3) was isolated from this process, a regioisomeric allylic ether, which was tenatively identified as **29**, was unexpectedly formed as a minor product (<10%). The reason(s) for the significant difference observed in the stereochemical outcome of the solvolyses of the allylic mesylates derived from **25** and **26** in water and in methanol is (are) not readily apparent, and any speculation on this point is presently premature. Nevertheless, the stereo- and regiochemical outcome of the methanolyses of these two mesylates to give **28** is consistent with a working model that involves preferential attack by methanol upon an intermediate allylic carbocation in a pseudoaxial sense[3b,6c,d,13] at the less hindered terminus of the allylic array from the convex (exo) face of the *cis*-3a-hydroindole.

At this juncture, completion of the syntheses of (±)-crinine (**1**) and (±)-buphanisine (**2**) merely required removal of the *N*-benzyl protecting groups from **25** and **28** and subsequent cyclization of the resulting secondary amines **30** and **31** by a classical Pictet–Spengler protocol. Thus, reaction of **25** with α-chloroethyl chloroformate (ACE-Cl)[14] in the presence of 1,8-bis(dimethylamino)-naphthalene (Proton Sponge) followed by heating the resulting crude carbamate in methanol at reflux gave **30** in 85% yield. A slightly improved two-step procedure was also developed for effecting this conversion. This process entailed prior protection of the allylic alcohol of **25** as its *tert*-butyldimethylsilyl ether (**25**, TBDMSOTf,[15] *i*-Pr_2EtN, CH_2Cl_2) followed by sequential treatment with ACE-Cl and then methanol at reflux to deliver **30** in 94% overall yield. Similarly, *N*-debenzylation of **28** to furnish **31** was directly achieved in virtually quantitative yield through the agency of ACE-Cl. Subjection of the crude secondary amines **30** and **31** to the action of 37% aqueous formaldehyde in the presence of 6 N aqueous HCl completed the construction of the B ring and provided (±)-crinine (**1**) and (±)-buphanisine (**2**) in 85% and 71% overall yields from **25** and **28**, respectively. The synthetic (±)-crinine and (±)-buphanisine thus obtained were spectroscopically identical (^1H and ^{13}C NMR, IR, MS, TLC) with authentic samples.[16]

Thus, our general procedure for the facile elaboration of a quaternary carbon atom at the carbonyl carbon of a ketone function has been exploited in the design and execution of remarkably concise total syntheses of the Amaryllidaceae alkaloids (±)-crinine (**1**) and (±)-buphanisine (**2**), the latter of which has not previously succumbed to total synthesis. Further extensions of this and related methods to problems in the natural products area are the subject of current investigations and will be recorded in due course.

Experimental Section

General. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected. Diethyl ether (Et_2O),

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(13) Goering, H. L. *Rec. Chem. Prog.* **1960**, *21*, 109.
(14) Olofson, R. A.; Senet, J.-P.; Martz, J. T.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(15) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(16) We thank Professor L. E. Overman (UC Irvine) and Dr. H. M. Fales (NIH) for providing generous samples of authentic (−)-crinine and (−)-buphanisine.

tetrahydrofuran (THF), and benzene were distilled from either sodium- or potassium/benzophenone ketyl immediately prior to use. Methanol (MeOH) was distilled from magnesium methoxide, and dimethylformamide (DMF) was distilled from barium oxide. Triethylamine, diisopropylamine, acetonitrile, chloroform, and methylene chloride were distilled from calcium hydride and stored under nitrogen. All reactions involving organometallic reagents or other moisture-sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven-dried glassware. IR and NMR spectra were determined as solutions in $CHCl_3$ and $CDCl_3$, unless otherwise specified. Low resolution mass spectra were obtained at an ionization voltage of 70 eV. Preparative high performance liquid chromatography (HPLC) was performed on either a Waters Prep LC 500 instrument (sample size >500 mg) or on a Waters 6000A solvent delivery system equipped with a Model U6K injector and two Porasil A columns (0.6 m × 7.8 mm) (sample size < 500 mg). Unless otherwise specified, column chromatography was conducted by using Brinkmann silica gel G using the indicated ratio of hexane or Skelly B and ethyl acetate (EtOAc) as solvent. Bulb-to-bulb distillations were executed in a Kugelrohr apparatus. Spectra and yields are reported for samples judged to be ≥95% homogeneous by chromatography (GLC or HPLC).

[(Allyloxy)carbonyl]benzyl(2-bromoethyl)amine (10). A flask containing a solution of *N*-benzylethanolamine (10.00 g, 66.1 mmol) in 48% HBr (23.50 g, 139 mmol) was heated at 150–155 °C (oil bath temperature) for 4 h, during which time the head temperature rose to 110–120 °C and water (ca. 12 mL) had been removed by distillation. Upon cooling to room temperature, the white solid that formed was isolated by suction filtration to yield 19.25 g (98%) of benzylbromoethylammonium bromide that was utilized in the subsequent reaction without further purification. A portion of this salt (5.00 g, 16.78 mmol) was dissolved with stirring in a two-phase mixture of H_2O/Et_2O (1:1, 120 mL) containing K_2CO_3 (2.43 g, 17.6 mmol) at 0 °C. A second portion of K_2CO_3 (2.43 g, 17.6 mmol) was then added followed by the dropwise addition of allyl chloroformate (2.38 g, 19.8 mmol). The resultant mixture was stirred at 0 °C for 30 min, whereupon the layers were separated. The aqueous phase was extracted with Et_2O (2 × 40 mL), and the combined Et_2O phases were washed with H_2O (2 × 50 mL), saturated NaCl (1 × 75 mL), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure followed by chromatography on SiO_2 (50 g, 9:1 Skelly B/EtOAc) yielded 4.34 g (86%) of **10** as a clear colorless oil that underwent cyclization to form an oxazolidinone upon attempted distillation: ^{1}H NMR (90 MHz) δ 7.28 (br s, 5 H), 6.0 (m, 1 H), 5.27 (br t, *J* = 10 Hz, 2 H), 4.56 (dd, *J* = 1, 9 Hz, 2 H), 4.51 (s, 2 H), 3.50 (br m, 4 H); ^{13}C NMR (20 MHz) δ 155.3, 137.0, 132.3, 128.2, 127.1, 117.0, 65.8, 50.9, 48.3 and 48.0, 28.5; IR (film) 1710 cm^{-1}; mass spectrum, *m/e* 299, 297.0353 ($C_{13}H_{16}NO_2{}^{79}Br$ requires 297.0364), 258/256, 214/212, 177, 168, 132, 122/120, 104, 91 (base), 65, 41.

2-[2-[[(Allyloxy)carbonyl]benzylamino]ethyl]-2-[3,4-(methylenedioxy)phenyl]-5-oxohexanal (11). To a well stirred solution of *n*-butyllithium (2.98 M in hexane) (4.66 mL, 13.89 mmol) in THF (45 mL) at −78 °C was added dropwise a solution of diethyl (benzylidineamino)methylphosphonate (3.68 g, 14.43 mmol) in THF (10 mL). The resulting solution was stirred at −78 °C for 1 h after which **8**[6d] (2.93 g, 11.1 mmol) in THF (10 mL) was slowly added, and stirring was continued at −78 °C for an additional 30 min. The cold bath was removed, and the solution was allowed to warm to room temperature (ca. 1 h) and then heated at reflux for 2 h. The resulting dark solution of 2-azadiene was cooled to −78 °C, and *n*-butyllithium (4.66 mL, 13.89 mmol) was added slowly. After stirring at −78 °C for 1 h, a solution of **10** in THF (10 mL) was slowly added, and the resulting solution was allowed to gradually warm to room temperature and then stirred for 10 h. To the flask was added 3 N HCl (80 mL), and the heterogeneous mixture was stirred vigorously for 4 h at which time saturated NaCl (150 mL) and Et_2O (100 mL) were added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organics were sequentially washed with 1 N HCl (3 × 150 mL), saturated $NaHCO_3$ (2 × 150 mL), and saturated NaCl (1 × 250 mL) and dried ($MgSO_4$). Evaporation of the excess solvents under reduced pressure followed by chromatography on SiO_2 [80 g, gradient elution (Skelly B to 30% EtOAc/Skelly B in 10% increments)] returned 4.15 g (83%) of **11** as a clear yellow dense oil which could not be distilled: ^{1}H NMR (90 MHz) δ 9.40 (s, 1 H), 7.19 (comp, 5 H), 6.95–6.52 (comp, 3 H), 5.98 (s, 2 H), 6.10–5.75 (m, 1 H), 5.27 (m, 2 H), 4.65 (d, *J* = 7 Hz, 2 H), 4.43 (s, 2 H), 3.30–2.70 (m, 2 H), 2.35–1.75 (comp, 9 H); ^{13}C NMR (90 MHz) δ 206.8, 200.5, 155.6, 148.3, 146.8, 137.3, 132.7, 131.0, 128.3, 127.7, 127.3, 120.5, 117.3, 108.3, 107.3, 101.0, 65.9, 54.7, 50.6, 48.2, 42.0, 37.5, 29.7, 29.6, 25.3; IR 2885, 1725, 1705 cm^{-1}; mass spectrum, *m/e* 451.1984 ($C_{26}H_{29}NO_6$ requires 451.1995), 423, 365 (base), 374, 324, 215, 204, 174, 149, 131, 91.

4-[2-[[(Allyloxy)carbonyl]benzylamino]ethyl]-4-[3,4-(methylenedioxy)phenyl]-2-cyclohexenone (12). A solution of **11** (2.07 g, 4.59 mmol) in MeOH (22 mL) and 33% aqueous HOAc containing freshly distilled pyrrolidine (424 mg, 6.0 mmol) was stirred at room temperature for 24 h after which time 1 N HCl (25 mL) was added, and stirring was continued for 30 min. Saturated NaCl (50 mL) and Et_2O (50 mL) were added and the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organics were washed sequentially with 1 N HCl (2 × 40 mL), H_2O (2 × 50 mL), saturated $NaHCO_3$ (2 × 75 mL), and saturated NaCl (1 × 100 mL) and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure followed by chromatography on SiO_2 [10 g, gradient elution (Skelly B to 40% EtOAc/Skelly B, 10% increments)] returned 1.70 g (85%) of pure **12** as a dense yellow oil which could not be distilled: ^{1}H NMR (90 MHz) δ 7.40–7.00 (comp, 5 H), 6.91 (d, *J* = 10 Hz, 1 H), 6.75–6.47 (comp, 3 H), 6.05 (d, *J* = 10, 1H), 5.90 (s, 2 H), 6.10–5.70 (m, 1 H), 5.39–5.10 (m, 2 H), 4.58 (d, *J* = 7 Hz, 2 H), 4.35 (s, 2 H), 3.06 (br t, *J* = 8 Hz, 2 H), 2.40–1.75 (comp, 6 H); ^{13}C NMR (90 MHz) δ 198.5, 155.7, 153.8, 148.1, 146.3, 137.4, 136.3, 132.8, 129.4, 128.5, 127.4, 127.0, 119.8, 117.4, 108.0, 106.8, 101.0, 66.0, 50.7, 43.1, 42.5, 38.9, 38.7, 36.2, 34.2; IR 1705 cm^{-1}; mass spectrum, *m/e* 433.1879 ($C_{26}H_{27}NO_5$ requires 433.1889), 215 (base), 204, 91.

4-[2-[[(Allyloxy)carbonyl]benzylamino]ethyl]-4-[3,4-(methylenedioxy)phenyl]cyclohexadienone (14). To a solution of **12** (2.80 g, 6.47 mmol) in anhydrous EtOAc (215 mL) containing concentrated H_2SO_4 (0.16 mL) at room temperature was added phenyltrimethylammonium perbromide (3.16 g, 8.41 mmol) in a single portion, and the resulting orange solution was stirred for 20 h in the dark. Saturated $NaHCO_3$ (150 mL) was then added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (1 × 200 mL) and saturated NaCl (1 × 200 mL) and dried ($MgSO_4$). Excess solvent was removed under reduced pressure to afford 4.00 g of the crude α′-bromo enone, which was immediately redissolved in anhydrous benzene (215 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.92 g, 32.35 mmol), and the resulting solution was heated at reflux for 17 h. After being cooled to room temperature, benzene was removed under reduced pressure, and the residue was partitioned between EtOAc (120 mL) and 1 N HCl (2 × 100 mL). The combined acidic washes were back-extracted with EtOAc (2 × 75 mL), and the combined EtOAc layers were washed with saturated $NaHCO_3$ (2 × 100 mL) and saturated NaCl (1 × 150 mL) and dried ($MgSO_4$). Evaporation of solvent under reduced pressure followed by chromatography of the residue by preparative HPLC, eluting with Skelly B/EtOAc (12:1), afforded 1.98 g (71%) of **14** as a dense, translucent yellow oil: ^{1}H NMR (90 MHz) δ 7.30 (br s, 5 H), 6.80 (d, *J* = 10 Hz, 2 H), 6.75 (s, 3 H), 6.33 (d, *J* = 10 Hz, 2 H), 5.95 (m, 1 H), 5.95 (s, 2 H), 5.34 (br t, J = 8 Hz, 2 H), 4.70 (br d, *J* = 5 Hz, 2 H), 4.48 (br s, 2 H), 3.19 (br m, 2 H), 2.23 (br m, 2 H; ^{13}C NMR (90 MHz) δ 185.4, 155.7, 152.9, 148.2, 147.0, 137.4, 132.8 (2 C's), 128.6, 127.6, 119.5, 117.6, 108.5, 106.9, 101.2, 66.2, 51.2, 47.1, 43.8, 35.6; IR 1690, 1668, 1625 cm^{-1}; mass spectrum, *m/e* 431.1741 ($C_{26}H_{25}NO_5$ requires 431.1733), 245, 227, 218, 213, 204 (base), 197, 185, 169, 131, 91, 41.

(3a*S,7a*R**)-*N*-Benzyl-3a-[3,4-(methylenedioxy)-phenyl]-2,3,3a,6,7,7a-hexahydro-1*H*-indol-6-one (15).** A solution of **14** (1.95 g, 4.52 mmol) in CH_2Cl_2 (90 mL) containing 2-ethylhexanoic acid (1.56 g, 10.9 mmol), tetrakis(triphenylphosphine)palladium(0) (104 mg, 0.09 mmol), and triphenylphosphine (107 mg, 0.41 mmol) was stirred at room temperature for 24 h. The solvent was then removed under reduced pressure, and the resulting yellow residue was partitioned between Et_2O (15 mL) and 1 N HCl (3 × 10 mL). The combined acidic extracts

were made basic by addition of solid K_2CO_3 (pH ca. 9) and then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue (1.50 g) was purified by chromatography on SiO_2 [15 g, gradient elution (Skelly B to 15% EtOAc, 5% increments)] to deliver 1.37 g (87%) of **15** as a clear colorless oil which solidified upon standing. Recrystallization from 10% EtOAc/hexane provided white crystalline material, mp 99–99.5 °C: ^{1}H NMR (500 MHz) δ 7.30–7.21 (comp, 5 H), 6.87 (d, J = 1.8 Hz, 1 H), 6.81 (dd, J = 1.8, 8.1 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.68 (dd, J = 2.0, 10.1 Hz, 1 H), 6.11 (d, J = 10.1 Hz, 1 H), 5.97 (s, 2 H), 4.06 (d, J = 13.0 Hz, 1 H), 3.22 (d, J = 13.0 Hz, 1 H), 3.08 (br m, 1 H), 3.03 (br m, $W_{1/2}$ = 8 Hz, 1 H), 2.67 (dd, J = 3.1, 16.6 Hz, 1 H), 2.54 (dd, J = 3.1, 16.6 Hz, 1 H), 2.50 (q, J = 8.6 Hz, 1 H), 2.38 (m, 1 H), 2.09 (dt, J = 13.4, 7.9 Hz, 1 H); ^{13}C NMR (90 MHz) δ 197.4, 152.7, 148.2, 146.6, 138.8, 136.7, 128.6, 128.4, 127.1, 126.9, 119.9, 108.1, 107.2, 101.1, 71.03, 57.6, 52.3, 51.1, 38.4, 36.8; IR 1700 cm^{-1}; mass spectrum, m/e 347.1502 ($C_{22}H_{21}NO_3$ requires 347.1521), 214, 146, 91 (base).

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.05; H, 6.14; N, 4.10.

Aluminum Hydride Reduction of Indolone 15. To a solution of freshly generated AlH_3 in THF (ca. 0.6 M) (10 mL, 6 mmol) at 0 °C was slowly added a solution of **15** (320 mg, 0.92 mmol) in THF (2 mL). The resulting mixture was stirred at 0 °C for 2 h, whereupon the reaction was quenched by the slow addition of THF/H_2O (1:1 v/v, 5 mL). The mixture was warmed to room temperature, and 13% NaOH (2.5 mL) was added with stirring. The clear supernatant was decanted from the white, gelatinous solid, which was then washed thoroughly with EtOAc (3 × 20 mL). The combined organics were washed with saturated NaCl (1 × 30 mL) and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure to provide a mixture (283 mg) of the epimeric allylic alcohols **25** and **26**, which were separated by semipreparative HPLC (20% EtOAc/hexane, 1% triethylamine) to yield 149 mg (47%) of **25** as a foamy solid and 99 mg (31%) of **26** as a white solid.

For (3a*S,6*R**,7a*R**)-*N*-benzyl-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole (25)**: ^{1}H NMR (500 MHz) δ 7.22–7.31 (comp, 5 H), 6.88 (d, J = 1.9 Hz, 1 H), 6.83 (dd, J = 1.9, 8.1 Hz, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.85 (dt, J = 10.1, 1.6 Hz, 1 H), 5.65 (dt, J = 10.1, 1.6 Hz, 1 H), 4.48–4.51 (br m, $W_{1/2}$ = 20 Hz, 1 H), 4.09 (d, J = 13.1 Hz, 1 H), 3.17 (d, J = 13.1 Hz, 1 H), 3.06 (dt, J = 2.0, 8.6 Hz, 1 H), 2.61 (br s, $W_{1/2}$ = 8 Hz, 1 H), 2.32 (q, J = 8.9 Hz, 1 H), 2.26 (ddd, J = 2.1, 8.8, 13.2 Hz, 1 H), 2.20 (m, 1 H), 1.94 (dt, J = 13.2, 8.8 Hz, 1 H), 1.45 (ddd, J = 2.6, 10.5, 13.4 Hz, 1 H); ^{13}C NMR (90 MHz) δ 147.6, 145.8, 141.0, 139.3, 134.6, 129.1, 128.6, 128.2, 126.8, 120.2, 107.7, 107.6, 100.9, 71.2, 64.1, 58.3, 53.1, 49.7, 39.07, 30.6; IR 3340, 3030, 2940, 2800, 1620 cm^{-1}; mass spectrum, m/e 349.1686 ($C_{22}H_{23}NO_3$ requires 349.1678), 331, 279, 210, 198, 188, 146, 91 (base), 65.

For (3a*S,6*S**,7a*R**)-*N*-benzyl-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole (26)**: mp 147–147.5 °C; ^{1}H NMR (500 MHz) δ 7.24–7.34 (comp, 5 H), 6.84 (d, J = 1.7 Hz, 1 H), 6.78 (dd, = 1.7, 8.2 Hz, 1 H), 6.75 (d, J = 8.2, 1 H), 6.16 (ddd, J = 1.0, 5.3, 10.0 Hz, 1 H), 5.94 (s, 2 H), 5.72 (dd, J = 1.3, 10.0 Hz, 1 H), 5.50 (br s, 1 H), 4.32 (d, J = 12.5 Hz, 1 H), 4.08 (br m, $W_{1/2}$ = 10.5 Hz, 1 H), 3.13 (d, J = 12.5 Hz, 1 H), 3.11 (m, 1 H), 2.85 (br s, $W_{1/2}$ = 8 Hz, 1 H), 2.44 (dt, J = 8.4, 8.1 Hz, 1 H), 2.32 (ddd, J = 4.4, 8.2, 13.2 Hz, 1 H), 2.28 (br d, J = 14.9 Hz, 1 H), 1.99 (dt, J = 13.2, 8.2 Hz, 1 H), 1.72 (ddd, J = 2.6, 3.6, 14.9 Hz, 1 H); ^{13}C NMR (90 MHz) δ 147.8, 146.0, 139.8, 138.2, 134.2, 128.8, 128.4, 128.2, 127.2, 119.9, 107.9, 107.3, 101.0, 71.7, 63.2, 59.1, 53.1, 50.0, 38.9, 27.2; IR 3310, 3025, 2815, 1615 cm^{-1}; mass spectrum, m/e 349.1669 ($C_{22}H_{23}NO_3$ requires 349.1678), 331, 279 (base), 146, 91.

Conversion of 26 into 25. To a well-stirred solution of **26** (69 mg, 0.197 mmol) and triethylamine (100 mg, 1.0 mmol) in THF (3 mL) at 0 °C was slowly added freshly prepared methanesulfonic acid anhydride (172 mg, 0.99 mmol) in THF (2 mL), and the reaction was stirred at 0 °C for 30 min. The solvent was removed at 0 °C under reduced pressure, the residue was dissolved in DMF and transferred via syringe to a flask containing freshly prepared cesium acetate (568 mg, 2.96 mmol), and the resulting suspension was stirred at room temperature for 40 h. The solids were removed by suction filtration and washed thoroughly with EtOAc (3 × 5 mL). The combined filtrates and washings were concentrated under reduced pressure to afford a residue that was dissolved in 1 N HCl (6 mL), and the aqueous solution was washed with Et_2O (2 × 10 mL). The aqueous phase was rendered basic with solid K_2CO_3 (pH ca 9) and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to yield 73 mg of the crude allylic acetate which was immediately dissolved in MeOH (5 mL) containing powdered K_2CO_3 (250 mg). The resulting mixture was stirred at room temperature for 2 h, whereupon the MeOH was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (10 mL), which was washed with saturated $NaHCO_3$ (2 × 7 mL), and the combined aqueous washes were back-extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by semipreparative HPLC (20% EtOAc/hexane, 1% triethylamine) to give 53 mg (75%) of **25** together with 5 mg (7%) of **26**.

(3a*S,6*R**,7a*R**)-*N*-Benzyl-3a-[3,4-(methylenedioxy)phenyl]-6-[(*tert*-butyldimethylsilyl)oxy]-2,3,3a,6,7,7a-hexahydro-1*H*-indole.** To a stirred solution of **25** (148 mg, 0.42 mmol) and diisopropylethylamine (109 mg, 0.85 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was added *tert*-butyldimethylsilyl triflate (168 mg, 0.64 mmol), and the reaction was stirred at 0 °C for 45 min. The volume was reduced to ca. 0.5 mL under reduced pressure, and the residue was transferred to a column of silica gel (3 g). The column was then eluted with hexane (8 × 3 mL) and then 5% EtOAc/hexanes (6 × 3 mL), and fractions 8–14 were combined and concentrated under reduced pressure to afford 184 mg (94%) of the silyl ether as a clear colorles oil: ^{1}H NMR (500 MHz) δ 7.23–7.35 (comp, 5 H), 6.90 (d, J = 1.9 Hz, 1 H), 6.85 (dd, J = 1.9, 8.1 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.77 (dt, J = 10.2, 1.4 Hz, 1 H), 5.59 (dt, J = 10.2, 1.4 Hz, 1 H), 4.56 (br m, $W_{1/2}$ = 19.9 Hz, 1 H), 4.09 (d, J = 13.0 Hz, 1 H), 3.13 (d, J = 13.0 Hz, 1 H), 3.03 (t, J = 9.2 Hz, 1 H), 2.57 (br s, $W_{1/2}$ = 7.9 Hz, 1 H), 2.22–2.33 (comp, 2 H), 2.06 (m, 1 H), 1.89–1.95 (m, 1 H), 1.55 (ddd, J = 2.5, 2.8, 12.1 Hz, 1 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (90 MHz) δ 147.5, 145.7, 141.4, 139.2, 133.8, 130.1, 128.8, 128.3, 126.9, 120.3, 107.8, 107.6, 100.9, 72.0, 64.8, 59.4, 53.3, 49.4, 39.2, 30.7, 26.0, 18.36, −4.45 and −4.57; mass spectrum, m/e 463.2531 ($C_{28}H_{37}NO_3Si$ requires 463.2543), 279 (base), 188, 147, 146, 91, 75.

(3a*S,6*R**,7a*R**)-3a-[3,4-(Methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole (30). Method A.** A solution of the β-silyloxyindole prepared above (155 mg, 0.33 mmol) in anhydrous 1,2-dichloroethane (5 mL) containing α-chloroethyl chloroformate (ACE-Cl) (144 mg, 1.0 mmol) was stirred at 0 °C for 10 min and then heated at a gentle reflux for 2 h. The solvent and excess ACE-Cl were evaporated under reduced pressure, and the residue was dissolved in MeOH (5 mL) and heated at reflux for 1 h. The MeOH was evaporated under reduced pressure, and the residue was partitioned between 1 N HCl (6 mL) and Et_2O (2 × 10 mL). The aqueous phase was rendered basic with concentrated NH_4OH (pH ca. 10) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield **30** as a white foamy solid (86 mg, ca. 100%): ^{1}H NMR (360 MHz) δ 6.89 (d, J = 1.6 Hz, 1 H), 6.84 (dd, J = 1.6, 8.2 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 5.92 (s, 2 H), 5.89 (d, J = 10.4 Hz, 1 H), 5.62 (d, J = 10.4 Hz, 1 H), 4.38 (br m, $W_{1/2}$ = 21.0 Hz, 1 H), 3.32 (br s, $W_{1/2}$ = 10.0 Hz, 1 H), 3.06 (t, J = 6.9 Hz, 2 H), 2.70–2.91 (br m, 1 H), 2.45 (dt, J = 12.9, 6.9 Hz, 1 H), 2.12 (dt, J = 13.2, 4.1 Hz, 1 H), 1.94 (dt, J = 12.9, 6.9 Hz, 1 H), 1.58 (ddd, J = 4.1, 9.7, 13.2 Hz, 1 H); ^{13}C NMR (90 MHz) δ 147.7, 145.9, 139.8, 134.3, 130.2, 119.8, 107.8, 107.4, 100.9, 64.7, 63.0, 49.9, 45.8, 40.7, 33.0; mass spectrum, m/e 259.1202 ($C_{15}H_{17}NO_3$ requires 259.1208), 241, 216, 189, 120, 91, 85, 83, 77, 56 (base).

Method B. To a solution of **25** (89 mg, 0.25 mmol) and 1,8-bis(dimethylamino)naphthalene (Proton Sponge) (68 mg, 0.32 mmol) in anhydrous 1,2-dichloroethane (5 mL) at 0 °C was added ACE-Cl (145 mg, 0.10 mmol), and the resulting solution was stirred at 0 °C for 15 min and then at reflux for 3 h. The volume was reduced to ca. 1 mL, and cold EtOAc (10 mL) was added. The organic phase was then washed with cold 0.25 N HCl (2 × 5 mL), cold saturated $NaHCO_3$ (1 × 7 mL), and cold saturated NaCl (1

× 7 mL) and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure yielded a dense yellow oil that was immediately redissolved in MeOH (5 mL) and heated at reflux for 2 h. The MeOH was evaporated under reduced pressure to yield a yellow oil which was partitioned between 1 N HCl (5 mL) and Et_2O (2 × 5 mL). The aqueous phase was made basic by the dropwise addition of concentrated NH_4OH (pH ca. 10) and then extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue (66 mg) was purified by column chromatography (3 g of Al_2O_3, 10% MeOH/$CHCl_3$) to return 55 mg (85%) of **30**.

(±)-Crinine (1). Compound **30** (86 mg, 0.33 mmol) was dissolved in a mixture of MeOH (0.4 mL) and 37% aqueous formaldehyde (0.9 mL), and after stirring at room temperature for 5 min, 6 N HCl (25 mL) was added and stirring continued for 2 h. The aqueous solution was washed with Et_2O (2 × 20 mL), rendered alkaline by the slow addition of solid K_2CO_3 (pH ca. 10), and extracted with $CHCl_3$ (3 × 15 mL). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 120 mg of crude **1**, which was purified by column chromatography on SiO_2 [1.5 g, gradient elution ($CHCl_3$ to 20% MeOH/$CHCl_3$, 5% increments)] to afford 72 mg (85%) of (±)-**1** as white solid. Recrystallization from acetone afforded white crystals, mp 172.5–174 °C (lit.[3a] mp 174–175 °C), and the synthetic material proved to be spectroscopically identical with an authentic sample:[16] ^1H NMR (500 MHz) δ 6.85 (s, 1 H), 6.59 (d, J = 10.0 Hz, 1 H), 6.48 (s, 1 H), 5.96 (ddd, J = 1.1, 5.3, 10.0 Hz, 1 H), 5.89 (dd, J = 1.4, 7.7 Hz, 2 H), 4.40 (d, J = 16.8, 1 H), 4.35 (br m, $W_{1/2}$ = 13.0 Hz, 1 H), 3.78 (d, J = 16.8 Hz, 1 H), 3.33–3.40 (comp, 2 H), 2.89 (ddd, J = 5.9, 9.1, 12.9 Hz, 1 H), 2.16 (ddd, J = 4.3, 9.1, 12.1 Hz, 1 H), 1.98 (m, 1 H), 1.93 (ddd, J = 5.9, 10.6, 12.1 Hz, 1 H), 1.74 (dt, J = 4.1, 13.6 Hz, 1 H); ^{13}C NMR (90 MHz) δ 146.1, 145.7, 138.3, 132.4, 128.3, 127.4, 126.4, 107.0, 102.8, 100.8, 64.2, 62.8, 62.4, 53.6, 44.3, 32.7; mass spectrum, m/e 271, 228, 199 (base), 187, 157, 128, 115, 77, 56.

(3a*S,6*R**,7a*R**)-*N*-Benzyl-3a-[3,4-(methylenedioxy)-phenyl]-6-methoxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole (28).** To a stirred suspension of $LiAlH_4$ (17 mg, 0.45 mmol) in THF (1.5 mL) at 0 °C was added a solution of **15** (52 mg, 0.15 mmol) in THF (1.5 mL), and the resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by the sequential addition of H_2O (5 drops) and 10% NaOH (1 mL). The solids were removed by suction filtration through a pad of Celite, and the flask and Celite pad were washed with EtOAc (2 × 5 mL). The filtrates were diluted with saturated aqueous NaCl (5 mL) and the layers separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The organics were combined and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure to yield 51 mg (98%) of a mixture (1:1.5) of **25** and **26**, which was redissolved in THF (3.5 mL) containing triethylamine (103 mg, 1.02 mmol) at 0 °C. A solution of freshly prepared methanesulfonic acid anhydride (178 mg, 1.02 mmol) in THF (1 mL) was then added with stirring, and after 30 min MeOH (4.0 mL) was added dropwise and the stirring continued at 0 °C for 30 min and then at room temperature for 48 h. The volume was reduced to approximately 2 mL under reduced pressure, and Et_2O (10 mL) was added. The ethereal solution was washed with 1 N HCl (2 × 8 mL), and the combined acidic washes were made basic with solid Na_2CO_3 (pH ca. 10) and then extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the crude mixture thus obtained was separated by semipreparative HPLC (20% EtOAc/hexane) to afford 40 mg (75%) of **28** as a clear oil, which solidified upon standing, together with an isomeric allylic ether tentatively assigned as being **29** (4 mg, 7%). An analytical sample of **28** was prepared by recrystallization from hexane to provide white crystalline material; mp 100–100.5 °C.

For 28: mp 100–100.5 °C; ^1H NMR (360 MHz) δ 7.23–7.35 (comp, 5 H), 6.89 (d, J = 1.7 Hz, 1 H), 6.85 (dd, J = 1.7, 8.1 Hz, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 5.93 (s, 2 H), 5.92 (d, J = 10.0 Hz, 1 H), 5.68 (d, J = 10.0 Hz, 1 H), 4.05 (d, J = 13.2 Hz, 1 H), 4.05 (m, 1 H), 3.36 (s, 3 H), 3.25 (d, J = 13.2 Hz, 1 H), 3.10 (dt, J = 2.0, 8.6 Hz, 1 H), 2.60 (br s, $W_{1/2}$ = 8.6 Hz, 1 H), 2.37 (q, J = 8.6 Hz, 1 H), 2.28 (ddd, J = 2.0, 8.4, 13.2 Hz, 1 H), 2.18 (m, 1 H), 1.95 (dt, J = 13.2, 8.4 Hz, 1 H), 1.45 (ddd, J = 2.2, 10.3, 13.2 Hz, 1 H); ^{13}C NMR (90 MHz) δ 147.6, 145.8, 140.9, 139.4, 134.9, 128.7, 128.2, 126.8, 126.4, 120.2, 107.7, 107.6, 100.9, 72.6, 71.7, 58.5, 55.6, 53.4, 50.0, 38.9, 25.6; mass spectrum, m/e 363.1828 ($C_{23}H_{25}NO_3$ requires 363.1834), 279, 146, 91 (base).

For (3a*S,4*R**,7a*R**)-*N*-Benzyl-3a-[3,4-(methylenedioxy)phenyl]-4-methoxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole (29):** ^1H NMR (360 MHz) δ 7.17–7.34 (comp, 5 H), 6.93 (d, J = 1.7 Hz, 1 H), 6.88 (dd, J = 1.7, 8.5 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 5.90–6.00 (comp, 4 H), 3.85 (d, J = 12.6 Hz, 1 H), 3.84 (s, 1 H), 3.37 (d, J = 12.6 Hz, 1 H), 3.18 (s, 3 H), 3.13 (m, 1 H), 2.78 (t, J = 8.6 Hz, 1 H), 2.20–2.38 (comp, 3 H), 1.92–2.10 (m, 2 H); ^{13}C NMR (125 MHz) δ 147.6, 145.5, 143.1, 139.7, 130.3, 128.6, 128.11, 127.8, 126.7, 119.5, 107.8, 107.5, 100.9, 85.7, 71.6, 58.6, 58.3, 56.0, 51.7, 31.1, 27.5; mass spectrum, m/e 363.1839 ($C_{23}H_{25}NO_3$ requires 363.1834), 331, 279 (base), 188, 158, 130, 91.

(3a*S,6*R**,7a*R**)-3a-[3,4-(Methylenedioxy)phenyl]-6-methoxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole (31).** To a stirred solution of **28** (135 mg, 0.372 mmol) in anhydrous 1,2-dichloroethane (7.5 mL) at 0 °C was added ACE-Cl (160 mg, 1.1 mmol). After being stirred at 0 °C for 10 min, the solution was heated at a gentle reflux for 3 h, whereupon the solvent and excess ACE-Cl were removed under reduced pressure. The residue was dissolved in MeOH (7.5 mL), the solution was heated at 50 °C overnight, the solvent was evaporated under reduced pressure, and the residue was partitioned between 1 N HCl (5 mL) and Et_2O (3 × 5 mL). The aqueous phase was rendered alkaline (pH ca. 10) by the addition of concentrated NH_4OH and extracted with $CHCl_3$ (3 × 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide crude **31** (101 mg, ca. 100%) as a yellow oil, which was used immediately in the subsequent Pictet–Spengler reaction: ^1H NMR (360 MHz) δ 6.98 (d, J = 1.8 Hz, 1 H), 6.92 (dd, J = 1.8, 8.5 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 6.05 (d, J = 10.9 Hz, 1 H), 5.98 (s, 2 H), 5.74 (d, J = 10.9 Hz, 1 H), 4.08 (br m, $W_{1/2}$ = 21.5 Hz, 1 H), 3.49 (s, 3 H), 3.42 (d, J = 6.9 Hz, 1 H), 3.18 (t, J = 6.9 Hz, 2 H), 2.46 (dt, J = 13.3, 6.9 Hz, 1 H), 2.20 (dt, J = 13.3, 6.9 Hz, 1 H), 2.04 (dt, J = 13.4, 7.0 Hz, 1 H), 1.66 (ddd, J = 3.9, 9.8, 13.4 Hz, 1 H).

(±)-Buphanisine (2). A solution of crude **31** (101 mg, 0.37 mmol) in a mixture of MeOH (0.4 mL) and 37% aqueous formaldehyde (1 mL) was stirred for 3 min at room temperature, whereupon 6 N HCl (30 mL) was added and stirring was continued for 2.5 h. The aqueous solution was rendered alkaline (pH ca 10) by the addition of solid Na_2CO_3, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the **2** thus obtained was purified by chromatography on neutral Al_2O_3 (5 g, gradient elution, Skelly B to 35% EtOAc/hexanes, 3-mL fractions, eight fractions per increment) to deliver 75 mg (71%) of **2** as a clear oil which solidified upon standing. Recrystallization from hexane yielded (±)-**2** as white crystals, mp 100–101.5 °C, which was spectroscopically identical with an authentic sample:[16] ^1H NMR (500 MHZ) δ 6.84 (s, 1 H), 6.62 (d, J = 9.8 Hz, 1 H), 6.47 (s, 1 H), 5.97 (dd, J = 4.5, 9.8 Hz, 1 H), 5.88 (d, J = 8.7 Hz, 1 H), 5.86 (d, J = 8.7 Hz, 1 H), 4.41 (d, J = 16 Hz, 1 H), 3.83 (br m, $W_{1/2}$ = 11.3 Hz, 1 H), 3.27 (d, J = 16.0 Hz, 1 H), 3.31–3.40 (comp, 5 H), 2.90 (ddd, J = 6.3, 10.5, 14.8 Hz, 1 H), 2.17 (ddd, J = 5.3, 9.7, 14.8 Hz, 1 H), 2.08 (m, 1 H), 1.93 (dt, J = 6.3, 10.5 Hz, 1 H), 1.61 (dt, J = 3.4, 13.5 Hz, 1 H); ^{13}C NMR (90 MHz) δ 146.1, 145.7, 138.6, 132.9, 126.5, 125.4, 106.8, 102.9, 100.6, 72.4, 63.1, 62.5, 56.3, 53.6, 44.4, 29.0; mass spectrum, m/e 285.13598 (base) ($C_{17}H_{19}NO_3$ requires 285.13649), 270, 254, 215, 157, 115.

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Registry No. (±)-**1**, 7679-55-2; (±)-**2**, 111958-06-6; **8**, 92143-67-4; **10**, 111923-03-6; (±)-**11**, 111923-04-7; (±)-**12**, 111923-05-8; **14**, 111923-06-9; (±)-**15**, 111923-07-0; **16**, 3886-69-9; **17**, 114635-89-1; **18**, 114635-90-4; **19**, 80548-31-8; **20**, 114635-91-5; (4*R*)-**21**, 114635-93-7; (4*S*)-**21**, 114635-92-6; **22**, 114635-94-8; **23**, 114635-95-9; **24**, 114635-96-0; (±)-**25**, 111923-08-1; (±)-**25** (*tert*-butyldi-

methylsilyl ether), 114635-87-9; (±)-**26**, 111923-09-2; (±)-**28**, 111923-10-5; (±)-**29**, 114635-88-0; (±)-**30**, 111923-11-6; (±)-**31**, 111923-12-7; $HO(CH_2)_2NHCH_2Ph$, 104-63-2; $Br(CH_2)_2NHCH_2Ph \cdot HBr$, 33538-02-2; EtO_2CCH_2Br, 105-36-2.

Supplementary Material Available: Experimental details and spectral information for other new compounds not described in the present Experimental Section (3 pages). Ordering information is given on any current masthead page.

Synthesis of (Allyloxy)methyl-Substituted Diaza-18-crown-6 Compounds for Attachment to Silica Gel

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(Allyloxy)methyl-substituted *N,N'*-dibenzyldiaza-18-crown-6 was prepared by five different processes. A simple Okahara ring closure of an (allyloxy)methyl-substituted diazahexaethylene glycol proved to be the most convenient method. The corresponding *N,N'*-dihexyl- and *N,N'*-diethyldiaza-18-crown-6 compounds were also prepared. These (allyloxy)methyl-substituted crown compounds were covalently bonded to silica gel by first forming a diethoxymethylsilane containing the crown and coating this silane material onto silica gel and heating. The new silica gel–crown material separated Hg(II) ions from Cd(II) and Zn(II) when an aqueous solution of pH 2 containing equal concentrations of all three cation nitrates was passed over it.

Introduction

We are interested in the design of macrocyclic compounds for the selective complexation and separation of metal ions. An extensive compilation of equilibrium constant (K) data on cation–macrocycle complexation has been published.[1] In general, preferential complexation results when the relative sizes of the cation and ligand cavities are matched. This is particularly true with the crown ethers where 18-crown-6 forms a stronger complex with potassium than with any of the other alkali-metal ions while 21-crown-7 forms a stronger complex with cesium ions.[2] Often, the nature of the donor atoms in the macroring exert an even greater effect on complexation. This is particularly true with the nitrogen atom containing aza-crowns which are complexed much more strongly by the soft transition-metal ions than by the hard alkali-metal ions.[1]

Much of the recent work on the separation of metal ions using macrocyclic ligands has involved either the extraction of metal ions into organic solvents or the transport of metal ions through liquid membranes. We and others have studied macrocyclic systems that are selective in the extraction and/or transport of lithium,[3,4] copper(II),[5] potassium,[6] calcium,[7] and silver[8] ions to name only a few of the cations that have been studied.

One of the major problems with using organic solvents as the extraction/membrane solvent is that complexation of the macrocycle with metal ions is greatly changed in the organic solvent over that of water.[9] Often, the selectivity of a macrocycle for one cation over another observed in aqueous solution is reversed in the organic solvent.[10] The most extensive complexation data have been obtained in water or methanol–water mixtures.[1]

We have reported recently the synthesis of three silica gel bound crown compounds.[11] These new materials formed complexes with various metal ions with log K values which were within about 10% of the log K value for the association of the same cation with unbound crown in water. We now report the synthesis of the (allyloxy)-methyl-substituted diaza-18-crown-6 compounds needed to prepare the silica gel bound diaza-crowns. A preliminary study of the separation of certain heavy metal ions using this silica gel material is also presented.

Table I. Comparison of the Synthesis of Crown 1 in Number of Steps and Overall Yields

procedure	starting materials (no. of steps)	overall yield,[a] %
A (Scheme I)	**5** (2) + **6** (1) + (3)	12
B (Scheme I)	**13** (4) + diiodide (1) + (2)	6
C (Scheme I)	**15** (3) + **6** (1) + (1)	11
D (Scheme I)	**17** (4) + **6** (1) + (1)	14
E (Scheme II)	**21** (2) + (1)	34

[a] Yield is the product of all intermediate yields.

Results and Discussion

Our goal was to find a convenient and high yield, two- or three-step procedure to prepare the desired (allyl-

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