Alkaloid Synthesis via Intramolecular Ene Reactions. 1. Application to (±)-Crinane

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Abstract: A general approach to the cis-fused octahydroindole skeleton of representative Amaryllidaceae alkaloids is described. A key feature of the approach is the intramolecular ene reaction of an acylnitroso olefin to give ene product **12**, corresponding formally to annulation of a five-membered N-containing ring onto a six-membered carbocycle. The total synthesis of *dl*-crinane which contains the basic octahydroindole nucleus is described. Ene product **12**, obtained from thermal unraveling and concomitant ene reaction of protected nitroso olefin **13**, was converted, in three reductive steps, to 3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (**11**). Amine **11**, thus obtained, is cyclized via conventional Pictet–Spengler conditions or by exposure to Eschenmoser's salt to give *dl*-crinane.

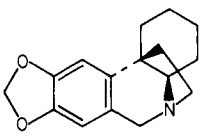
Introduction

The alkaloids of the Amaryllidaceae family constitute one of the most widespread[1] and intensively studied[2] classes of nitrogen containing compounds. Representative examples of this group include mesembrine (**1**),[3] crinine (**2**),[4] elwesine (**3**),[5] lycorine (**4**),[6] and the nonbasic antitumor substances lycoricidine (**5**) and narciclasine (**6**)[7] (Chart I). Interest in this class of alkaloids has been heightened recently by reports of significant antitumor activity exhibited by pretazettine **7**.[8,9]

With the notable exceptions of lycoricidine and narciclasine, each of these substances possesses very similar structural features with respect to their basic skeleton. All possess a structure which may be regarded as a carbocyclic six-membered ring, an appended aryl substituent, and a five-membered nitrogen containing ring annulated onto the carbocyclic six-membered ring. This similarity of structural features has led us to investigate general methods for the construction of such skeletons. The successful utilization of intramolecular ene reactions of acylnitroso enophiles for this purpose is disclosed herein.

We are by no means the first to investigate general approaches to the Amaryllidaceae alkaloids. The elegant methods of Martin[10] and Stevens[11] are perhaps the best currently available for generation of the cis-fused octahydroindole moiety common to many of these structures. Indeed, these methods are so efficient as to perhaps discourage further effort. However, we felt that the approach detailed below promised to be a viable route not only to the types of structures discussed above, but also to a number of other alkaloid systems not amenable to synthesis by the methods of Stevens or Martin.

As the goal of our initial efforts, we chose the relatively simple problem posed by (±)-crinane (**8**).[12] Although not naturally occurring, this substance possesses the basic structure of interest



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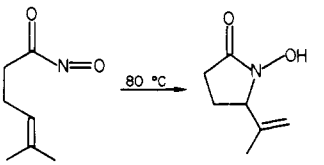
and has been reported to posess some analgesic activity.[12] Thus, (±)-crinane (**8**) was selected as an optimal initial target for synthesis.

We have previously reported that the intramolecular ene reaction of acylnitroso enophiles offers a useful method for the synthesis of a number of substituted lactams in very high yields and under mild conditions, attractive for utilization in natural product synthesis.[13] The conversion of **9** to **10** represents one



9 10

example generating a five-membered nitrogen-containing ring. Although our initial report recorded only reactions of *acyclic* acylnitroso compounds, a simple modification of the starting structure, i.e., by utilizing a *carbocyclic* olefin, should afford a simple approach to the kinds of structures discussed above. Moreover, we realized that the synthesis of the tetracyclic ring system of crinane really requires only the preparation of the known[12] bicyclic amine **11**, since the viability of introducing the final carbon by Pictet–Spengler cyclization has been documented by Wildman.[12]

We thus envisioned that amine **11** could arise by reduction of the unsaturated hydroxamic acid **12**, which would result from intramolecular ene reaction of acylnitroso olefin **13**. Importantly, no ambiguity regarding the stereochemistry of the ring fusion present in **12** exists by using this approach, which is mechanism enforced to lead only to the desired cis material[14] (see Scheme I).

One remaining obstacle was to devise a suitable method for construction of the acylnitroso intermediate **13**, since our previous approach[13] (alkylation or condensation reactions of a protected acylnitrosomethane) was clearly inadequate for generation of the requisite quaternary center. Hence, we decided to elaborate the acylnitroso unit from the corresponding acid **14**, which should be readily prepared by Claisen reorganization of an appropriate

(1) Wildman, W. C. In "The Alkaloids"; Vol. VI, Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VI, p 289.
(2) Wildman, W. C., ref 1, p 295.
(3) Popelak, A.; Lettenbauer, G. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1967; p 467.
(4) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **88**, 3670 (1966). See also: Whitlock, H. W.; Smith, G. L. *Ibid.* **89**, 3600 (1967).
(5) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. See also ref 4.
(6) See ref 1. See also: Nakagawa, Y.; Uyeo, S. *J. Am. Chem. Soc.* **1959**, *81*, 3736.
(7) Ceriotti, G. *Nature (London)* **1967**, *213*, 595. Okamoto, T.; Torii, A.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860.
(8) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749.
(9) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1970**, *92*, 5538.
(10) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391.
(11) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580.
(12) Wildman, W. C. *J. Am. Chem. Soc.* **1956**, *78*, 4180.
(13) Keck, G. E.; Webb, R. R. *Tetrahedron Lett.* **1979**, 1185.
(14) Oppolozer, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 486.

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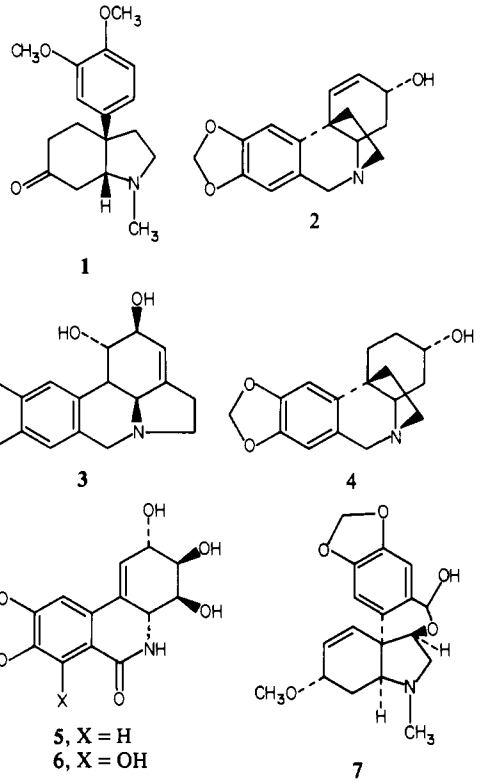
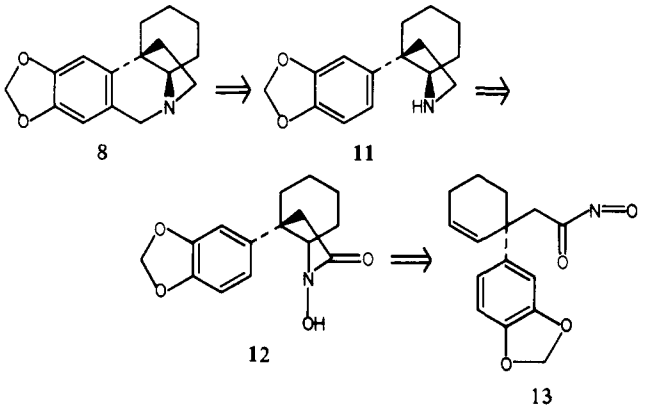
Chart I



Scheme I



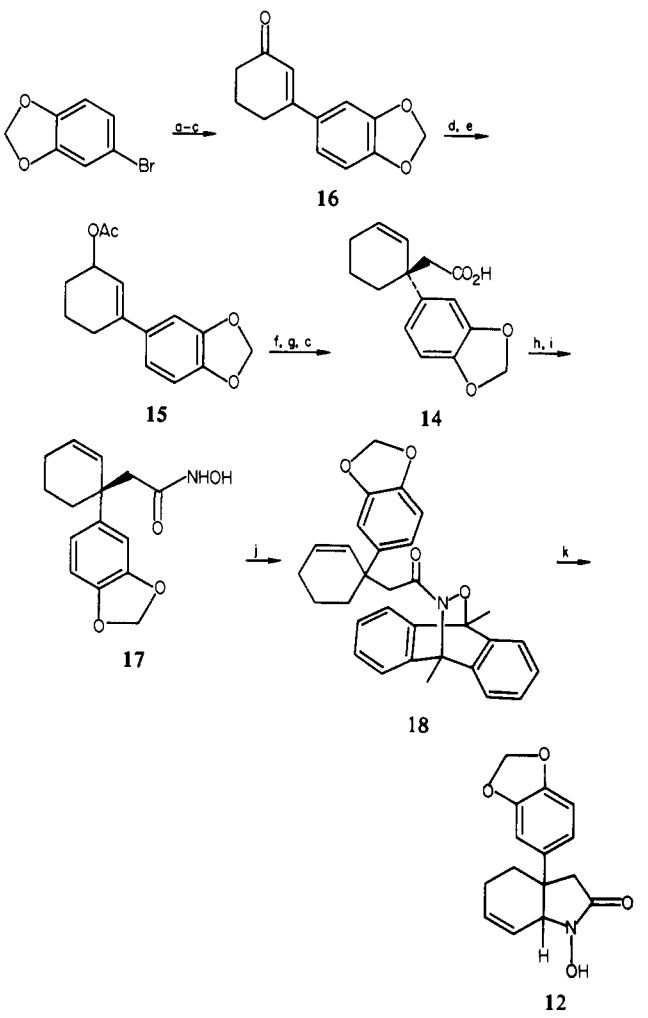
acetate, **15**, via the method of Ireland.[15]

Results

Our first task was thus to assemble the allylic acetate **15** required for the Claisen rearrangement. Although compounds similar to the corresponding enone **16** are in fact known, their reported[16] laborious and low-yielding preparation prompted us to develop a more efficient route to this material. 4-Bromobenzodioxole,[17] readily available on a large scale by treatment of benzodioxole with bromine in acetic acid at 23 °C, was treated with *n*-butyllithium at 0 °C to effect metal–halogen exchange and then reacted with 3-methoxycyclohexenone. Workup with aqueous acid afforded the desired enone **16** (mp 100–103 °C) in 80% isolated yield.

Reduction of the enone ($NaBH_4$, EtOH, 0 °C) gave a rather sensitive alcohol which was immediately acetylated to afford the crystalline acetate **15**. Claisen rearrangement was then effected

Scheme II[a]



[a] a, *n*-BuLi; b, 3-methoxycyclohexenone; c, H_3O^+; d, $NaBH_4$, EtOH; e, Ac_2O, py.; f, LDA, THF; g, *t*-Bu$(CH_3)_2$SiCl; h, $SOCl_2$; i, $NH_2OH{\cdot}HCl$; j, *n*-Pr_4NIO_4, $CHCl_3$, 9,10-DMA; k, toluene, reflux.

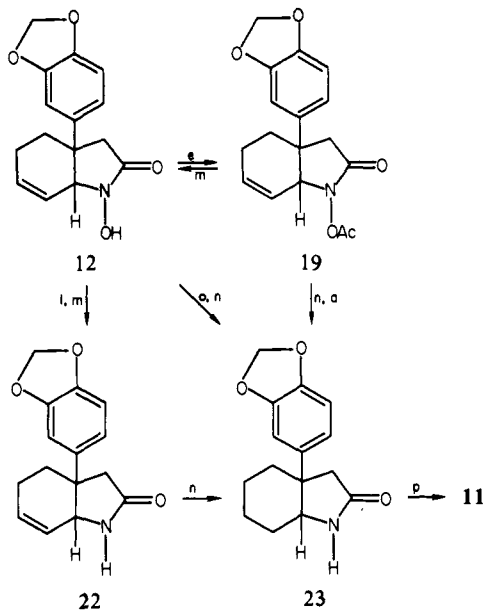
by using the general procedure of Ireland.[15] After considerable experimentation, this transformation could be effected in 80% isolated yield to afford the nicely crystalline acid **14**.

Transformation of the acid **14** to the corresponding hydroxamic acid **17** was accomplished without incident (93% overall yield) by the general procedure of Jones and Hurd.[18] Thus, conversion of **14** to the acid chloride ($SOCl_2$, PhH, reflux, 2 h) was followed by dilution with ether, addition of solid hydroxylamine hydrochloride and sodium carbonate, and slow infusion of sufficient water (with gentle stirring) to generate a two-phase system. Acidification and extractive workup then afforded the desired hydroxamic acid.

Conversion of **17** to acylnitroso compound **13** and hence ene product **12** requires more detailed comment. In principle, this transformation could be accomplished simply by oxidation of the hydroxamic acid according to well-developed[19] procedures. This method has been used effectively to generate acylnitroso compounds for trapping via [4 + 2] cycloaddition.[20] In this latter case, however, the products contain no labile hydrogens and are perfectly stable under the oxidative conditions employed. In contrast, the cyclic hydroxamic acids which would result from

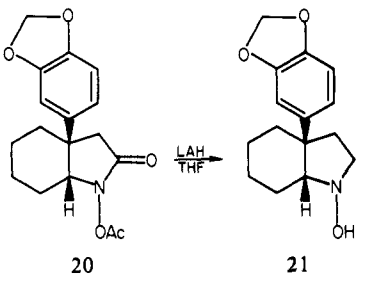
(15) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(16) White, A. C.; Sugden, R. F. (Wyeth, J., Ltd.) British Patent 1 520 611 (Cl. C07D487/04), 1978.
(17) Jones, T. G. H.; Robinson, R. *J. Chem. Soc.* **1917**, 918.
(18) Jones, L. W.; Hurd, C. D. *J. Am. Chem. Soc.* **1921**, *43*, 2422. The preparations of hydroxamic acids have been reviewed: Sandler, S. R.; Kera, W. "Organic Functional Group Preparations"; Wasserman, H., Ed.; Academic Press: New York, Vol II, Chapter 12, and references therein.
(19) Kirby, G. W.; Sweeney, J. G. *J. Chem. Soc., Chem. Commun.* **1972**, 704.
(20) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.

Scheme III[a]

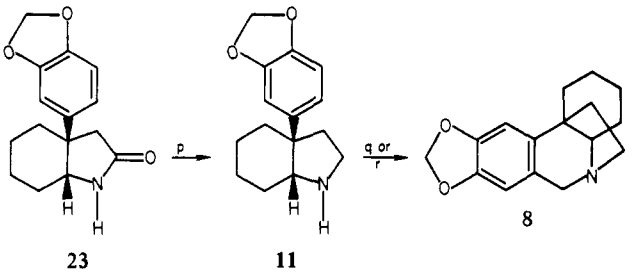


[a] l, CH_2=$CHCH_2Br$, K_2CO_3, acetone, reflux; m, Na(Hg), EtOH; n, H_2, Pd/C, EtOAc; o, $TiCl_3$, MeOH-H_2O, Na_2CO_3; p, $LiAlH_4$, THF, reflux.

Scheme IV



Scheme V[a]



[a] p, $LiAlH_4$, THF, reflux; q, $(CH_3)_2N^+$ =CH_2I^-, THF, 40 °C; r, CH_2O (aqueous), concentrated HCl, 60 °C.

intramolecular ene reaction are well-known to be highly unstable with respect to oxidation, suffering conversion to acyl nitroxyls which can then undergo further reactions.[21] Indeed, our attempts to effect such ene reactions by direct oxidation with tetrapropylammonium periodate have been uniformly unrewarding, resulting typically in very low yields and dark, intractable reaction products. However, our previously described technique of "intramolecular enophile transfer", when applied to the problem at hand, yielded extremely gratifying results. Oxidation of hydroxamic acid **17** in the presence of 9,10-dimethylanthracene very cleanly afforded **18**, the product of Diels–Alder cycloaddition, in 85% yield after purification by column chromatography. Thermal release of the acylnitroso moiety with concomitant ene reaction was effected by heating a toluene solution of **18** at reflux for 30 min to give the desired cyclic hydroxamic acid **12** in 100% isolated yield after removal of 9,10-dimethylanthracene by rapid chromatography on a short silica gel column (see Scheme II).

Conversion of **12** to the desired amine **11** requires three reductive processes: cleavage of the N–O bond, reductive removal of carbonyl, and hydrogenation of the extraneous unsaturation present. Several methods are available for the reductive removal of the N–O bond. Our previously described procedure[13] of acetylation followed by reduction with 6% sodium amalgam was found to lead to substantial quantities of hydroxamic acid **12** in this case. The difficulty may well be due to a more basic preparation of sodium amalgam than that used in our earlier work. This problem could be circumvented by sodium amalgam reduction of the *O*-allyl ether derived from **12** by exposure to allyl bromide and potassium carbonate in refluxing acetone. Alternatively, either **12**, its corresponding acetate **19**, or the saturated materials obtained from **19** by hydrogenation over palladium on carbon could be cleaved in high yield by the very convenient procedure of Miller and Mattingly[22] (see Scheme III).

Attempts to effect the hydrogenation (see Scheme III) and cleavage in one step by using various catalysts were disappointing. Equally unsatisfactory were our attempts to reduce acetate **20** directly to amine **11** using the procedure of House.[23] In this case, reduction of **20** (Scheme IV) with lithium aluminum hydride in refluxing THF for 5 h afforded a single, more polar, crystalline product, which contained neither acetate nor lactam carbonyl in the infrared, exhibited an appropriate NMR spectrum, but analyzed for $C_{15}H_{19}NO_3$ rather than $C_{15}H_{19}NO_2$, and afforded a monoacetate with carbonyl absorption at 1751 cm^{-1}. These observations lead us to suggest the hydroxylamine structure **21** for this material. Operationally, the most convenient process for converting **12** to **11** proved to be acetylation, hydrogenation over Pd/C in ethyl acetate, reduction with $TiCl_3$ according to the procedure of Miller and Mattingly,[22] and reduction with lithium aluminum hydride in refluxing THF. The overall yield of amine **11** obtained by this sequence, which is easily conducted without purification of intermediates, was 90%.

For completion of the synthesis of (±)-crinane, it remained only to subject amine **11** to Pictet–Spengler cyclization according to the previously published procedure.[12] Thus, heating amine **11** in aqueous formalin acidified with hydrochloric acid yielded (±)-crinane (**8**; see Scheme V).

However, we were interested in developing a somewhat milder method for inserting the final carbon, since we envisioned eventual application to intermediates containing carbon–carbon double bonds, which could undergo Prins reactions under these conditions. Use of Eschenmoser's salt[25] (*N,N*-dimethylmethyleneammonium iodide) seemed an ideal solution. Thus, amine **11** and 1.5 equiv of Eschenmoser's salt were heated to 40 °C in THF for 30 h. Standard extractive workup and chromatography over silica gel afforded (±)-crinane in 90% yield, demonstrating the efficiency of this method as an alternative to conventional Pictet–Spengler conditions (see Scheme V).

Conclusions

The foregoing describes a potentially general approach to a number of alkaloids of the Amaryllidaceae. It can be seen that the synthesis of mesembrine (**1**) and elwesine (**3**) should prove possible provided that a method for regio- and stereospecific hydroxylation of the double bond generated (note **12**) by the ene process can be developed. Perhaps more importantly, the method may, in principle, be extendable to alkaloids of other structural types. The methodology detailed above provides a rational foundation for a vigorous attack on more complex naturally occurring materials. Extensions and further application of the methodology described herein are under active investigation in

(21) Kirby, G. W., Sweeney, J. G. *J. Chem. Soc., Chem. Commun.* **1973**, 704. Moffatt, J. G.; Lerch, U. *J. Org. Chem.* **1971**, *36*, 3391.
(22) Miller, M. J.; Mattingly, P. G. *J. Org. Chem.* **1980**, *45*, 410.
(23) House, H. O.; Magin, R. W. *J. Org. Chem.* **1963**, *28*, 647.
(24) Note: Ibuka, T.; Inubushi, Y.; Saji, I.; Tanaka, K.,; Masaki, N. *Tetrahedron Lett.* **1975**, *5*, 323 and references cited therein.
(25) Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, 4763.

our laboratories and will be reported in due course.

Experimental Section

Melting points were recorded on a Mel-temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Acculab 3 IR spectrometer. NMR spectra were recorded at 90 MHz by using a Varian EM-390 or at 300 MHz by using a Varian SC-300. Chemical shifts are in parts per million downfield from internal Me_4Si; coupling constants are given in hertz. Solvents and reagents were purified as follows: tetrahydrofuran by distillation from benzophenone ketyl under argon: hexanes and ethyl acetate by distillation; HMPA, toluene, methylene chloride, pyridine, and diisopropylamine by distillation from calcium hydride. Mallinckrodt anhydrous ether and Fisher acetic anhydride were employed as received. Mass spectra were recorded on a Varian Mat 112-S in the electron impact or chemical ionization mode with the indicated reagent gas. Elemental analyses were performed by Galbraith Laboratories. All yields reported are isolated yields of material judged homogeneous by thin-layer chromatography and NMR spectroscopy and, for crystalline solids, having the indicated melting point. Thin-layer chromatography was performed on Merck 0.25-mm glass silica gel plates; visualization of developed plates was by fluorescence quenching and staining with phosphomolybdic acid (or with $FeCl_3$ for hydroxamic acids). Column chromatography was performed by using Merck silica gel 60 (60–240 mesh). MPLC refers to medium-pressure liquid chromatography over Merck silica gel 60 (230–400 mesh) with an FMI lab pump operated at 60–100 psi, Altex columns, a UV detector, and an ISCO fraction collector.

4-Bromo-1,2-(methylenedioxy)benzene. This material was prepared by the procedure of Jones and Robinson.[17] Thus a solution of (methylenedioxy)benzene (Crown Zellerbach; 22.79 g, 0.186 mol) in acetic acid (250 mL) was treated dropwise with bromine (14.4 mL, 0.28 mol). After the addition was complete, the light orange mixture was stirred an additional hour, poured into ether (200 mL), and extracted with 2 M KOH until basic. The combined aqueous layers were back-extracted with ether (5 × 20 mL), and the organic layers were combined, washed with brine, dried over anhydrous K_2CO_3, and concentrated in vacuo to a light yellow oil. Distillation yielded 31.9 g (85%) of colorless liquid: bp 90–95 °C (0.1 mm); homogeneous by VPC analysis (silanized glass column of 5% OV-1 on Varaport 30, 160 °C, 25 mL/min flow rate of N_2 carrier gas, starting material retention time 4 min, product bromide 15 min; ^1H NMR ($CDCl_3$) 7.13 (m, 2 H, Ar H), 6.8 (d, 1 H, Ar H), 6.15 (s, 2 H, methylenedioxy); IR (film) 3100 (w), 3005 (m), 2990, 2905 (s), 2780 (m), 1605, 1500 (vs), 1480 (vs), 1250 (s, br) 1060 (s), 950 (s), 890 (s, sharp), 815 cm^{-1}; mass spectrum (CI, isobutane), *m/e* 122.1, 164.1, 200.1, 201.1 (M + 1), 202.1, 203.1.

3-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-one (16). Prepared by the method of Howell and Taylor.[24] Thus, 4-bromo-1,2-(methylenedioxy)benzene (20.4 g, 0.10 mol) was metalated with *n*-butyllithium (Alfa; 2.5 M in hexane, 46.6 mL, 0.112 mol) at 0 °C in ether (300 mL) and treated with 3-methoxy-2-cyclohexene-1-one (14.1 g, 0.112 mol). Acid hydrolysis and standard extractive workup furnished a yellow solid. Recrystallization from ether gave 12.0 g (80%) of colorless needles: mp 100–103 °C; ^1H NMR ($CDCl_3$, Me_4Si) 7.30 (nm, 2 H) 7.05 (d, 1 H) 6.45 (nm, 1 H) 6.20 (s, 2 H) 2.73 (t, J = 6, 2 H) 2.50 (t, J = 6, 2 H) 2.10 (quintet, J = 6, 2 H); IR ($CHCl_3$) 2960 (s), 2800, 1730 (s), 1660 (m), 1235 (vs), 1045 cm^{-1} (s); ^{13}C NMR ($CDCl_3$, Me_4Si) 199.5, 158.79, 149.2, 148.8, 132.5, 123.8, 120.5, 108.1, 105.9, 101.5, 36.7, 27.6, 22.3; mass spectrum (CI, isobutane), *m/e* 218.2 (M + 1), 217.1 (P), 216.2. Anal. ($C_{13}H_{12}O_3$) C, H.

3-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-yl Acetate (15). A suspension of enone **16** (3.80 g, 17.5 mmol) in anhydrous EtOH (50 mL) was treated with $NaBH_4$ (Alfa; 0.90 g, 22.7 mmol) and allowed to stir overnight at −22 °C (cold room). Acetone was added to destroy excess borohydride, and the solution was allowed to warm to room temperature and then concentrated in vacuo to a slurry which was partitioned between water and ethyl acetate. The crude product was then immediately exposed to acetic anhydride (excess) in pyridine (10 mL). After 10 h, the mixture was concentrated in vacuo with toluene azeotrope to give a light yellow oil which was chromatographed by MPLC on a 1.5 × 200 cm silica gel column slurry packed in 20% THF–hexanes. Elution was with 20% THF–hexanes, and 20-mL fractions were collected. Fractions 16–30 were combined and concentrated in vacuo to a colorless oil which crystallized on storage at −35 °C for 1 day to give 3.64 g (80%) of colorless needles, mp 58–60 °C. Repeated attempts to isolate the alcohol both by chromatography and recrystallization resulted in decomposition, with concomitant loss of material: ^1H NMR ($CDCl_3$, Me_4Si) 7.05 (m, complex, 3 H) 6.10 (m, 1 H, vinylic), 6.05 (s, 2 H, methylene), 5.50 (br m, 1 H), 2.45 (m, complex, 2 H), 2.05 (s, 3 H, CH_3), 1.89 (m, 4 H); IR ($CHCl_3$) 2960 (s), 2780 (w), 1720 (vs), 1640 (w), 1610, 1490 (vs), 1550, 1370, 1200–1240 (s, br), 1040, 920 cm^{-1}; UV (EtOH) 294 nm (ϵ 3900), 262 (5400); ^{13}C NMR ($CDCl_3$, Me_4Si) 170.7, 147.6, 147.1, 141.4, 135.2, 121.1, 118.7, 107.7, 105.7, 100.8, 68.6, 27.5, 27.1, 20.8, 18.9. Anal. ($C_{15}H_{16}O_4$) C, H.

[β-[3,4-(Methylenedioxy)phenyl]cyclohex-2-enyl]acetic Acid (14). The claisen rearrangement of acetate **15** was effected by using Ireland's modification.[14] Thus, a solution of the acetate (8.33 g, 0.032 mol) in anhydrous THF (135 mL) was added slowly dropwise, via syringe, to a solution of 1.2 equiv of lithium diisopropylamide containing 5% HMPA under argon at −78 °C. After the addition was complete, the solution was stirred for 5 min and then treated in one batch with *tert*-butyldimethylchlorosilane (Petrarch, 11.0 g, 0.070 mol) dissolved in THF (15 mL). The bath was then removed, and the solution heated at reflux for 3 h. Then 3:1:1 MeOH–H_2O–acetic acid (20 mL) was added to effect hydrolysis of the silyl ester, and after the mixture was stirred 3 h, standard extractive workup yielded a dark yellow oil which was chromatographed by MPLC on a 2 × 200 cm silica gel column slurry packed in 20% THF–hexanes and eluted with the same: fractions 1–12, nil; 13–17, silylated impurities; 18–20, nil; 21–30, unidentified; 31–33 overlap; 34–46, product; 47–60, nil (60 fractions total, 20 mL each). Fractions 34–46 were combined and concentrated in vacuo to yield 6.60 g (80%) of colorless crystalline material, pure by NMR and TLC analysis. One crystallization from CH_2Cl_2–pentane afforded an analytical sample as colorless plates: mp 127 °C; NMR ($CDCl_3$, Me_4Si) 11.5 (s, 1 H), 7.05 (s, 1 H), 6.95 (s, 2 H), 6.10 (q, J = 12, 2 H), 6.05 (s, 2 H, OCH_2O, overlapped with vinyl), 2.89 (narrow AB q, 2 H), 2.02 (m, 4 H), 1.55 (m, 2 H); IR ($CHCl_3$) 2560–3200 (br), 2910 (s), 1710 (vs, br), 1605, 1595, 1500, 1470 (s), 1320, 1200–1260 (s, br), 1150, 1030, 920 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 178.0, 147.9, 146.1, 141.1, 132.2, 129.3, 120.4, 108.1, 107.9, 101.2, 46.8, 41.7, 37.5, 25.1, 18.7; mass spectrum (CI, isobutane), *m/e* 261.3 (M^+), 262.3 (M + 1), 201.2 (M − CH_2CO_2H), 139.1 (parent). Anal. ($C_{15}H_{16}O_4$) C, H.

[β-[3,4-(Methylenedioxy)phenyl]cyclohex-2-enyl]acetohydroxamic Acid (17). To a solution of the acid **14** (1.30 g, 5.0 mmol) in benzene (30 mL) was added $SOCl_2$ (0.5 mL, 6 mmol). The resulting mixture was heated at reflux for 2 h, cooled to 0 °C, and diluted with ether (20 mL); solid NH_2OH·HCl (0.5 g, 6 mmol) and anhydrous Na_2CO_3 (1.5 g, 12 mmol) were then added. After the mixture was stirred for 5 min, 5 mL of H_2O was added followed by another 5 mL 5 min later. The mixture was allowed to warm to room temperature over 12 h and then acidified to pH 2 with concentrated HCl, and the layers were separated. The aqueous phase was extracted with EtOAc (5 × 20 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield 1.29 g (93%) of a light yellow oil which was used in the next step without purification: NMR ($CDCl_3$, Me_4Si) 8.28 (s, br, 2 H) 7.05 (s, 1 H) 6.98 (s, 2 H) 6.10 (s, 4 H, methylene overlapping vinyl) 2.58 (s, 2 H) 2.00 (m, complex, 4 H) 1.55 (m, 2 H); IR ($CHCl_3$) 3400 (w), 2810–3200 (s, br), 1760 (s, br), 1480 (s), 1430, 1195–1245 (br), 1050 (vs), 940, 917 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 169.3, 147.8, 145.9, 140.6, 131.6, 129.4, 120.2, 107.9, 100.9, 46.0, 41.7, 36.5, 24.8, 18.3.

12-[[1-[3,4-(methylenedioxy)phenyl]cyclohex-2-enyl]acetyl]-9,10-dihydro-9,10-dimethyl-10,9-(epoxyimino)anthracene (18). A solution of hydroxamic acid **17** (1.29 g, 4.7 mmol) in $CHCl_3$ (5 mL) and DMF (1 mL) was added slowly and dropwise (syringe drive) to a suspension of 9,10-dimethylanthracene (0.967 g, 4.7 mmol) and tetrapropylammonium periodate[25] (1.94 g, 5.17 mmol) in $CHCl_3$ (10 mL) and DMF (2 mL). The syringe drive was adjusted to deliver 1 drop every 8–10 s, and the addition was completed after 5 h. The dark yellow solution was then poured into CH_2Cl_2 overlaid with saturated aqueous sodium thiosulfate solution, and the phases were separated. The aqueous phase was back-extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a brown solid. The crude product was dissolved in CH_2Cl_2–THF and chromatographed on a 1 × 100 cm silica gel column slurry packed in 35% THF–hexanes (elution with the same): fractions 1–10, nil; 11–12, 9,10-dimethylanthracene; 13–15 unidentified impurity; 16–18, nil; 19–33, product; 34–40, nil (40 fractions total, 30 mL each). Fractions 19–33 were combined and concentrated in vacuo to give 1.90 g (85%) of white solid, homogeneous by NMR and TLC analysis: mp 67–70 °C dec; 300-MHz ^1H NMR ($CDCl_3$, Me_4Si) 7.43 (nm, complex, 4 H), 7.29 (nm, complex, 4 H) 6.77 (d, J = 2, 1 H), 6.57 (d, J = 8, 1 H), 6.48 (dd, J = 2, 8, 1 H), 5.90 (s, 2 H), 5.83 (d, J = 6, 1 H), 5.71 (dt, J = 3, 6, 12, 1 H), 2.70 (AB q, J = 18, 2 H), 2.63 (s, 3 H), 2.26 (s, 3 H), 1.88 (m, 2 H), 1.6 (m, 2 H), 1.34 (m, 2 H); IR ($CHCl_3$) 3060, 3020, 2980, 2921, 1680 (s, br), 1498, 1480 (vs), 1466, 1440, 1369, 1238 (s, br), 1170, 1040 (s), 920 (s), 732 (vs) cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 176.6, 147.1, 145.0, 142.2, 141.5, 141.2, 141.1, 141.0, 133.0, 127.5, 127.4, 127.3, 127.1, 121.4, 121.3, 120.5, 120.4, 119.3, 107.4, 107.3, 100.5, 79.5, 63.6, 46.6, 41.6, 37.5, 24.6, 18.2, 16.2, 14.8. Anal. ($C_{31}H_{29}NO_4$) C, H.

***N*-Hydroxy-2-oxo-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole (12).** Diels–Alder adduct **18** (0.9 g, 1.87 mmol) was

decomposed in refluxing toluene (250 mL). After 15 min, TLC detailed the consumption of starting material with formation of 9,10-dimethylanthracene and a polar UV spot which stained purple on exposure to $FeCl_3$ (2% in EtOH, 1% HCl). The crude yellow solid that remained after removal of the toluene was chromatographed on a 1 × 50 cm silica gel column slurry packed in chloroform and eluted with 2% MeOH in chloroform: fractions 1–5, nil; 6–10, 9,10-dimethylanthracene; 11–20, nil; 21–25, product; 26–30, nil (30 fractions total, 20 mL each). Fractions 21–25 were combined and concentrated in vacuo to yield 508 mg (100%) of light pink solid. One crystallization from CH_2Cl_2–pentane yielded analytically pure material as colorless rosettes: mp 160–163 °C; ^1H NMR ($CDCl_3$) 9.70 (br s, 1 H), 6.90 (m, 3 H), 6.32 (s, 2 H), 6.05 (s, 2 H), 4.45 (br s, 1 H), 2.70 (s, 2 H), 1.80 (m, 4 H); IR ($CHCl_3$ solution) 2600–3400 (s, br), 1690 (s), 1470 (s), 1420, 1370, 1200–1240 (m, br) 1050, 920, 860 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 168.7, 148.3, 146.8, 138.6, 134.5, 122.6, 119.0, 108.4, 106.7, 101.4, 60.4, 43.5, 33.9, 22.0; mass spectrum (EI), *m/e* 274.3 (M^+), 273.3 (P), 256.3 (P – H_2O), 228.3 (P – CH_2CO), 151.1 (P – $C_7H_5O_2$, aromatic). Anal. ($C_{15}H_{15}NO_4$) C, H.

***N*-Acetoxy-2-oxo-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (20).** A solution of 0.214 g (0.78 mmol) of ene product **12** in 5 mL of pyridine was treated with excess Ac_2O for 2 min. The solvent was then removed in vacuo (toluene), and the residue was taken up in ethyl acetate and hydrogenated by using 10% Pd on charcoal as a catalyst. After 8 h, the mixture was filtered to remove the catalyst and concentrated in vacuo to a colorless oil which crystallized on standing to yield 0.239 g (98%) of colorless solid: mp 150 °C; ^1H NMR ($CDCl_3$) 7.00 (m, 3 H), 6.19 (s, 2 H), 4.48 (m, 1 H), 2.62 (s, 2 H), 2.34 (s, 3 H), 2.00 (m, 4 H); IR ($CHCl_3$) 3405 (w), 2925 (s), 1800 (s), 1720 (vs), 1495 (m), 1445 (m), 1375, 1180–1270 (m, br), 1050, 950, 860 m^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 170.7, 168.1, 148.4, 146.5, 138.2, 119.7, 108.3, 107.4, 101.4, 61.5, 45.6, 40.8, 35.7, 23.6, 21.2, 19.8, 18.2. Anal. ($C_{17}H_{17}NO_4$) C, H.

***N*-Allyloxy-2-oxo-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole.** A solution of the ene product **12** (198.9 mg, 0.65 mmol) in reagent grade acetone (10 mL) was treated with excess (2.0 equiv) allyl bromide and excess anhydrous K_2CO_3 (4.0 equiv), and the resulting suspension was stirred for 2 h at reflux. Examination of the crude mixture by TLC revealed the absence of the starting material and the presence of the allyl ether (R_f 0.35, 50% THF–hexanes) which stained purple on exposure to $FeCl_3$ only after the plate had been heated considerably. The mixture was then diluted with dichloromethane, filtered, concentrated in vacuo, and chromatographed on a 1 × 100 cm silica gel column slurry packed with 8% MeOH–$CHCl_3$ (elution with the same): fractions 1–5, nil; 6–10, unidentified material; 11–13, nil; 14–20, product; 21–30, nil (30 fractions total, 5 mL each). Fractions 14–20 were combined and concentrated in vacuo to yield 160 mg (75%) of the allyl ether as a colorless oil: ^1H NMR ($CDCl_3$) 6.68 (nm, 3 H, Ar H), 6.16 (nm, 3 H, vinylic), 5.98 (s, 2 H, methylene), 5.46 (m, complex, 2 H, vinylic), 4.50 (d, J = 8, 2 H, allylic), 4.31 (m, 1 H, methine), 2.62 (s, 2 H, $CH_2C{=}O$), 1.85 (m, 4 H); IR ($CHCl_3$) 3050 (w), 3010, 2950 (s), 2840, 1715 (vs), 1600 (w), 1505, 1460, 1410, 1255 (s), 1148, 1032, 910, 850, 708 cm^{-1}.

2-Oxo-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole (22). A solution of 0.180 g (0.622 mmol) of the allyl ether above in 20 mL of anhydrous ethanol was treated with 0.265 g (1.86 mmol) Na_2HPO_4, and the suspension was cooled to −20 °C (cold room) under argon. Then, freshly ground 6% sodium amalgam was added in portions, and the solution was stirred overnight. The next day, TLC revealed the total absence of starting material and the presence of a much lower R_f spot (0.09, 8% MeOH–$CHCl_3$). Filtration and concentration in vacuo yielded 155 mg (100%), of a colorless oil which crystallized on standing: mp 214–216 °C; ^1H NMR ($CDCl_3$) 7.43 (s, 1 H, NH), 6.70 (nm, 3 H, Ar H), 5.90 (m, 2 H, vinyl), 5.88 (s, 2 H, methylene), 4.20 (nm, 1 H, methine) 2.66 (AB q, J = 18, 2 H, methylene next to carbonyl), 1.78 (m, 4 H); IR ($CHCl_3$) 3400, 2960, 1690 (s), 1474 (m), 1440 (w, br) 1180–1240 (br) 1041, 936 cm^{-1}; mass spectrum (CI, isobutane), *m/e* 260.1 (M + 1), 259.1, 258.1 (base), 257.1. Anal. ($C_{15}H_{15}NO_3$) C, H.

2-Oxo-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (23). A solution of acetate **20** (50 mg, 0.16 mmol) in 5 mL of H_2O and 3 mL of MeOH was treated with 0.358 g (0.32 mmol) anhydrous Na_2CO_3, and the suspension stirred for 1 h at room temperature. Then excess $TiCl_3$ was added in small portions until the purple color persisted. The suspension was allowed to stir 12 h at room temperature under argon, diluted with brine, and extracted exhaustively with ether. The combined ether layers were concentrated in vacuo to a colorless oil which was crystallized from CH_2Cl_2–pentane to yield 42 mg (100%) of colorless plates: mp 142–144 °C (lit.[4] mp 142–144 °C); ^1H NMR ($CDCl_3$, Me_4Si) 7.33 (br s, 1 H) 7.00 (m, 3 H), 6.2 (s, 2 H), 4.25 (t, 1 H), 2.55 (AB q, J = 16, 2 H) 1.85 (m, 4 H), 1.56 (m, 4 H); IR ($CHCl_3$) 3420 (m, sharp), 2960 (s), 1710 (vs), 1622 (w), 1500, 1460, 1395, 1345, 1200–1260 (br), 1060, 955, 930 cm^{-1}; mass spectrum (CI, isobutane), *m/e* 262.1 (M + 1), 261.1 (M^+), 260.1; ^{13}C NMR ($CDCl_3$, Me_4Si) 177.3, 148.3, 146.3, 139.0, 119.8, 108.3, 107.7, 101.3, 57.1, 48.9, 45.3, 35.3, 26.6, 21.2, 20.0. Anal. ($C_{15}H_{17}NO_3$) C, H.

3a-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (11). A solution of 489 mg of lactam **23** (1.88 mmol) in 10 mL of THF was treated with excess $LiAlH_4$ (150 mg, 3.8 mmol, Alfa), and the suspension was refluxed for 3 h, cooled to 0 °C (ice bath), quenched by the addition of a $Na_2SO_4{\cdot}10H_2O$–Celite (1:1) mixture, diluted with THF, and filtered through a Celite pad. The filter cake was washed with 10–5 mL portions of 10% NEt_3 in THF, and the filtrate was concentrated in vacuo with toluene. The residue was dissolved in Et_2O and saturated with HCl gas; the Et_2O was then removed in vacuo, and the residue remaining was dissolved in a minimal amount of $CHCl_3$. Hexane was added until the mixture turned cloudy, followed by a small amount of $CHCl_3$ until it was clear again. The solution was allowed to stand for 2 days at room temperature until colorless plates had formed. These crystals of amine hydrochloride were collected by vacuum filtration, washed with Et_2O, pentane, and once with purified $CHCl_3$, and dried in a desiccator, giving 486 mg (91%) of product: mp 224–226 °C; 300-MHz NMR ($CDCl_3$, Me_4Si) 10.33 (br s, 1 H), 9.33 (br s, 1 H), 6.78 (nm, complex, 3 H), 5.94 (s, 2 H), 4.0 (br s, 1 H), 3.67 (nm, 1 H), 3.43 (nm, 1 H), 1.84–2.16 (m, complex, 8 H), 1.58 (nm, 2 H); IR ($CHCl_3$) 2925 (vs), 2761 (m) 1595, 1480 (m), 1446, 1119–1240 (m, br), 1126 (w), 1046 (s, sharp), 940 cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 148.6, 146.6, 136.3, 119.3, 108.5, 107.1, 101.4, 61.2, 47.2, 41.3, 40.2, 32.2, 32.1, 23.6, 21.0, 19.8; mass spectrum (CI, methane, probe), *m/e* 246.0, 245.0 (p), 244.0, 216.0 (M – CH_2CH_2), 202.0 (M – $CH_2CH_2NH_2$), 187.9 (M – 2 CH_2CH_2), 123.0. Anal. ($C_{15}H_{20}NO_2Cl$) C, H.

***dl*-Crinane (8).** A solution of 200 mg (0.71 mmol) of the hydrochloride of amine **11** in 15 mL of H_2O and 5 mL of concentrated HCl was treated with 8 mL of 37% aqueous formaldehyde solution and the resulting mixture heated for 18 h at 60 °C. The solution was then cooled to 0 °C, basified to pH 8 with concentrated NH_4OH, and extracted with Et_2O and CH_2Cl_2. The combined organic layers were dried over K_2CO_3 and concentrated in vacuo to a yellow oil which was chromatographed on a 1 × 50 cm silica gel column slurry packed in $CHCl_3$ and eluted with 4% MeOH in $CHCl_3$: fractions 1–5, nil; 6–10, impurity believed to arise from formaldehyde; 11–20, nil; 21–45, product; 46–60, nil (60 fractions total, 5 mL each). Fractions 21–45 were combined and concentrated in vacuo to give 101 mg (53%) of a colorless oil: 300-MHz ^1H NMR ($CDCl_3$, Me_4Si) 6.72 (s, 1 H), 6.44 (s, 1 H), 5.9 (s, 2 H), 4.38 (m, 1 H), 3.74 (m, 1 H), 3.39 (m, complex, 1 H), 2.8 (m, complex, 2 H), 2.36 (d, J = 13, 1 H), 2.24 (dd, J = 6, 13, 1 H), 1.79 (m, complex, 4 H), 1.58 (m, complex, 2 h), 1.2 (m, complex, 2 H); IR ($CHCl_3$, film) 2965 (s), 2880 (m), 1603 (w), 1486, 1460, 1370, 1190–1250 (m, br), 1050 (s), 1016 (s), 944, 868 cm^{-1}; mass spectrum (EI), *m/e* 258.1, 257.1, 228.1, 185.0, 86.0, 84.0 (P); ^{13}C NMR ($CDCl_3$, Me_4Si) 146.6, 145.9, 142.5, 126.2, 106.5, 103.5, 100.9, 67.5, 62.2, 52.0, 42.9, 37.9, 29.0, 27.6, 24.4, 21.7.

A picrate was prepared for analysis; mp 214–216 °C (lit.[12] mp 218–220 °C). Anal. ($C_{22}H_{22}N_4O_9$) C, H.

***dl*-Crinane (8), Prepared with Eschenmoser's Salt.** A solution of 30 mg (0.122 mmol) of amine **11** in 10 mL of THF was treated with 35 mg (0.18 mmol, 1.5 equiv) of Eschenmoser's salt,[23] and the suspension was heated to 40 °C for 30 h, cooled, basified (pH 8) with aqueous NH_4OH, and extracted with Et_2O. The combined ether layers were dried over K_2CO_3 (anhydrous) and concentrated in vacuo to a yellow oil which was chromatographed on a 0.5 × 100 cm silica gel column (slurry packed in $CHCl_3$), elution was with 2% MeOH in $CHCl_3$: fractions 1–4, nil; 5–9, impurity; 10–20, nil; 21–33, impurity; 24, nil; 25–42, product; 43–60, nil (60 fractions total, 4 mL each). Fractions 25–42 were combined and concentrated in vacuo to give 25 mg (90%) of *dl*-crinane as a colorless oil, spectroscopically identical with that prepared by Pictet–Spengler cyclization.

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