Electrophilic-Induced Cyclization Reaction of Hexahydroindolinone Derivatives and Its Application toward the Synthesis of (±)-Erysotramidine

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A convenient synthesis of variously substituted octahydroindolo[7a,1a]-isoquinolinones has been achieved by an acid-induced cyclization of hexahydroindolinones bearing tethered phenethyl groups. The formation of a single lactam diastereomer is the result of the stereoelectronic preference for axial attack by the aromatic ring onto the initially formed *N*-acyliminium ion from the least hindered side. Additional experiments showed that a variety of hexahydroindolinones containing tethered π-bonds undergo a related acid-induced cyclization reaction. Treatment of the 3-methylbut-3-enyl-substituted hexahydroindolinone with acid furnished a 3:1 mixture of isomeric octahydropyrido-[2,1-*i*]indolinones in near-quantitative yield. Interestingly, cyclization of the closely related 1-(3-methoxybut-3-enyl)-substituted hexahydroindolin-one afforded a pyrrolo[3,2,1-*ij*]quinolinone as the exclusive product. With this system, initial protonation takes place on the more nucleophilic enol ether π-bond and the resulting carbonium ion undergoes a subsequent cyclization with the enamido π-bond to give the observed product. The electrophilic promoted cyclizations were extended to include the related hexahydro[1]pyrindinone and 1*H*-quinolinone systems. An NBS-promoted intramolecular electrophilic aromatic substitution reaction of 1-[2-(3,4-dimethoxyphenyl)ethyl]-1,4,5,6-tetrahydroindolinone was used to assemble the tetracyclic core of the erythrinone skeleton. The resulting cyclized product was transformed into (±)-erysotramidine in three additional steps.

The hexahydroindolinone nucleus is a structurally characteristic component found in a wide variety of alkaloids,[1] including the amaryllidaceae,[2] aspidosperma,[3] erythrina,[4] and strychnos[5] families. The distinctive structural feature of these natural products sharing the hexahydroindolinone framework has attracted much attention in synthetic organic chemistry.[6] Strategies to prepare this skeleton include [4 + 2]-cycloadditions,[7] sigmatropic rearrangements,[8] Pummerer-induced cyclizations,[9] intramolecular condensation of amines onto carbonyl compounds,[10] 1,3-dipolar cycloadditions,[11] reactions of isocyanates with isocyanides,[12] and transition-metal-mediated cyclization reactions.[13] The related 1-azaspirocyclic structure of the erythrina alkaloids has long been of interest in development of synthetic strate-

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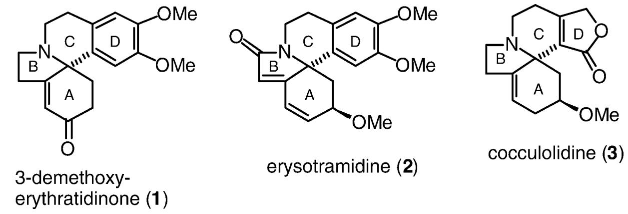

3-demethoxy-erythratidinone (**1**) erysotramidine (**2**) cocculolidine (**3**)

FIGURE 1.

gies for the efficient formation of their core ring system.[14] Erythrina alkaloids are generally classified into two groups according to their structural features:[15] those whose D-rings are aromatic (e.g., 3-demethoxyerythratidinone (**1**) and erysotramidine (**2**)) and the others whose D-rings possess an unsaturated lactone (e.g., cocculolidine (**3**) (Figure 1).[16] Many different approaches have been employed for the synthesis of this class of natural products. Taking the final step of bond formation into consideration, the methods for building up the erythrinan ring system can be loosely classified into seven different reaction types: (1) C-ring formation with the C-5 quaternary center being constructed by intramolecular cyclization;[17] (2) C-ring formation by electrophilic substitution;[18] (3) A-ring formation by an intramolecular aldol reaction;[19] (4) A-ring formation from a benzoindolizidine fragment;[20] (5) B-ring formation utilizing a C-5 spiroisoquinoline system;[21] (6) B- and C-ring formation by intramolecular annulation of dibenzazonine;[22] and (7) an assortment of miscellaneous methods.[23]

On the basis of our earlier work with the erythrina skeleton,[24] we felt that a suitably substituted hexahydroindolinone *N*-acyliminium ion precursor might allow for a facile entry to the tetracyclic core of erysotramidine (**2**). *N*-Acyliminium ions have historically occupied an important position as versatile intermediates for the construction of a wide array of nitrogen-containing molecules, due to their susceptibility to nucleophilic attack.[25] Of particular importance are the reactions of cyclic *N*-acyliminium ions with π-nucleophiles in carbon–carbon bond-forming processes, with a great deal of attention given to cyclizations leading to alkaloids and other nitrogen-containing biologically active compounds.[25] These intramolecular α-amidoalkylations proceed stereoselectively[26] due to steric control by the substituents already present in the ring[27] or along the chain connecting the π-nucleophiles and the nitrogen atom.[28] In this paper, we detail our observations dealing with the intramolecular electrophilic aromatic substitution reaction of various hexahydroindolinones which are readily formed by the condensation of an appropriate amine with a (1-substituted-2-oxocyclohexyl)acetic acid derivative. To highlight the method, the above synthetic strategy was used to assemble (±)-erysotramidine (**2**).[29]

Results and Discussion

The potential of using hexahydroindolinone derivatives for the synthesis of various erythrina alkaloids prompted us to first carry out some model studies to probe the likelihood of this approach for 1-azaspirocyclic ring assemblage. Our synthesis of the starting bicyclic lactam substrates follows a methodology similar to that previ-

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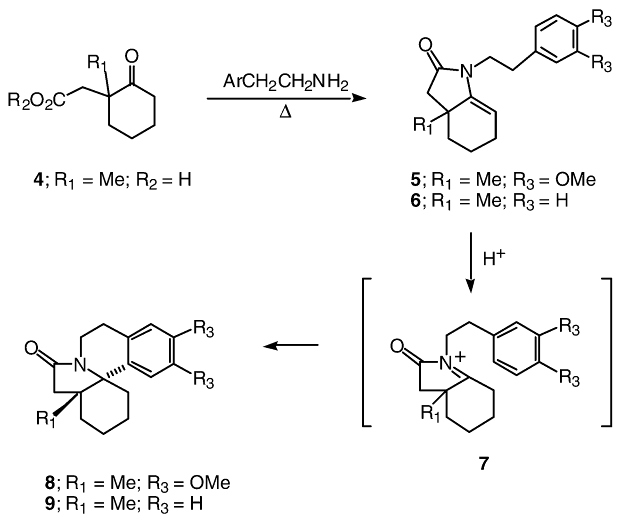
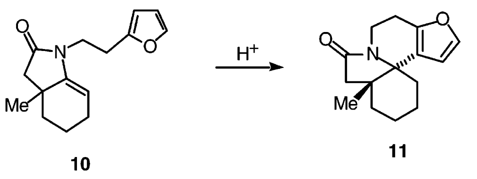
SCHEME 1



SCHEME 2

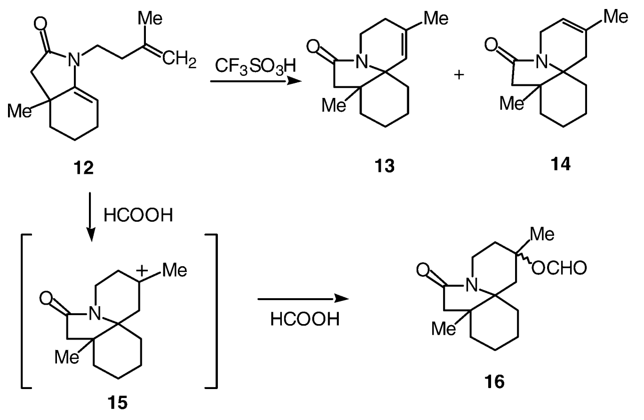


ously described in the literature.[30] Condensation of the appropriate amine with a (1-substituted-2-oxocyclohexyl)-acetic acid derivative (i.e., **4**) under Dean–Stark conditions in xylene at 160 °C for 1 h afforded the desired bicyclic lactams in high yield. The resulting aryl lactam precursors (i.e., **5** and **6**) were smoothly converted to the desired tetracyclic products in essentially quantitative yield when treated with either trifluoroacetic acid (**8**) or trifluoromethanesulfonic acid (**9**). The formation of a single lactam diastereomer is the result of the stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion (**7**) from the least hindered side (Scheme 1).[31]

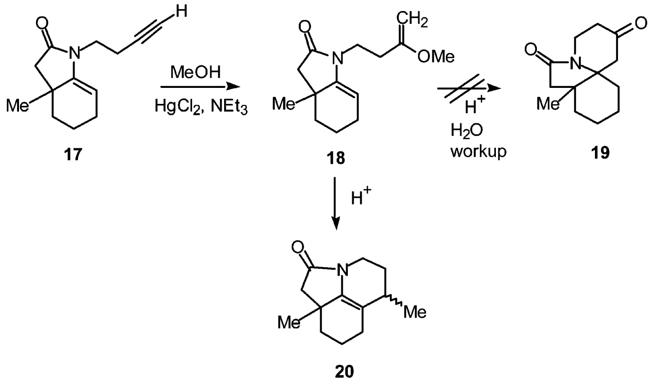
A series of additional experiments showed that this electrophilic-induced cyclization succeeds with a variety of substrates containing tethered π-bonds. Thus, we were pleased to find that the analogous furanyl substituted hexahydroindolinone system **10** also underwent a related acid-induced cyclization to give the tetracyclic substituted lactam **11** in 78% yield (Scheme 2). This cyclization is especially noteworthy considering that none of the previously reported syntheses of the nonaromatic erythroidine alkaloids have employed this strategy of assemblage.[32]

Because all of the previous examples involved aromatic π-bond cyclizations, we decided to study a hexahydroindolinone system that possesses a simple olefinic tether.

SCHEME 3



SCHEME 4



We found that treatment of the 3-methylbut-3-enyl-substituted lactam **12** with trifluoromethanesulfonic acid furnished a 3:1-mixture of octahydropyrido[2,1-*i*]indolones **13** and **14** in near quantitative yield. When the reaction was carried out in formic acid, the major product formed corresponded to formate **16** which was obtained as a 1:1 mixture of diastereomers. Formation of the above products can be nicely explained in terms of cyclization of the initially generated *N*-acyliminium ion onto the terminal π-bond to give carbocation **15** which subsequently reacts with HCO_2H to give **16** or else undergoes loss of a proton to produce **13** and **14** (Scheme 3).

Cationic cyclizations of alkynes have been exploited in a variety of transformations including polyene cyclizations[33] and reactions with *N*-acyliminium [34] and iminium ions.[35] We found, however, that the annulative ring cyclization of *N*-but-3-ynylhexahydroindolinone **17** failed to give any discernible products. Since we had a sample of **17** on hand, we converted it to the corresponding vinyl enol ether **18** by reaction with $HgCl_2$ in methanol. We then conducted the acid-catalyzed reaction of **18** and found, somewhat to our surprise, that the cyclization gave rise to pyrrolo[3,2,1-*ij*]quinolinone **20** in 48% yield as a 1:1 mixture of diastereomers (Scheme 4). While the acid-catalyzed cyclization of **18** did not achieve its intended

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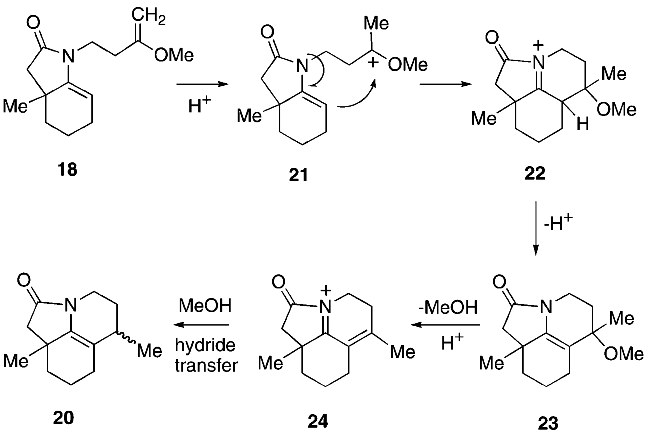
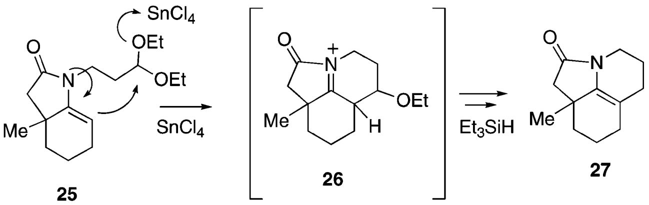
SCHEME 5



SCHEME 6



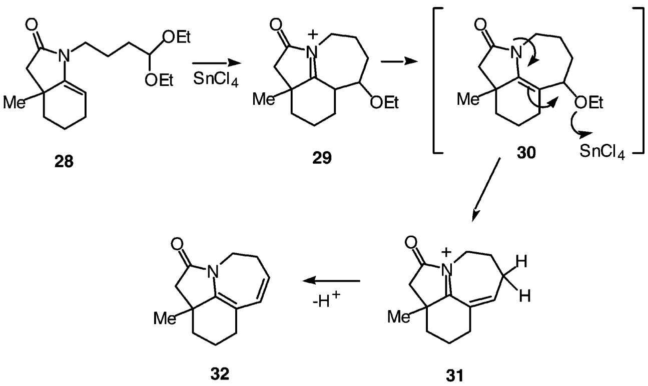
purpose of providing access to keto-lactam **19** it did undergo a novel reductive cyclization.

Scheme 5 outlines a working mechanistic hypothesis to rationalize the formation of **20**. We surmise that the initial protonation takes place with the more nucleophilic enol ether π-bond and that the resulting carbocation **21** undergoes a subsequent cyclization on the enamido π-bond to furnish *N*-acyliminium ion **22**. The most obvious path available to **22** is proton loss thereby providing **23** as a transient and nondetectable intermediate. More than likely, under the acidic conditions, **23** suffers loss of methanol and the resulting iminium ion **24** reacts further by a hydride transfer from methanol to give **20**. In support of this proposal, we found that the yield of **20** could be significantly increased (93%) when the reaction of **18** was carried out using *p*-TsOH in the presence of Et_3SiH as the reducing agent.

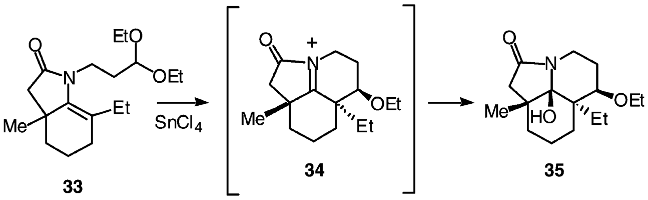
To provide still additional evidence for the mechanistic proposal outlined in Scheme 5, we prepared the *N*-(3,3-diethoxypropyl)-substituted hexahydroindolinone **25**. When **25** was treated with $SnCl_4/Et_3SiH$ in toluene it reacted further to furnish pyrrolo[3,2,1-*ij*]quinolinone **27** in 85% yield (Scheme 6). The conversion of **25** into **27** undoubtedly proceeds via the intermediacy of **26** and this transformation provides good support for the mechanistic paradigm presented in Scheme 5.

A somewhat related cyclization reaction was also observed with the homologous acetal **28**. In this case, the product isolated in 82% yield corresponded to azepino-[3,2,1-*ji*]indolone **32**. A stepwise sequence of cyclizations with the eventual generation of intermediate **31** may be reasonably invoked (i.e., **28** → **29** → **30** → **31**). With this system, loss of a proton from **31** to give **32** is apparently faster than bimolecular reduction with Et_3SiH (Scheme 7). This difference is probably related to the larger ring size present in **31**, which ultimately leads to a less strained π-bond in the final product. The same product (i.e., **32**) was formed in the absence of Et_3SiH.

SCHEME 7



SCHEME 8

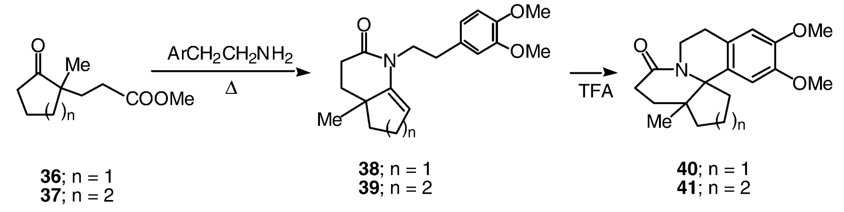


At this point in our studies we became interested in determining what effect an alkyl substituent on the enamido π-bond would have on the Lewis acid promoted reaction. We were specifically interested in determining what would happen to the *N*-acyliminium ion (i.e., **34**) derived from the cyclization of **33** since there is no possibility for proton loss. With this in mind, we treated the *N*-(3,3-diethoxypropyl)-7-ethyl-substituted hexahydroindolinone **33** with $SnCl_4$ in toluene, and this resulted in the formation of pyrrolo[3,2,1-*ij*]quinolinone **35** in 84% yield as a crystalline solid. The assignment of the stereochemistry of **35** was unequivocally established by an X-ray crystallographic study. The stereochemistry of the final product is the result of axial attack of water onto the thermodynamically most stable *N*-acyliminium ion intermediate (i.e., **34**), and this takes place from the least hindered β-face (Scheme 8).

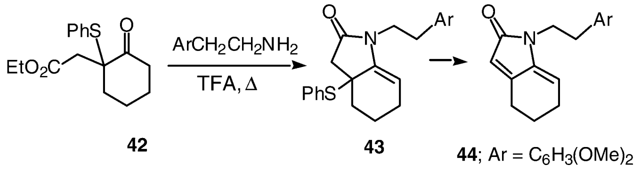
To further explore the scope and generality of these electrophilic-promoted cyclizations, we extended our studies to include the related hexahydro[*1*]pyrindinone **38** and 1*H*-quinolinone **39** systems. These compounds were prepared from the condensation of 2-(3,4-dimethoxyphenyl)ethylamine with either 3-(1-methyl-2-oxocyclopentyl) or 3-(1-methyl-2-oxocyclohexyl)propionic acid methyl ester (**36** or **37**) under Dean–Stark conditions. The resulting [6,5] and [6,6] lactams (i.e., **38** and **39**) were easily converted to the expected tetracyclic lactams **40** and **41** in 80% yield (Scheme 9). These two additional examples nicely demonstrate the facility with which the acid-induced cyclization cascade occurs using a variety of cyclic enamido lactams.

Encouraged by these results, we decided to apply the acid-catalyzed cyclization of hexahydroindolinones to the synthesis of erysotramidine (**2**) itself. To this end, bicyclic lactam **44** was prepared in 73% yield by condensation of 3,4-dimethoxyphenethylamine with ketoester **42** in the presence of TFA (Scheme 10). The formation of the α,β-unsaturated ene-amide **44** presumably involves initial generation of the expected hexahydroindolinone **43** followed by an acid-catalyzed elimination of the phenyl-

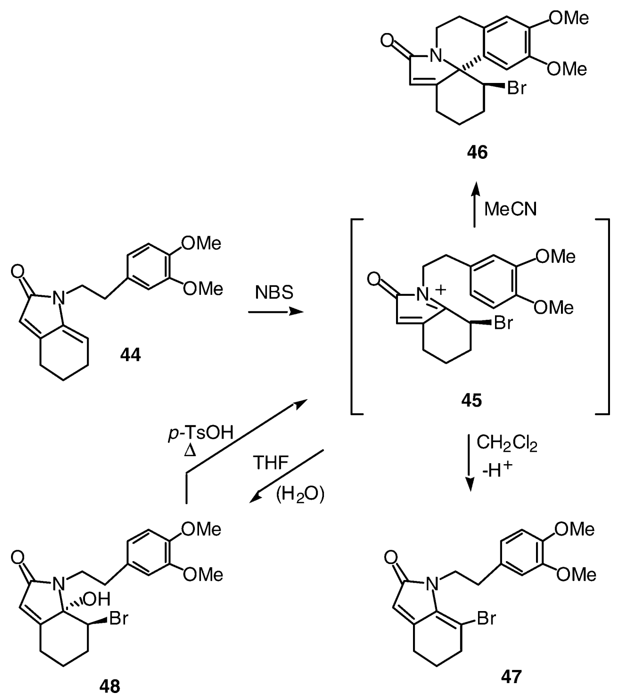
SCHEME 9



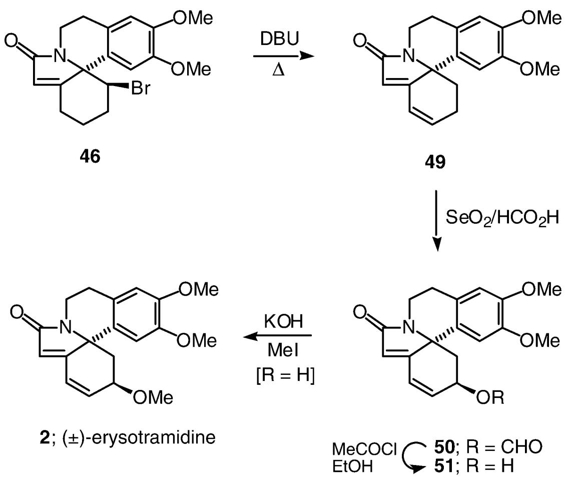
SCHEME 10



SCHEME 11



SCHEME 12



sulfanyl group. With **44** in hand, we attempted to induce an acid-promoted cyclization but all of our efforts failed to produce any characterizable products, perhaps as a consequence of the antiaromatic character of the resulting cationic intermediate. Alternatively, the failure of **44** to cyclize might be a consequence of protonation alpha to the lactam carbonyl group. The resulting cationic species would be incapable of cyclization.[36]

We were pleased to discover, however, that bicyclic lactam **44** underwent an extremely smooth cyclization to the desired erythrinan skeleton (i.e., **46**) in 78% yield when treated with NBS in acetonitrile. It is of interest to note that this reaction is markedly dependent on the nature of the solvent and that acetonitrile is the only solvent used which favors cyclization (Scheme 11). Thus, when **44** was subjected to NBS in CH$_2$Cl$_2$, bromoenamide **47** was obtained in 87% yield and its formation can be attributed to a competitive deprotonation of the presumed *N*-acyliminium ion intermediate **45**. The reaction of **44** with NBS in THF furnished aminal **48** in 77% yield which, in turn, gave a 5:3 mixture of **46** and **47** when heated with a trace of *p*-TsOH in CH$_3$CN. These unanticipated findings can be linked to the polarity of the solvent and consequently the reactivity of the incipient *N*-acyliminium ion **45**. The more polar solvent (CH$_3$CN) stabilizes the *N*-acyliminium ion and allows the cyclization to proceed. The other solvents favor deprotonation (CH$_2$Cl$_2$) or trapping of the cation by some adventitious water that was present in THF.

Subjection of **46** to DBU in refluxing xylene furnished the $\alpha,\beta,\gamma,\delta$-unsaturated diene-amide **49** in 75% yield. This product is presumably formed by an initial dehydrobromination followed by isomerization of the π-bond into the thermodynamically most stable position. Stereoselective allylic oxidation with selenium dioxide in the presence of formic acid gave a 1:1 mixture of formate **50** and alcohol **51** in 60% yield (based on recovered starting material) as single diastereomers. The stereochemical outcome of the oxidation involves attack by the oxidant from the least hindered α-position. Formate **50** was quantitatively transformed into alcohol **51** by treatment with acetyl chloride in ethanol.[37] Finally, compound **51** was converted into (±)-erysotramidine (**2**) in 91% yield by O-methylation using KOH/MeI in THF according to Tsuda's method (Scheme 12).[38]

In summary, we have shown that the intramolecular electrophilic aromatic substitution reaction of hexahy-

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(36) This suggestion was made by one of the reviewers.

(37) Lee, Y. S.; Lee, J. Y.; Kim, D. W.; Park, H. *Tetrahedron* **1999**, *55*, 4631.

(38) (a) Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (c) Hosoi, S.; Nagao, M.; Tsuda, Y.; Isobe, K.; Sano, T.; Ohta, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1505.

droindolinones allows for the rapid construction of the tetracyclic erythrinane skeleton. The cyclization reaction is also successful using variously substituted aryl-, furanyl-, and alkenyl-substituted bicyclic lactams under acidic conditions. The formation of the cyclized product as a single diastereomer is the result of the stereoelectronic preference for axial attack by the tethered π-bond onto the initially formed *N*-acyliminium ion from the least hindered side. The cyclization method was used to prepare (±)-erysotramidine. We expect that the total syntheses of other nonaromatic erythroidine alkaloids will also benefit from this general strategy. These investigations are currently underway and will be reported at some future date.

Experimental Section

General Procedure for the Preparation of Hexahydroindol-2-ones. To a 50 mL round-bottom flask equipped with a Dean–Stark trap and a reflux condensor was added (1-methyl-2-oxo-cyclohexyl)acetic acid[39] (**4**) (5.0 mmol) and the appropriate primary amine (5.5 mmol) in 25 mL of xylene. The mixture was heated in an oil bath at 160 °C for 1 h during which time water was collected in the Dean–Stark trap. The solvent was removed by distillation, and the residue was purified by flash chromatography on silica gel using 50% ether/hexane as the eluent.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (5) was prepared in 84% from keto acid **4** and 3,4-dimethoxyphenethylamine: IR (neat) 1717, 1672, 1514, 1260, 1028 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.01 (s, 3H), 1.40–1.50 (m, 1H), 1.64–1.78 (m, 3H), 1.98–2.12 (m, 1H), 2.15 (d, 2H, J = 2.5 Hz), 2.16–2.24 (m, 1H), 2.65–2.80 (m, 2H), 3.31 (ddd, 1H, J = 14.3, 8.9, 5.7 Hz), 3.78 (s, 3H), 3.81 (s, 3H), 3.80–3.88 (m, 1H), 4.75 (t, 1H, J = 3.5 Hz), 6.67–6.75 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.4, 22.7, 26.0, 32.4, 33.9, 36.2, 40.4, 46.3, 55.9, 97.2, 111.2, 112.0, 120.8, 131.1, 145.5, 147.6, 148.8, 173.6; HRMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1831.

3a-Methyl-1-phenethyl-1,3,3a,4,5,6-hexahydroindol-2-one (6) was prepared in 93% from keto acid **4** and phenethylamine: IR (neat) 1718, 1682, 1454, 1407, 1314, 1164 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.08 (s, 3H), 1.44–1.56 (m, 1H), 1.71–1.81 (m, 3H), 2.02–2.23 (m, 2H), 2.21 (s, 2H), 2.75–2.90 (m, 2H), 3.38 (ddd, 1H, J = 14.3, 9.2, 5.7 Hz), 3.90 (ddd, 1H, J = 13.7, 9.2, 7.3 Hz), 4.79 (t, 1H, J = 3.5 Hz), 7.16–7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5, 22.8, 26.1, 33.0, 34.1, 36.3, 40.5, 46.4, 97.3, 126.6, 128.6, 129.0, 138.7, 145.7, 173.7; HRMS calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1622.

11,12-Dimethoxy-4a-methyl-1,2,3,4,4a,5,8,9-octahydroindolo[7a,1a]isoquinolin-6-one (8). To a solution of 0.05 g (0.16 mmol) of hexahydroindolone **5** in 3 mL of CH$_2$Cl$_2$ was added trifluoroacetic acid (0.04 mL, 0.48 mmol). The mixture was stirred at rt for 4 h, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give the title compound **8** as a colorless oil in 94% yield: IR (neat) 1682, 1515, 1258, 1207, 1093 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.71 (s, 3H), 1.57–1.90 (m, 6H), 1.92 (d, 2H, J = 16.2 Hz); 2.20 (d, 1H, J = 13.6 Hz), 2.65 (dd, 1H, J = 15.9, 2.9 Hz), 2.82 (t, 1H, J = 9.5 Hz), 2.86 (t, 1H, J = 7.3 Hz), 2.99 (ddd, 1H, J = 13.0, 13.0, 4.1 Hz), 3.84 (s, 3H), 3.86 (s, 3H), 4.24 (ddd, 1H, J = 13.0, 6.0, 1.6 Hz), 6.59 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.3, 21.5, 26.9, 29.1, 33.7, 34.2, 37.9, 40.5, 42.7, 55.9, 56.3, 64.1, 110.0, 112.2, 126.5, 131.6, 147.0, 147.6, 171.4; HRMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1840.

4a-Methyl-1,2,3,4,4a,5,8,9-octahydroindolo[7a,1a]isoquinolin-6-one (9). A solution of hexahydroindolone **6** (0.08 g, 0.3 mmol) in 1 mL of trifluoromethanesulfonic acid was heated in a microwave reactor at 10 W, 60 °C, for 5 min. The mixture was diluted with ether (20 mL) and neutralized with a saturated solution of NaHCO$_3$. The organic layer was separated, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 100% EtOAc as the eluent. The title compound **9** was obtained as a colorless oil in 88% yield (0.07 g): IR (neat) 1688, 1488, 1452, and 1307 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.69 (s, 3H), 1.55–1.98 (m, 7H), 1.92 (d, 1H, J = 16.3 Hz), 2.16–2.23 (m, 1H), 2.75 (ddd, 1H, J = 15.9, 4.1, 1.6 Hz), 2.85 (d, 1H, J = 16.3 Hz), 2.90 (ddd, 1H, J = 15.9, 12.0, 6.0 Hz), 3.05 (tdd, 1H, J = 13.0, 4.4, 1.3 Hz), 4.23 (ddd, 1H, J = 13.0, 6.4, 2.2 Hz), 7.10–7.21 (m, 3H), 7.42–7.48 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.8, 21.3, 26.9, 29.5, 33.4, 34.2, 37.0, 40.4, 42.7, 64.4, 126.0, 126.4, 126.6, 130.0, 134.0, 139.6, 171.5; HRMS calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1616.

1-(2-Furan-2-ylethyl)-3a-methyl-1,3a,4,5,6-hexahydroindol-2-one (10) was prepared in 65% yield from keto acid **4** and 2-furan-2-yl-ethylamine: IR (thin film) 2860, 1674, 1449, 1072 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.12 (s, 3H), 1.51 (m, 1H), 1.73–1.77 (m, 3H), 2.10–2.23 (m, 4H), 2.87 (t, 2H, J = 7.2 Hz), 3.45 (m, 1H), 3.93 (m, 1H), 4.77 (t, 1H, J = 3.2 Hz), 6.06 (t, 1H, J = 2.4 Hz), 6.26 (t, 1H, J = 2.0 Hz), 7.30 (t, 1H, J = 1.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5, 22.8, 25.6, 26.1, 34.1, 36.3, 37.9, 46.4, 97.3, 106.5, 110.4, 141.5, 145.4, 152.7, 173.8; HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1411.

1,2-Furo[3,2-*c*]-7a-methyl-3,4,7,7a,8,9,10,11-octahydropyrido[2,1-*i*]indol-6-one (11). To a solution of 0.31 g (1.3 mmol) of hexahydroindolone **10** in 13 mL of CH$_2$Cl$_2$ was added trifluoroacetic acid (0.3 mL, 3.8 mmol). The mixture was stirred at rt for 4 h, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using EtOAc as the eluent. The title compound **11** was obtained as a colorless oil in 78% yield: IR (thin film) 2861, 1687, 1452, 1416, 1327 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.72 (s, 3H), 1.47–1.58 (m, 4H), 1.71–1.78 (m, 3H), 1.90 (d, 1H, J = 16.4 Hz), 2.10 (m, 1H), 2.70 (m, 2H), 2.79 (d, 1H, J = 16.4 Hz), 3.01 (dddd, 1H, J = 24.4, 11.2, 6.0, 1.6 Hz), 4.38 (ddd, 1H, J = 12.6, 6.0, 1.6 Hz), 6.38 (d, 1H, J = 1.6 Hz), 7.30 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.9, 22.1, 23.4, 26.5, 33.7, 33.8, 36.5, 40.2, 42.1, 63.9, 108.5, 119.9, 141.3, 147.8, 172.3; HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1406.

3a-Methyl-1-(3-methylbut-3-enyl)-1,3,3a,4,5,6-hexahydroindol-2-one (12) was prepared in 81% yield from keto acid **4** and 3-methylbut-3-enylamine: IR (neat) 1717, 1679, 1619, 1454, 1406, 1318 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.14 (s, 3H), 1.44–1.56 (m, 1H), 1.70–1.81 (m, 3H), 1.75 (s, 3H), 2.02–2.14 (m, 1H), 2.17–2.27 (m, 3H), 2.21 (s, 2H), 3.22 (dt, 1H, J = 13.7, 6.7 Hz), 3.80 (dt, 1H, J = 13.7, 8.3 Hz), 4.68 (s, 1H), 4.74 (s, 1H), 4.76 (t, 1H, J = 3.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.6, 22.4, 22.9, 26.3, 34.1, 34.7, 36.3, 37.4, 46.5, 97.1, 112.3, 142.7, 145.7, 173.8; HRMS calcd for $C_{14}H_{21}NO$ 219.1623, found 219.1620.

2,7a-Dimethyl-3,4,7,7a,8,9,10,11-octahydropyrido[2,1-*i*]indol-6-one (13). A solution of hexahydroindolone **12** (0.2 g, 0.9 mmol) in 1 mL of trifluoromethanesulfonic acid was stirred at rt for 2 h. The mixture was diluted with ice–water (20 mL) and neutralized with a saturated solution of NaHCO$_3$. After extraction with ether, the organic layer was combined, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 50% ether in hexane as the eluent to give a 3:1 mixture of lactams **13** and **14**. Compound **13** was obtained pure in 75% yield (0.14 g) as a white solid: mp 77–79 °C; IR (KBr) 1688, 1452, 1422, 1307 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.78 (s, 3H), 1.15–1.42 (m, 4H), 1.52–1.65 (m, 3H), 1.68 (s, 3H), 1.77 (d, 1H, J = 16.0 Hz), 1.83 (dd, 1H, J = 16.8, 4.8 Hz), 1.91 (dq, 1H, J = 13.0, 2.8 Hz), 2.02–2.14 (m,

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[39] Asselin, A. A.; Humber, L. G.; Dobson, T. A.; Komlossy, J.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 787.

1H), 2.63 (d, 1H, $J = 16.0$ Hz), 2.80 (dddd, 1H, $J = 13.0$, 11.8, 4.8, 1.3 Hz), 4.03 (ddd, 1H, $J = 13.0$, 6.7, 0.6 Hz), 5.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.2, 23.9, 25.7, 29.2, 33.4, 33.6, 36.0, 40.3, 42.4, 62.6, 121.7, 132.3, 172.0; HRMS calcd for $C_{14}H_{21}NO$ 219.1623, found 219.1631.

2,7a-Dimethyl-1,4,7,7a,8,9,10,11-octahydropyrido[2,1-*i*]indol-6-one (14) was obtained from the chromatographic separation in 25% yield (0.05 g) as a white solid: mp 49−52 °C; IR (KBr) 1697, 1669, 1438, 1394 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.20−1.59 (m, 8H), 1.64 (s, 3H), 1.78−1.86 (m,1H), 2.12 (s, 2H), 2.16−2.26 (m, 1H), 3.19−3.28 (m, 1H), 4.26−4.35 (m, 1H), 5.29 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.9, 22.2, 24.1, 29.2, 36.0, 36.4, 37.9, 38.2, 45.1, 61.6, 117.1, 131.8, 175.1; HRMS calcd for $C_{14}H_{21}NO$ 219.1623, found 219.1631.

Formic Acid 2,7a-Dimethyl-6-oxodecahydropyrido[2,1-*i*]indol-2-yl Ester (16). A solution of hexahydroindolone **12** (0.1 g, 0.46 mmol) in 2 mL of anhydrous formic acid was stirred at rt for 5 h. The mixture was diluted with water (20 mL) and neutralized with a saturated solution of $NaHCO_3$. After extraction with ether, the organic layer was combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ether as the eluent. A 1:1 mixture of the two diastereomers of **16** was obtained as the major product in 58% yield. The minor product (15%) was identified as 2,7a-dimethyl-3,4,7,7a,8,9,10,11-octahydropyrido[2,1-*i*]indol-6-one (**13**).

The title compound **16** showed the following spectral properties: IR (neat) 1721, 1687, 1445, 1411, 1135 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 and 1.00 (s, 3H), 1.25−1.50 (m, 5H), 1.52 and 1.69 (s, 3H), 1.53−1.61 (m, 2H), 1.70−1.77 (m, 1H), 1.82−1.90 (m, 2H), 1.95 and 2.09 (d, 2H, $J = 14.8$ Hz), 2.12 and 2.45 (dd, 1H, $J = 14.8$, 1.4 Hz), 2.36 (m, 1H), 2.82 (dt, $J = 14.3$, 7.1 Hz) and 2.90 (ddd, $J = 13.8$, 13.8, 1.9 Hz) (1H), 3.90 (ddd, $J = 13.8$, 5.2, 1.9 Hz) and 3.94 (dt, $J = 14.$, 5.2 Hz) (1H), 7.88 and 8.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.6, 21.7, 21.8, 23.2, 23.5, 26.2, 28.0, 30.2, 32.7, 33.1, 34.3, 34.5, 35.1, 35.3, 35.7, 36.2, 39.1, 39.2, 39.7, 43.4, 43.6, 62.3, 81.5. 82.4, 160.2, 160.8, 174.7; HRMS calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1685.

1-But-3-ynyl-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (17) was prepared in 67% yield from (1-methyl-2-oxocyclohexyl)acetic acid (**4**) and but-3-ynylamine: IR (neat) 1720, 1678, 1405, 1314, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.42−1.53 (m, 1H), 1.68−1.80 (m, 3H), 1.92 (t, 1H, $J = 2.1$ Hz), 2.00−2.19 (m, 2H), 2.20 (s, 2H), 2.33−2.43 (m, 2H), 3.30 (ddd, 1H, $J = 13.9$, 7.6, 6.0 Hz), 3.80 (dt, 1H, $J = 15.9$, 7.6 Hz), 4.77 (t, 1H, $J = 3.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 18.5, 22.7, 26.2, 33.9, 36.4, 37.8, 46.3, 70.0, 81.0, 97.4, 145.2, 173.8; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1308.

1-(3-Methoxybut-3-enyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (18). To a solution of the above but-3-ynylhexahydroindolone **17** (0.37 g, 1.8 mmol) and NEt_3 (0.4 mL, 2.7 mmol) in anhydrous methanol (10 mL) was added $HgCl_2$ (0.37 g, 1.4 mmol). The suspension was stirred vigorously under reflux for 4 h. The solvent was removed under reduced pressure, and the residue was diluted with ether. The precipitate that formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel using 50% of ether in hexane with 3% NEt_3 as the eluent. The title compound **18** was obtained as a colorless oil in 63% yield (0.27 g): IR (neat) 1724, 1677, 1403, 1314, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.45−1.55 (m, 1H), 1.70−1.80 (m, 3H), 2.01−2.13 (m, 1H), 2.15−2.35 (m, 3H), 2.21 (s, 2H), 3.30 (ddd, 1H, $J = 14.0$, 7.4, 6.4 Hz), 3.48 (s, 3H), 3.78 (dt, 1H, $J = 14.0$, 7.4 Hz), 3.86 (s, 2H), 4.78 (t, 1H, $J = 3.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 22.8, 26.3, 32.6, 34.1, 36.3, 37.3, 46.5, 54.9, 82.5, 97.0, 145.7, 161.0, 173.8; HRMS calcd for $C_{14}H_{21}NO_2$ 235.1572, found 235.1568.

6,9a-Dimethyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (20). To a solution of the above enol ether **18** (0.12 g, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was slowly added trifluoroacetic acid (0.12 mL, 1.5 mmol). The mixture was allowed to warm to rt, stirred for 2 h, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 50% ether in hexane as the eluent. The title compound was obtained as a 1:1 mixture of diastereomers: IR (neat) 1728, 1690, 1404, 1365, 1312 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 and 0.96 (d, 3H, $J = 7.1$ Hz), 1.08−1.10 (s, 3H), 1.34−1.50 (m, 2H), 1.63−1.75 (m, 3H), 1.77−2.08 (m, 3H), 2.12−2.21 (m, 3H), 3.14 (td, 1H, $J = 13.8$, 3.8 Hz) and 3.25 (ddd, 1H, $J = 12.4$, 8.1, 4.3 Hz), 3.60 (ddd, 1H, $J = 12.4$, 8.1, 4.8 Hz) and 3.72 (dt, 1H, $J = 12.9$, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 18.7, 18.8, 19.9, 24.1, 24.9, 25.8, 28.8, 29.5, 29.8, 30.0, 33.9, 34.0, 35.1, 35.2, 35.4, 36.9, 46.8, 47.2, 110.8, 111.3, 137.9, 138.1, 172.7, 172.9; HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1474.

1-(3,3-Diethoxypropyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (25) was prepared in 76% yield from keto acid **4** and 3,3-diethoxypropylamine: IR (neat) 1722, 1680, 1408, 1129, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, 3H, $J = 7.0$ Hz), 1.17 (t, 3H, $J = 7.0$ Hz), 1.21 (s, 3H), 1.43−1.55 (m, 1H), 1.66−1.90 (m, 5H), 2.06 (dtd, 1H, $J = 17.8$, 8.6, 3.5 Hz), 2.12−2.20 (m, 1H), 2.19 (s, 2H), 3.21 (ddd, 1H, $J = 14.0$, 8.3, 5.7 Hz), 3.38−3.50 (m, 2H), 3.55−3.72 (m, 3H), 4.45 (t, 1H, $J = 5.7$ Hz), 4.77 (t, 1H, $J = 3.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 18.5, 22.8, 26.1, 31.4, 34.0, 35.4, 36.3, 46.4, 61.6, 61.8, 97.3, 101.3, 145.7, 173.7; HRMS calcd for $C_{16}H_{27}NO_3$ 281.1991, found 281.1986.

9a-Methyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (27). To a solution of the above acetal **25** (1.0 mmol) in 10 mL of anhydrous toluene cooled in an ethylene glycol−CO_2 bath were added Et_3SiH (0.16 mL, 1.0 mmol) and $SnCl_4$ (0.12 mL, 1.0 mmol). The solution was allowed to warm to rt, stirred for 1 h, and then quenched by the addition of 10 mL of water. The mixture was extracted with ether, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 50% ether/hexane as the eluent to give **27** in 85% yield: IR (neat) 1691, 1676, 1456, 1409, and 1366 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.40−1.51 (m, 1H), 1.60−2.09 (m, 9H), 2.22 (dd, 2H, $J = 20$, 15.9 Hz), 3.19 (ddd, 1H, $J = 13.0$, 9.5, 3.2 Hz), and 3.77 (dt, 1H, $J = 13.0$, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 21.6, 25.5, 25.7, 27.0, 34.2, 35.3, 38.8, 47.2, 106.8, 138.8, 173.1. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.10; H, 9.00; N, 7.20.

1-(4,4-Diethoxybutyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (28) was prepared in 75% from keto acid **4** and 4,4-diethoxybutylamine: IR (neat) 1720, 1677, 1401, 1127, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.18 (t, 6H, $J = 7.0$ Hz), 1.45−1.82 (m, 8H), 2.08 (dtd, 1H, $J = 17.8$, 8.6, 3.5 Hz), 2.16−2.22 (m, 1H), 2.22 (s, 2H), 3.14−3.24 (m, 1H), 3.46 (dq, 2H, $J = 9.5$, 7.3 Hz), 3.56−3.67 (m, 3H), 4.47 (t, 1H, $J = 5.1$ Hz), 4.77 (t, 1H, $J = 3.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 18.5, 22.2, 22.8, 26.3, 31.1, 34.1, 36.3, 39.0, 46.5, 61.2, 61.5, 97.2, 102.6, 145.8, 173.9; HRMS calcd for $C_{17}H_{29}NO_3$ 295.2147, found 295.2144.

10a-Methyl-4,5,8,9,10,10a-hexahydro-1*H*-azepino[3,2,1-*hi*]indol-2-one (32). To a solution of the above acetal **28** (1.0 mmol) in 10 mL of anhydrous toluene cooled in an ethylene glycol−CO_2 bath were added Et_3SiH (0.16 mL, 1.0 mmol) and $SnCl_4$ (0.12 mL, 1.0 mmol). The solution was allowed to warm to rt, stirred for 1 h, and then quenched by the addition of 10 mL of water. The mixture was extracted with ether, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 50% ether/hexane as the eluent to give **32** in 82% yield: IR (neat) 1716, 1662, 1615, 1363, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.41−1.52 (m, 1H), 1.69−1.82 (m, 3H), 2.10−2.33 (m, 3H), 2.25 (d, 2H, J

= 1.9 Hz), 2.47 (dddd, 1H, J = 16.8, 7.0, 5.4, 1.3 Hz), 2.93 (dd, 1H, J = 13.0, 9.5 Hz), 4.26 (ddd, 1H, J = 13.0, 5.4, 2.9 Hz), 5.56 (dd, 1H, J = 11.4, 1.9 Hz), 5.71 (ddd, 1H, J = 11.4, 7.6, 4.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.7, 26.1, 29.3, 30.2, 33.6, 37.7, 41.0, 46.7, 108.4, 128.5, 129.3, 143.9, 173.4; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1312.

1-(3,3-Diethoxypropyl)-7-ethyl-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (33). A mixture of 1-(3,3-diethoxypropyl)-3a-methyl-7-vinyl-1,3,3a,4,5,6-hexahydroindol-2-one[40] (0.35 g, 1.14 mmol) and 10% of palladium on charcoal (0.05 g) in absolute ethanol (10 mL) was stirred at rt in a flask equipped with a balloon of hydrogen gas. After being stirred for 20 h, the mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using a 50% ether /hexane mixture as the eluent. The title compound **33** was obtained in 83% yield (0.29 g) as a colorless oil: IR (neat) 1714, 1676, 1371, 1133, 1061 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.98 (t, 3H, J = 7.6 Hz), 1.05 (s, 3H) 1.18 (t, 3H, J = 7.0 Hz), 1.19 (t, 3H, J = 7.0 Hz), 1.36−1.48 (m, 1H), 1.60−2.16 (m, 8H), 2.12 (d, 1H, J = 15.6 Hz), 2.20 (d, 1H, J = 15.6 Hz), 3.32−3.55 (m, 4H), 3.59−3.72 (m, 2H), 3.99 (ddd, 1H, J = 14.0, 10.2, 6.0 Hz), 4.51 (t, 1H, J = 5.7 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.3, 15.5, 18.8, 24.7, 25.5, 29.3, 32.2, 34.6, 38.5, 39.1, 47.0, 61.7, 62.4, 101.5, 115.5, 137.8, 175.4; HRMS calcd for $C_{18}H_{31}NO_3$ 309.2304, found 309.2312.

6-Ethoxy-6a-ethyl-9b-hydroxy-9a-methyloctahydropyrrolo[3,2,1-*ij*]quinolin-2-one (35). To a solution of the above acetal **33** (0.29 g, 0.94 mmol) in 10 mL of anhydrous toluene cooled in an ethylene glycol−CO$_2$ bath was added SnCl$_4$ (0.11 mL, 0.94 mmol). The solution was allowed to warm to rt, stirred for 2 h, and then quenched by the addition of 10 mL of water. The mixture was extracted with ether, and the combined organic phases were dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 50% ether/hexane as the eluent. The title compound **35** was obtained as a white solid in 84% yield (0.22 g): mp 131−133 °C; IR (KBr) 1690, 1454, 1398, 1098, 1067 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.76 (t, 3H, J = 7.1 Hz), 1.08 (s, 3H), 1.22 (t, 3H, J = 6.7 Hz), 1.30 (dddd, 1H, J = 14.8, 14.8, 7.6, 1.9 Hz), 1.39 (dt, 1H, J = 8.6, 13.3 Hz), 1.54 (dt, 1H, J = 13.8, 3.8 Hz), 1.57−1.72 (m, 4H), 1.75−1.88 (m, 3H), 1.89−1.99 (m, 1H), 2.26 (d, 1H, J = 16.9 Hz), 2.32 (d, 1H, J = 16.9 Hz), 3.16 (ddd, 1H, J = 13.3, 13.3, 4.8 Hz), 3.36 (ddt, 1H, J = 9.1, 7.1, 7.1 Hz), 3.49 (t, 1H, J = 2.9 Hz), 3.67 (ddt, 1H, J = 9.1, 7.1, 7.1 Hz), 3.94 (dd, 1H, J = 13.3, 6.2 Hz), 6.56 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 7.7, 15.5, 17.4, 19.9, 22.4, 26.0, 26.6, 31.5, 33.5, 38.9, 44.4, 48.9, 66.7, 78.8, 92.8, 171.6. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.57; H, 9.77; N, 4.96.

The structure of **35** was unequivocally established by an X-ray crystallographic study.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4a-methyl-1,3,4,4a,5,6-hexahydro[1]pyrindin-2-one (38) was prepared in 41% yield from 3-(1-methyl-2-oxocyclopentyl)propionic acid methyl ester (**36**) and 2-(3,4-dimethoxyphenyl)ethylamine: IR (neat) 1664, 1631, 1514, 1261, 1235, 1029 cm^{-1};^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04 (s, 3H), 1.60−1.70 (m, 2H), 1.73−1.86 (m, 2H), 2.27 (ddd, 1H, J = 15.6, 8.9, 3.2 Hz), 2.41−2.64 (m, 3H), 2.75 (t, 2H, J = 8.6 Hz), 3.66 (dt, 1H, J = 13.3, 7.9 Hz), 3.83 (s, 3H), 3.85 (s, 3H), 3.90 (dt, 1H, J = 13.3, 7.9 Hz), 4.78 (t, 1H, J = 2.2 Hz), 6.69−6.79 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.1, 28.4, 29.7, 32.8, 33.1, 39.6, 42.7, 45.1, 56.0, 101.7, 111.3, 112.2, 120.9, 131.7, 147.3, 147.7, 149.0, 168.7; HRMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1842.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4a-methyl-3,4,4a,5,6,7-hexahydro-1*H*-quinolin-2-one (39). In a 10 mL reaction tube were placed 3-(1-methyl-2-oxocyclohexyl)propionic acid methyl ester (**37**) (1.0 mmol), 2-(3,4-dimethoxyphenyl)ethylamine (3.0 mmol), and xylene (1.0 mL). The reaction vessel was heated in a microwave reactor at 150 W at 160 °C for 5 h. The reaction mixture was allowed to cool to rt, and the crude product was purified by flash silica gel chromatography using a 50% ether in hexane mixture as the eluent. The title compound **39** was obtained in 67% yield as a colorless oil: IR (neat) 1663, 1636, 1514, 1261, 1233, 1158, 1028 cm^{-1};^{1}H NMR (400 MHz, CDCl$_3$) δ 1.03 (s, 3H), 1.37−1.47 (m, 1H), 1.52−1.70 (m, 5H), 2.05−2.16 (m, 1H), 2.17−2.27 (m, 1H), 2.46−2.60 (m, 2H), 2.68 (ddd, 1H, J = 13.3, 9.5, 7.3 Hz), 2.81 (ddd, 1H, J = 13.3, 9.5, 7.3 Hz), 3.80−3.88 (m, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 5.13 (dd, 1H, J = 5.1, 2.5 Hz), 6.73−6.79 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 17.9, 22.9, 24.9, 29.3, 32.5, 33.1, 34.2, 38.2, 45.1, 56.0, 105.0, 111.3, 112.1, 120.7, 130.9, 142.1, 147.6, 148.9, 168.5; HRMS calcd for $C_{20}H_{27}NO_3$ 329.1991, found 329.1988.

8,9-Dimethoxy-13a-methyl-1,2,5,6,11,12,13,13a-octahydrocyclopenta[2,3]pyrido-[2,1-*a*]isoquinolin-3-one (40). To a solution of 0.05 g (0.16 mmol) of hexahydro[1]pyrindin-2-one **38** in 1.0 mL of CH$_2$Cl$_2$ was added trifluoroacetic acid (0.1 mL). The mixture was stirred at rt for 16 h, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give **40** as a white solid in 80% yield (0.04 g): mp 118−120 °C; IR (neat) 1633, 1516, 1407, 1258, 1217 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.78 (s, 3H), 1.47 (dt, 1H, J = 12.9, 3.3 Hz), 1.93−2.18 (m, 4H), 2.20−2.35 (m, 2H), 2.37−2.52 (m, 4H), 2.66 (ddd, 1H, J = 14.3, 12.4, 1.9 Hz), 2.88 (ddd, 1H, J = 16.2, 12.4, 4.3 Hz), 3.83 (s, 6H), 4.87 (dd, 1H, J = 11.9, 3.8 Hz), 6.55 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.8, 21.5, 29.1, 29.9, 34.1, 39.9, 42.0, 42.5, 44.5, 55.9, 56.2, 73.7, 110.5, 111.8, 129.0, 133.6, 147.1, 147.3, 168.9. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.31; H, 8.04; N, 4.35.

7,8-Dimethoxy-13a-methyl-1,4,5,10,11,12,13,13a-octahydro-2*H*-3a-azabenzo[*d*]phenanthren-3-one (41). To a solution of hexahydro-1*H*-quinolinone **39** (0.2 g, 0.6 mmol) in 6.0 mL of CH$_2$Cl$_2$ was added several drops of trifluoromethanesulfonic acid, and the mixture was stirred at rt for 2 h. The mixture was diluted with ice−water (20 mL) and neutralized with a saturated solution of NaHCO$_3$. After extraction with ether, the organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ether as the eluent to give **41** in 80% yield (0.16 g) as a white solid: mp 143−144 °C; IR (KBr) 1631, 1514, 1409, 1258, 1218 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.62 (s, 3H), 1.14−1.20 (m, 1H), 1.57 (d, 1H, J = 14.8 Hz), 1.68−1.82 (m, 3H), 1.88−2.00 (m, 2H), 2.22−2.38 (m, 2H), 2.42−2.56 (m, 4H), 2.80−2.90 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.85−4.92 (m, 1H), 6.57 (s, 1H), 7.35 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.7, 21.9, 23.6, 28.6, 30.0, 30.1, 35.8, 36.1, 37.0, 38.4, 55.6, 56.3, 65.8, 112.1, 112.3, 130.1, 132.4, 145.8, 147.1, 168.4. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.70; H, 8.24; N, 4.26.

(2-Oxo-1-phenylthiocyclohexyl)acetic Acid Ethyl Ester (42). To a solution containing 2.1 g (10.2 mmol) of 2-phenythiocyclohexanone[41] in 30 mL of THF was added 0.45 g (11.2 mmol) of NaH at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The resulting mixture was added to 1.87 g (11.2 mmol) of ethyl bromoacetate at room temperature. The solution was stirred for 8 h at 25 °C and was quenched by the addition of water. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 2.4 g (82%) of keto ester **42** as a colorless oil: IR (neat) 2937, 1733, 1701 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.21 (t, 3H, J

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[40] Hexahydroindolinone **33** was prepared by the selective bromination of **28** followed by a palladium-catalyzed cross-coupling reaction with vinyl tributyltin and a subsequent catalytic hydrogenation of the vinyl group. Details of the procedure are described in the Supporting Information.

[41] Coates, R. M.; Pigott, H. D.; Ollinger, J. *Tetrahedron Lett.* **1974**, *15*, 3955.

= 7.2 Hz), 1.72−1.89 (m, 2H), 2.05−2.21 (m, 3H), 2.40 (ddd, 1H, J = 13.3, 4.0, 2.4 Hz), 2.47 (d, 1H, J = 16.8 Hz), 2.48−2.59 (m, 1H), 2.86 (d, 1H, J = 16.8 Hz), 3.21 (ddd, 1H, J = 15.3, 13.6, 6.0 Hz), 4.07 (dq, 2H, J = 7.2, 2.8 Hz), 7.29−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.3. 26.0, 36.3, 37.3, 40.7, 58.0, 60.4, 129.0, 129.4, 129.9, 136.9, 170.7, 204.8; HRMS calcd for $C_{16}H_{20}O_3SLi$ (M + Li$^+$) 299.1293, found 299.1289.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-1,4,5,6-tetrahydroindol-2-one (44). To a solution containing 2.3 g (7.9 mmol) of **42** in 16 mL of toluene at room temperature was added 2.1 g (11.8 mmol) of 3,4-dimethoxyphenethylamine. The reaction mixture was heated at reflux for 3 h and then cooled to room temperature. To the resulting mixture was added 1.35 g (11.8 mmol) of trifluoroacetic acid at 25 °C, and the solution was heated at reflux for an additional 48 h. After cooling, 30 mL of water was added to the reaction mixture. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 1.7 g (73%) of ene-amide **44** as a yellow pale oil: IR (neat) 2832, 1689, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (m, 2H), 2.28 (dt, 2H, J = 5.6, 4.8 Hz), 2.60 (dt, 2H, J = 6.8, 1.6 Hz), 2.80 (t, 2H, J = 7.6 Hz), 3.73 (t, 2H, J = 7.6 Hz), 3.85 (s, 6H), 5.47 (dt, 1H, J = 4.8, 1.6 Hz), 5.74 (d, 1H, J = 1.6 Hz), 6.69 (d, 1H, J = 1.6 Hz), 6.74 (dd, 1H, J = 8.4, 1.6 Hz), 6.79 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 24.2, 24.5, 34.7, 40.6, 55.77, 55.83, 110.0, 111.1, 112.0, 115.6, 120.6, 131.4, 139.7, 147.1, 147.5, 148.7, 170.1; HRMS calcd for $C_{18}H_{21}NO_3Li$ (M + Li$^+$) 306.1681, found 306.1673.

1-Bromo-11,12-dimethoxy-1,2,3,4,8,9-hexahydroindolo-[7a,1a]isoquinolin-6-one (46). To a solution containing 1.2 g (4.0 mmol) of **44** in 400 mL of acetonitrile was added 0.78 g (4.4 mmol) of NBS at 25 °C. The reaction mixture was stirred for 3 h at 25 °C, and the solvent was removed under reduced pressure. The mixture was quenched by the addition of water and extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 1.18 g (78%) of the cyclized product **46** as a white solid: mp 133−135 °C; IR (neat) 2934, 1686, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96−2.27 (m, 4H), 2.80−2.92 (m, 1H), 3.01 (t, 2H, J = 7.2 Hz), 2.94−3.08 (m, 1H), 3.56 (dt, 1H, J = 12.4, 7.2 Hz), 3.87 (s, 3H), 3.82−3.92 (m, 1H), 4.68 (brs, 1H), 3.88 (s, 3H), 6.10 (d, 1H, J = 1.6 Hz), 6.75 (s, 1H), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 27.4, 28.8, 29.2, 36.2, 55.9, 56.4, 59.7, 68.2, 110.1, 112.5, 124.8, 127.6, 128.1, 146.9, 148.8, 157.5, 169.5; HRMS calcd for $C_{18}H_{21}BrNO_3Li$ (M + H$^+$) 378.0705, found 378.0703.

7-Bromo-1-[2-(3,4-dimethoxyphenyl)ethyl]-1,4,5,6-tetrahydroindol-2-one (47). To a solution containing 0.6 g (1.9 mmol) of **44** in 20 mL of CH_2Cl_2 was added 0.38 g (2.1 mmol) of NBS. The reaction mixture was stirred for 1 h at 25 °C and was quenched by the addition of water. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 0.64 g (87%) of the brominated ene-amide **47** as tan solid: mp 122−124 °C; IR (neat) 2937, 1704, 1509, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (quint, 2H, J = 6.4 Hz), 2.62 (dt, 2H, J = 6.4, 1.6 Hz), 2.81 (t, 2H, J = 6.4 Hz), 2.85 (ddd, 2H, J = 8.0, 5.6, 2.0 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 4.16 (ddd, 2H, J = 8.0, 5.6, 2.0 Hz), 5.74 (s, 1H), 6.77−6.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5, 37.7, 41.7, 55.73, 55.75, 107.6, 111.0, 112.0, 115.2, 120.7, 131.0, 136.9, 147.4, 148.7, 148.8, 170.8; HRMS calcd for $C_{18}H_{20}BrNO_3Li$ (M + Li$^+$) 384.0787, found 384.0798.

7-Bromo-1-[2-(3,4-dimethoxyphenyl)ethyl]-7a-hydroxy-1,4,5,6,7,7a-hexahydroindol-2-one (48). To a solution containing 0.58 g (1.9 mmol) of **44** in 20 mL of THF was added 0.38 g (2.1 mmol) of NBS. The mixture was stirred for 1 h at 25 °C and was then quenched by the addition of water. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 0.59 g (77%) of aminal **48** as a white solid: mp 81−82 °C; IR (neat) 3251, 2946, 1681, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (brs, 1H), 1.76−1.92 (m, 2H), 1.98 (d, 1H, J = 13.6 Hz), 2.18−2.36 (m, 2H), 2.59 (d, 1H, J = 13.6 Hz), 2.55−2.95 (m, 1H), 3.11 (ddd, 2H, J = 8.8, 6.0, 3.2 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 3.83−3.87 (m, 1H), 4.50 (t, 1H, J = 2.8 Hz), 5.81 (d, 1H, J = 1.6 Hz), 6.74 (d, 1H, J = 1.6 Hz), 6.75 (dd, 1H, J = 8.0, 1.6 Hz), 6.81 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 25.2, 29.7, 34.2, 40.7, 54.7, 55.8, 89.7, 111.3, 112.1, 120.3, 120.6, 132.0, 147.5, 148.8, 158.3, 170.6; HRMS calcd for $C_{18}H_{22}BrNO_4Li$ (M + Li$^+$) 402.0892, found 402.0910.

11,12-Dimethoxy-1,2,8,9-tetrahydroindolo[7a,1a]isoquinolin-6-one (49). To a solution containing 1.0 g (2.8 mmol) of **46** in 10 mL of xylene was added 3 mL of DBU at 25 °C. The reaction mixture was heated at reflux for 48 h with stirring. After cooling, water was added and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 0.62 g (75%) of the $\alpha,\beta,\gamma,\delta$-unsaturated diene-amide **49** as a clear oil: IR (neat) 2929, 1687, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (dt, 1H, J = 12.0, 5.6 Hz), 2.14−2.26 (m, 1H), 2.32 (dd, 1H, J = 12.0, 4.6 Hz), 2.41 (dt, 1H, J = 19.2, 5.6 Hz), 2.97 (t, 2H, J = 6.8 Hz), 3.55 (dt, 1H, J = 12.8, 6.8 Hz), 3.76 (s, 3H), 3.84 (s, 3H), 4.03 (dt, 1H, J = 12.8, 6.8 Hz), 5.88 (s, 1H), 6.28 (ddd, 1H, J = 9.6, 5.6, 2.0 Hz), 6.69 (s, 1H), 6.81 (dd, 1H, J = 9.6, 2.8 Hz), 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 27.1, 34.9, 37.0, 55.8, 55.9, 64.6, 108.5, 112.0, 118.7, 123.9, 126.2, 128.5, 136.1, 146.8, 148.1, 158.0; HRMS calcd for $C_{18}H_{19}rNO_3Li$ (M + Li$^+$) 304.1525, found 304.1516.

Formic Acid 11,12-Dimethoxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7a,1a]isoquinolin-2-yl Ester (50). To a solution containing 0.55 g (1.8 mmol) of **49** in 7 mL of 1,4-dioxane at room temperature was added 2.0 g (18.5 mmol) of selenium dioxide and 0.85 g (18.5 mmol) of formic acid. The reaction mixture was heated at reflux for 7 days with stirring. After cooling, 15 mL of a 10% NaOH solution was added, and the mixture was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography provided 0.09 g (14%) of formate **50** as a yellow pale oil: IR (neat) 2933, 1720, 1686, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (dd, 1H, J = 11.2, 10.4 Hz), 2.84 (dd, 1H, J = 11.2, 5.2 Hz), 2.93−3.103 (m, 2H), 3.58 (dt, 1H, J = 12.8, 6.4 Hz), 3.77 (s, 3H), 3.85 (s, 3H), 4.00 (dt, 1H, J = 12.8, 7.6 Hz), 5.44−5.52 (m, 1H), 6.08 (s, 1H), 6.17 (d, 1H, J = 10.0 Hz), 6.71 (s, 1H), 6.80 (s, 1H), 6.99 (dd, 1H, J = 10.0, 2.4 Hz), 8.02 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 37.3, 41.1, 55.9, 56.1, 65.9, 68.1, 107.8, 112.4, 121.3, 125.6, 126.5, 127.8, 133.5, 147.2, 148.7, 155.9, 159.9, 170.6; HRMS calcd for $C_{19}H_{19}NO_5$ (M$^+$) 341.1263, found 341.1263.

Another fraction isolated from the column contained 0.09 g (15%) of 2-hydroxy-11,12-dimethoxy-1,2,8,9-tetrahydroindolo-[7a,1a]isoquinolin-6-one (**51**) which was isolated as a tan solid: mp 230−232 °C; IR (KBR) 3419, 2927, 1680, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (dd, 1H, J = 11.6, 10.0 Hz), 2.11 (brs, 1H), 2.81 (dd, 1H, J = 11.6, 4.8 Hz), 2.90−3.12 (m, 2H), 3.60 (ddd, 1H, J = 12.8, 6.8, 5.2 Hz), 3.75 (s, 3H), 3.85 (s, 3H), 3.91−4.02 (m, 1H), 4.30 (brs, 1H), 6.02 (s, 1H), 6.30 (d, 1H, J = 10.0 Hz), 6.71 (s, 1H), 6.79 (s, 1H), 6.87 (dd, 1H, J = 10.0, 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 37.4, 45.0, 55.9, 56.1, 66.4, 66.6, 108.0, 112.2, 120.1, 123.5, 126.4, 128.4, 139.4, 147.0, 148.5, 157.3, 171.0; HRMS calcd for $C_{18}H_{19}NO_4$ (M$^+$) 313.1314, found 313.1305.

Alcohol **51** could also be obtained from the solvolysis of formate **50**. To a solution of **50** (0.002 g, 0.064 mmol) in EtOH

(3 mL) was added 0.1 mL of acetyl chloride at 25 °C. The reaction mixture was stirred for 1 h at room temperature. Removal of the solvent under reduced pressure afforded 0.002 g (100%) of **51** as the exclusive product.

(±)-Erysotramidine (2). To a mixture containing 0.09 g (0.27 mmol) of **51** in 7 mL of THF and 4 mL of methyl iodide was added 0.18 g (3.2 mmol) of NaOH and 0.17 g (0.8 mmol) of tetraethylammonium bromide. The reaction mixture was stirred for 36 h at room temperature. The solution was poured into ice−water, and the resulting mixture was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by preparative TLC provided 0.08 g (91%) of (±)-erysotramidine **2** as a colorless oil:[42] IR (neat) 2930, 1666, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.71 (dd, 1H, $J = 11.6$, 10.4 Hz), 2.80 (dd, 1H, $J = 11.6$, 4.4 Hz), 2.90−3.24 (m, 2H), 3.34 (s, 3H), 3.61 (ddd, 1H, $J = 12.8$, 7.2, 6.0 Hz), 3.76 (s, 3H), 3.86 (s, 3H), 3.82−3.88 (m, 1H), 4.00 (ddd, 1H, $J = 12.8$, 8.4, 7.2 Hz), 6.02 (s, 1H), 6.33 (d, 1H, $J = 10.0$ Hz), 6.72 (s, 1H), 6.80 (s, 1H), 6.90 (dd, 1H, $J = 10.0$, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 37.2, 41.3, 55.8, 56.0, 56.3, 66.3, 74.8, 108.1, 120.2, 124.1, 126.5, 128.6, 136.2, 146.9, 148.5, 157.0, 170.8; HRMS calcd for $C_{19}H_{21}NO_4Li$ ($M + Li^+$) 334.1631, found 334.1633.

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Supporting Information Available: Spectroscopic and experimental procedures for 7-bromo-1-(3,3-diethoxypropyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one and 1-(3,3-diethoxypropyl)-3a-methyl-7-vinyl-1,3,3a,4,5,6-hexahydroindol-2-one. ^1H and ^{13}C NMR spectra for new compounds lacking elemental analyses together with an ORTEP drawing for structure **35**. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

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