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Synthesis of the Tetracyclic Framework of the Erythrina Alkaloids Using a [4 + 2]-Cycloaddition/Rh(I)-Catalyzed Cascade of 2-Imidofurans

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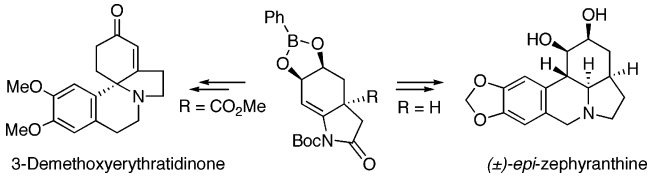

Several 2-imido substituted furans were found to undergo a rapid intramolecular [4 + 2]-cycloaddition to deliver oxabicyclo adducts in good to excellent yields. By using a Rh(I)-catalyzed ring opening of the resulting oxabicyclic adduct, it was possible to prepare several highly functionalized tetrahydro-1*H*-indol-2(3*H*)-one derivatives which were then used to prepare several erythrina alkaloids. By taking advantage of the Rh(I)-catalyzed reaction, it was possible to convert *tert*-butyl 3-oxo-5-carbomethoxy-10-oxa-2-azatricyclo[5.2.1.$0^{1,5}$]dec-8-ene-2-carboxylate into the ring opened boronate by reaction with phenylboronic acid. Treatment of the boronate with pinacol/acetic acid afforded the corresponding diol which was used in a successful synthesis of racemic 3-demethoxyerythratidinone. During the course of these studies, several novel rearrangement reactions were encountered while attempting to induce an acid-initiated Pictet Spengler cyclization of a key lactam intermediate. The IMDAF/Rh(I)-catalyzed ring opening cascade sequence was also applied to the total synthesis of (±)-erysotramidine as well as the lycorine type alkaloid (±)-*epi*-zephyranthine.

Introduction

The tetrahydroindoline nucleus is a structurally characteristic component found in a wide variety of alkaloids,[1] including the amaryllidaceae,[2] aspidosperma,[3] strychnos[4] and erythrina[5] families. The 1-azaspirocyclic structure of the erythrina family has long been of interest in the development of synthetic strategies for its efficient formation.[6] Many members of this family possess curare-like and hypnotic activity, and a variety of pharmacological effects are associated with the erythrinane skeleton, including sedative, hypotensive, neuromuscular blocking and CNS activity.[7] As a result, significant effort has been devoted to the assembly of the tetrahydroindoline framework associated with such alkaloids as well as to the synthesis of the natural products themselves.[8−15] Erythrina alkaloids are generally classified into two groups according to their structural features;[16] those whose D-rings are aromatic (e.g. 3-demethoxyerythratidinone (**1**) and

(1) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: New York, 1987; Vol. 30, pp 251−377. (b) Lewis, J. R. *Nat. Prod. Rep*. **1994**, *11*, 329. Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, pp 1−80.

(2) (a) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 199−384. (b) Saxton, J. E. *Nat. Prod. Rep*. **1993**, *10*, 349−395.

(3) (a) Boekelheide, V. *Alkaloids* **1960**, *7*, 201. (b) Hill, R. K. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 483.

(4) (a) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1988; Vol. 34, pp 211−329. (b) Aimi, N.; Sakai, S.; Ban, Y. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1989; Vol. 36, pp 1−68. (c) Bosch, J.; Bonjoch, J.; Amat, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1996; Vol. 48, pp 75−189.

(5) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, pp 1−98.

(6) Chawla, A. S.; Kapoor, V. K. In *The Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: 1995; Vol. 9, pp 86−153.

(7) Deulofeu, V. In *Curare and Curarelike Agents*; Bovet, D.; Bovet-Nitti, F.; Marini-Bettolo, G. B., Eds.; Elsevier: Amsterdam, 1959; p 163.

(8) For some leading references, see: (a) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671. (b) Grothjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579. (c) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783. (d) Backvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988. (e) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (f) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.

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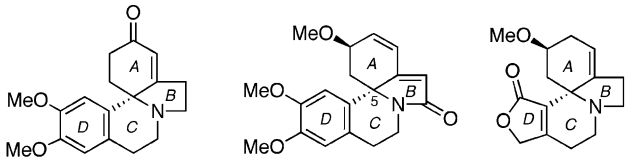


3-Demethoxyerythratidinone (**1**) Erysotramidine (**2**) Cocculolidine (**3**)

FIGURE 1. Some representative erythrina alkaloids.

erysotramidine (**2**)) and the others whose D-rings possess an unsaturated lactone (e.g. cocculolidine (**3**)) (Figure 1).[17] Taking the final step of bond formation into consideration, the methods for building up the erythrinan ring system have been loosely classified into seven different reaction types.[18−25]

Our approach toward the synthesis of a typical erythrina alkaloid such as 3-demethoxyerythratidinone (**1**) derives from a program underway in our laboratory designed to exploit the facile intramolecular Diels−Alder reaction (IMDAF) of 2-imidofurans for the purpose of natural product synthesis.[26] 3-Demethoxyerythratidinone (**1**) was first isolated in 1973 by Barton and his collaborators from *Erythrina lithosperma*.[27] Even though several syntheses have been reported,[20,28] we felt that this compound could serve to illustrate our methodology and also provide a basis for a general cycloaddition approach toward erythrina alkaloids. In particular, we considered the possibility that the erythrina framework of both **1** and erysotramidine (**2**) could be assembled from a tetrahydroindoline of type **5** by making use of the IMDAF cycloaddition of 2-imidofuran **4**. It was expected that appropriate precursors (i.e. **6** and **7**) to these two alkaloids would be derived from a Rh(I)-catalyzed ring opening reaction (vide infra) of the initially formed oxabicyclic adduct **5** with various nucleophilic reagents (Scheme 1). We now detail the successful implementation of this strategy. In addition, by using related chemistry, we were able to synthesize (±)-*epi*-zephyranthine (**9**), an azapolycycle that possesses the challenging tetracyclic galanthan skeleton found in the *Amaryllidaceae* family of alkaloids.

Results and Discussion

In an earlier report, we showed that 2-imidofuran **4a** rapidly reacted at room temperature to deliver the Diels−Alder cycloadduct **5a** in 77% yield.[29] The isolation of the somewhat labile (acid, heat) oxabicyclo adduct **5a** was attributed to the low reaction temperature employed as well as the presence of the carbonyl group, which diminished the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with related furanyl carbamates.[30] The facility of the cycloaddition was also shown to be due to the

(9) (a) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem*. **1981**, *46*, 2002. (b) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707. (c) Kuehne, M. E.; Brook, C. S.; Xu, F.; Parsons, R. *Pure Appl. Chem*. **1994**, *66*, 2095. (d) Nkiliza, J.; Vercauteren, J. *Tetrahedron Lett*. **1991**, *32*, 1787. (e) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem.* Soc. **1993**, *115*, 3030.

(10) (a) Overman, L. E.; Sugai, S. *Helv. Chim. Acta*. **1985**, *68*, 745. (b) Overman, L. E.; Robertson, G.; Robichaud, A. J. *J. Org. Chem*. **1989**, *54*, 1236. (c) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem*. **1983**, *48*, 2685.

(11) (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res*. **1984**, *17*, 35. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 4750. (c) Desmaële, D.; d'Angelo, J. *J. Org. Chem*. **1994**, *59*, 2292.

(12) (a) Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem*. **1990**, *55*, 1624. (b) Sole, D.; Bonjoch, J. *Tetrahedron Lett.* **1991**, *32*, 5183. (c) Bonjoch, J.; Sole, D.; Bosch, J. *J. Am. Chem.* Soc. **1993**, *115*, 2064. (d) Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem*. **1995**, *60*, 8044. (e) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc*. **1993**, *115*, 7904. (f) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc*. **1996**, *118*, 6210.

(13) (a) Padwa, A.; Price, A. T. *J. Org. Chem*. **1995**, *60*, 6258. (b) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662.

(14) (a) Rigby, J. H.; Qabar, M.; Ahmed, G.; Hughes, R. C. *Tetrahedron* **1993**, *49*, 10219. (b) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem*. **1998**, *63*, 5587. (c) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 7834. (d) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569. (e) Rigby, J. H.; Qabar, M. H. *J. Org. Chem*. **1993**, *58*, 4473.

(15) (a) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (b) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem*. **1994**, *59*, 5633. (c) Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1992**, 443.

(16) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. 48, pp 249−337.

(17) Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8003.

(18) (a) Belleau, B. *J. Am. Chem. Soc.* **1953**, *75*, 5765. (b) Mondon, A.; Hansen, K. F. *Tetrahedron Lett.* **1960**, 5. (c) Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ikeda, M. *Heterocycles* **1988**, *27*, 2787. (d) Tsuda, Y.; Hosoi, S.; Ishida, K.; Sangai, M. *Chem. Pharm. Bull.* **1994**, *42*, 204. (e) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995. (f) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 6887. (g) Parsons, A. F.; Williams, D. A. *Tetrahedron* **2000**, *56*, 7217. (h) Toyao, A.; Chikaoka, S.; Takeda, Y.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Tetrahedron Lett.* **2001**, *42*, 1729. (i) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135. (j) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464.

(19) (a) Toda, J.; Niimura, Y.; Takeda, K.; Sano, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 906. (b) Jousse, C.; Demaële, D. *Eur. J. Org. Chem.* **1999**, 909.

(20) Wasserman, H. H.; Amici, R. M. *J. Org. Chem.* **1989**, *54*, 5843.

(21) (a) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497.

(22) (a) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917. (b) Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1987**, *52*, 1478. (c) Irie, H.; Shibata, K.; Matsuno, K.; Zhang, Y. *Heterocycles* **1989**, *29*, 1033. (d) Kawasaki, T.; Onoda, N.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8003. (e) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619.

(23) (a) Gervay, J. E.; McCapra, F.; Money, T.; Sharma, G. M. *J. Chem. Soc., Chem. Commun*. **1966**, 142. (b) Tanaka, H.; Shibata, M.; Ito, K. *Chem. Pharm. Bull*. **1984**, *32*, 1578. (c) Chou, C. T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6898.

(24) (a) Mondon, A.; Ehrhardt, M. *Tetrahedron Lett.* **1966**, 2557. (b) Haruna, M.; Ito, K. *J. Chem. Soc., Chem. Commun*. **1976**, 345. (c) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 605. (d) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159. (e) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312.

(25) (a) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143. (b) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2003**, *44*, 8047. (c) Reimann, E.; Ettmayr, C. *Monatsh. Chem.* **2004**, *135*, 1143. (d) Allin, S. M.; Streetly, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493. (e) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (f) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, N. S.; Zhang, F. *Synthesis* **2005**, 3287.

(26) (a) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197. (b) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 6833. (c) Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247.

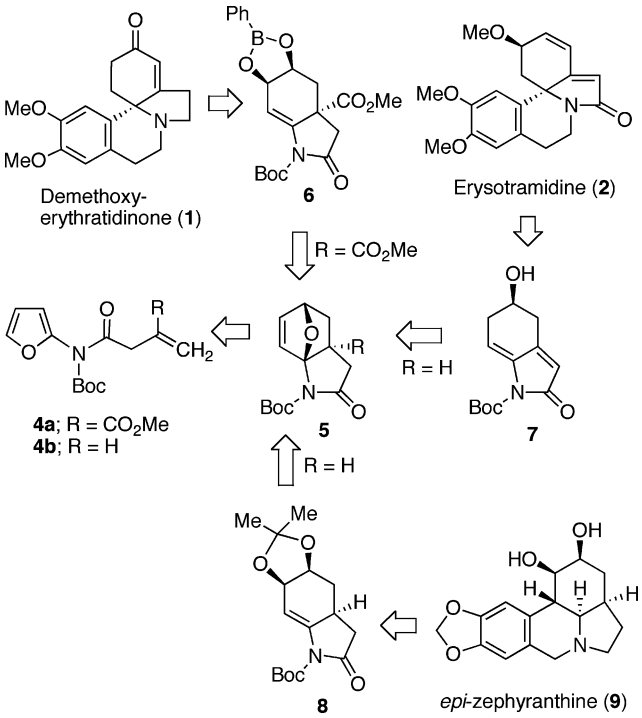
(27) Barton, D. H. R.; Gunatilaka, A. A. L.; Letcher, R. M.; Lobo, A. M. F. T.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 874.

(28) (a) Tsuda, Y.; Sakai, Y.; Nakai, A.; Kaneko, M.; Ishiguro, Y.; Isobe, K.; Taga, J.; Sano, T. *Chem. Pharm. Bull*. **1990**, *38*, 1462. (b) Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ishikawa, K.; Ikeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 907. (c) Irie, H.; Shibata, K.; Matsuno, K.; Zhang, Y. *Heterocycles* **1989**, *29*, 1033.

(29) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 3210.

(30) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 3, 5304. (b) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473. (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

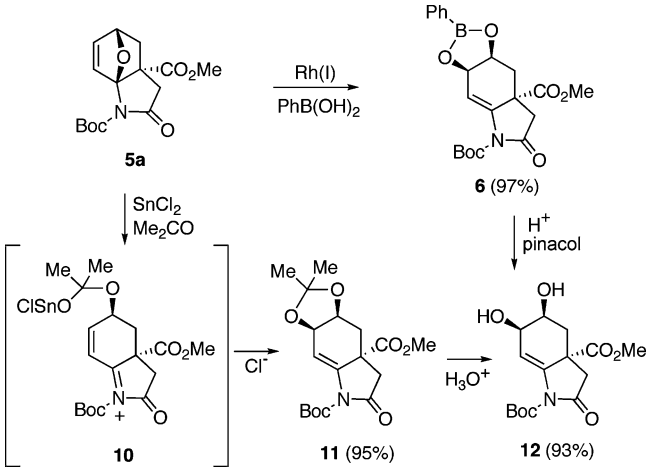
SCHEME 1. Some Key Disconnections toward Several Alkaloids



placement of the carbonyl center within the dienophile tether[31] as well as the presence of the carbomethoxy group which lowers the LUMO energy of the π-bond, thereby facilitating the cycloaddition.

In recent years, the Rh(I)-catalyzed addition of arylboronic acids to olefins has become an active research area in organic synthesis.[32] Conjugate addition generally occurs with electron-deficient olefins such as enones,[33] alkenyl-phosphonates,[34] and nitroalkenes.[35] The facile addition of boronic acids to oxabenzonorbornenes has also been achieved using a catalytic amount of a rhodium(I) complex.[36] A common step in these reactions is the carborhodation of the carbon−carbon double bond followed by hydrolysis of the organorhodium intermediate. Lautens and co-workers have shown that the Rh(I)-catalyzed ring-opening reaction of unsymmetrical oxabicyclic compounds is a highly regioselective process, giving rise to products derived from the attack of the nucleophile distal to the bridgehead substituent.[37] By taking advantage of this Rh(I)-catalyzed reaction, we were able to convert **5a** into the ring-opened boronate **6** (97%), which was then converted to the corresponding diol **12** by treatment with pinacol/acetic acid (Scheme 2).[38]

SCHEME 2. Rh(I)- and $SnCl_2$-Catalyzed Reactions



It was also possible to prepare the same diol **12** by first treating **5a** with catalytic amounts of $SnCl_2$ in acetone[39] to give dioxolane **11** followed by a subsequent hydrolysis reaction. The conversion of **5a** to the corresponding acetonide **11** most likely proceeds by an initial ring opening of **5a** by the mild Lewis acid $SnCl_2$, followed by addition to acetone to give intermediate **10**. Cyclization of this transient species onto the neighboring π-bond ultimately generates dioxolane **11** in 95% yield.

Acid-Catalyzed Rearrangements. Our initial plan to synthesize 3-demethoxyerythratidinone (**1**) involved the cyclization of a *N*-acyliminium ion derived from a suitable aryl enamide precursor[40,41] emanating from diol **12**. Toward this end, oxidation of the allylic alcohol group of **12** was carried out with MnO_2, and this was followed by protection of the secondary OH group with TBSCl. Removal of the Boc group, and subsequent *N*-alkylation with 4-(2-bromoethyl)-1,2-dimethoxybenzene afforded enamido lactam **13** in 65% yield for the three-step sequence (Scheme 3). Several acids were examined in our attempt to promote the planned acid-initiated Pictet−Spengler cyclization of lactam **13**. During the course of these studies, we encountered several novel rearrangement reactions. For example, when **13** was treated with polyphosphoric acid (PPA) in refluxing CH_2Cl_2, the rearranged benzo[4,5]azepino lactam **16** was isolated in 80% yield and its structure was unequivocally established by X-ray crystallography. This unusual reorganization can be rationalized by the pathway proposed in Scheme 4. We assume that the first step involves generation of the tetracyclic erythrina intermediate **14** by the traditional Pictet−Spengler type cyclization.[40] Intermediate **14** then undergoes a

(31) Dramatic effects on the rate of the Diels−Alder reaction were previously noted to occur when an amido group was used to anchor the diene and dienophile, see: (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (b) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, 3313. (c) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412. (d) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938.

(32) (a) Hayashi, T. *Synlett* **2001**, 879. (b) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (c) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.

(33) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(34) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591.

(35) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

(36) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390.

(37) (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677. (c) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067. (d) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (e) Lautens, M.; Chiu, P.; Colucci, J. T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281. (f) Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817.

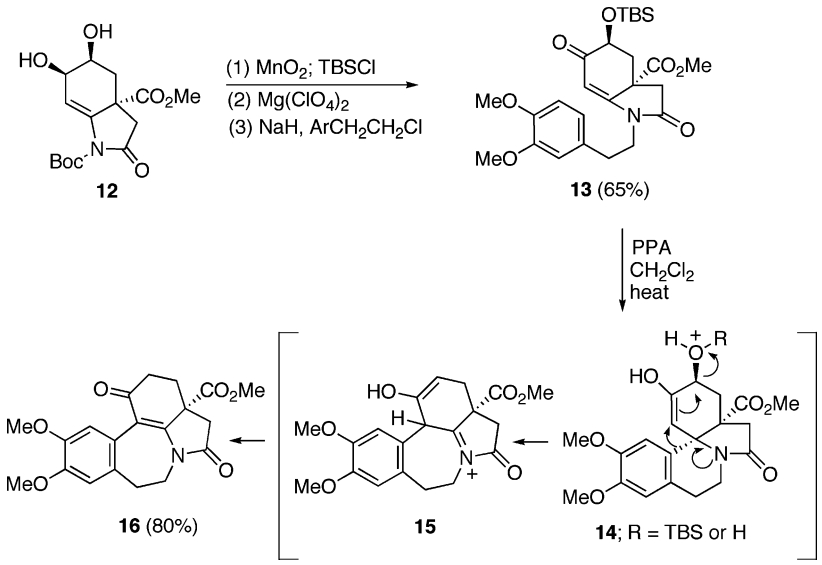
(38) Bertounesque, E.; Florent, J.-C.; Monneret, C. *Synthesis* **1991**, 270.

(39) Vyvyan, J. R.; Meyer, J. A.; Meyer, K. D. *J. Org. Chem.* **2003**, *68*, 9144.

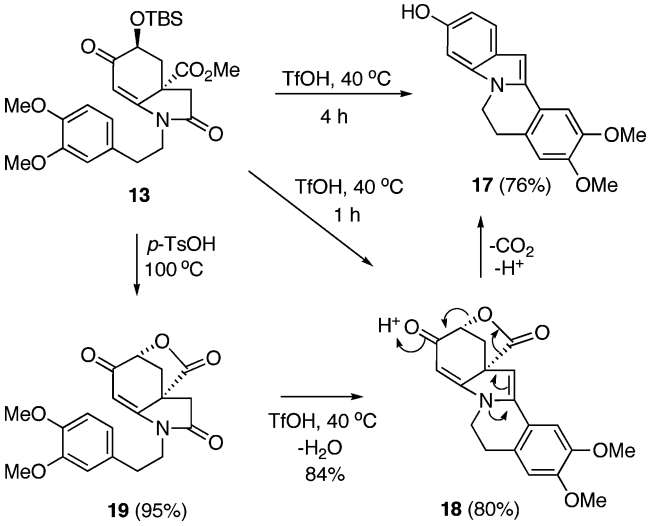
(40) (a) Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (c) Hosoi, S.; Nagao, M.; Tsuda, Y.; Isobe, K.; Sano, T.; Ohta, T. *J. Chem. Soc., Perkin Trans. 1* **2000**,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

(41) (a) Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888. (b) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. (c) Padwa, A.; Wang, Q. *Org. Lett.* **2006**, *8*, 601. (d) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067.

SCHEME 3. PPA-Induced Rearrangement



SCHEME 4. Triflic Acid-Induced Rearrangements



nitrogen-assisted 1,2-bond migration with simultaneous expulsion of water (or TBSOH) to produce the ring-expanded *N*-acyliminium ion **15**. Loss of a proton and subsequent tautomerization perfectly accounts for the formation of the observed product **16**.[41c]

In contrast to the rearrangement observed using PPA, heating a sample of **13** in CH_2Cl_2 with trifluoromethanesulfonic acid (TfOH) followed by base workup afforded phenol **17** in 76% yield.[42] Analysis of the rearrangement by ^{1}H NMR spectroscopy revealed that the reaction proceeded via the intermediacy of lactone **18**, which could be isolated in 80% yield by terminating the thermolysis after 1 h. Additional heating of **18** in the presence of TfOH afforded phenol **17** in 95% yield. Furthermore, when *p*-TsOH was employed as the acid promoter, a new, interesting intermediate (i.e., **19**) was obtained in 95% yield. The isolation of **19** under these milder acidic conditions suggests that the initial step in the conversion of **13** to **17** involves formation of the γ-lactone ring. Exposure of **19** to TfOH in refluxing CH_2Cl_2 (1 h) resulted in the preferential cyclization of the activated aromatic ring onto the amido carbonyl group, producing **18** in 90% yield (Scheme 4).

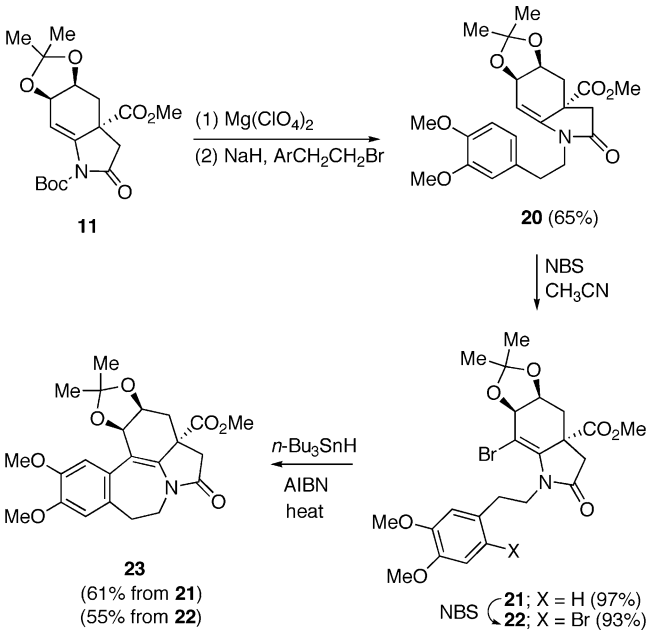
Free-Radical-Induced Cyclizations. Considering the difficulty encountered with the traditional Pictet−Spengler reaction of enamido lactam **13**, we modified our approach toward 3-demethoxy-erythratidinone (**1**). Acetonide **20** was prepared by removal of the Boc group of **11** followed by *N*-alkylation with 4-(2-bromoethyl)-1,2-dimethoxybenzene. In earlier work, we had found that NBS in acetonitrile could be used to promote an electrophilic substitution reaction of a tetrahydroindolinone to assemble the tetracyclic core of the erythrinone skeleton.[41d] Unfortunately, when acetonide **20** was subjected to an equivalent amount of NBS in acetonitrile, bromoenamide **21** was obtained as the exclusive product in 97% yield and its formation can be attributed to a faster deprotonation (vs cyclization) of the presumed *N*-acyliminium ion intermediate. If more than 1 equiv of NBS was used in this reaction, varying amounts of the dibrominated hydroindolinone **22** were isolated. When a sample of **21** was exposed to an additional equivalent of NBS in acetonitrile, dibromide **22** was isolated in 93% yield.

Radical cyclizations of highly reactive aryl and vinyl radicals onto double and triple bonds have proven to be very useful for construction of both carbocycles and heterocycles.[14,43] To investigate whether these bromo-substituted tetrahydroindolinones could be used as precursors for radical cyclization chemistry, we explored the reaction of **21** with *n*-Bu_3SnH under the standard radical-forming conditions. Exposure of **21** to *n*-Bu_3SnH/AIBN at 80 °C provided the azepinoindole derivative **23** in 61% yield. In this case, selective 7-*endo*-cyclization took place by addition of the vinyl radical onto the aromatic ring (Scheme 5). Interestingly, the closely related dibromide **22** also

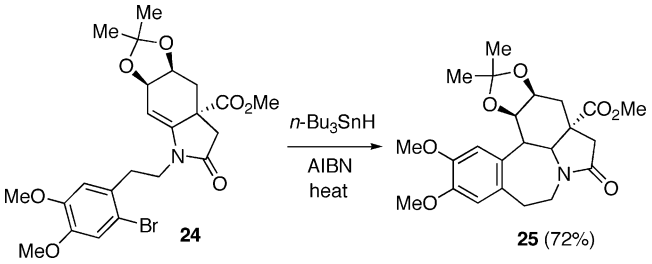
(42) The interesting switch in chemoselectivity of **13** as a function of the acid used is not at all obvious. It is possible that the specific rearrangement pathway followed may be related to subtle differences in the site(s) of protonation.

(43) (a) Neumann, W. P. *Synthesis* **1987**, 665. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986. (d) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649. (e) Aldabbagh, F.; Bowman, W. R. *Contemp. Org. Synth.* **1997**, *4*, 261. (f) Curran, D. P. Radical Addition Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715. (g) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. E., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

SCHEME 5. Free Radical Cyclization To Form the Azepinoindole Ring



SCHEME 6. 7-*endo-trig* Cyclization of Tetrahydroindolinone 24

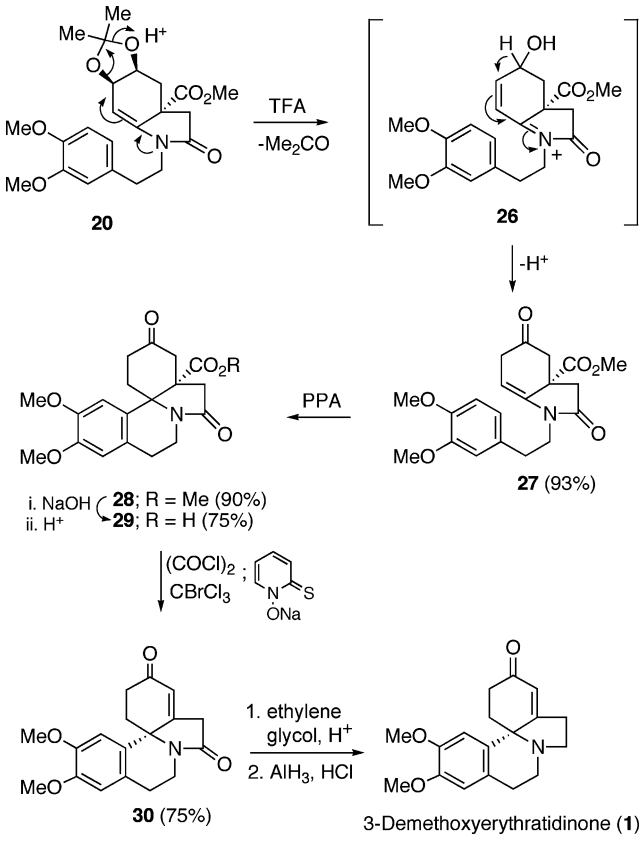


afforded **23** in 55% yield when it was allowed to react under the radical conditions. Even though it is not clear which particular bromine atom is attacked by the stannyl radical, seven-ring cyclization followed by bromine atom ejection represents the major reaction pathway that occurs with tetrahydroindolinone **22**.

The radical cyclization approach was also extended to tetrahydroindolinone **24** which was readily prepared by the reaction of acetonide **11** with NaH and 1-bromo-2-(2-bromoethyl)-4,5-dimethoxybenzene. In this case, both 6-*exo-trig* and 7-*endo-trig* modes of cyclization are possible. The regiochemical preferences in cyclization of vinyl and aryl radicals generally parallel the alkyl analogues.[44] When compound **24** was heated at 80 °C with *n*-Bu_3SnH/AIBN, the only product that could be isolated (72%) was that derived from a 7-*endo-trig* cyclization pathway (Scheme 6). Apparently, steric hindrance of the substituents sufficiently retards the 6-*exo-trig* cyclization so that the 7-*endo* closure becomes the predominant pathway.

Synthesis of 3-Demethoxyerythratidinone. As a consequence of the above result, we abandoned the radical cyclization approach toward 3-demethoxyerythratidinone (**1**) and instead decided to reinvestigate the Pictet−Spengler reaction, this time using tetrahydroindolinone **27** as the cyclization substrate. We found that treating acetonide **20** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 25 °C led to the desired tetrahydroindolinone **27** in 93% yield. As highlighted in Scheme 7, we believe that the

SCHEME 7. Pictet−Spengler Route toward 3-Demethoxyerythratidinone (1)



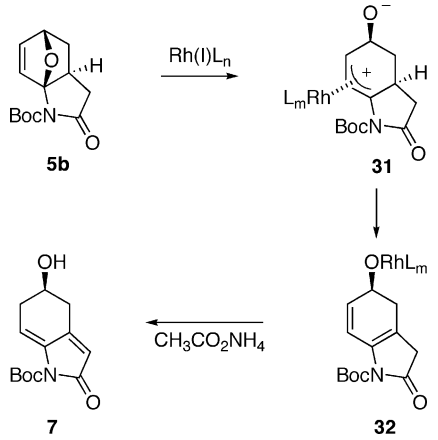
reaction of **20** proceeds by an acid-induced loss of acetone to generate *N*-acyliminium ion **26**, which then loses the available allylic proton so as to dissipate the positive charge. Ketonization of the resulting enol produces **27**. The Pictet−Spengler reaction of **27** was then carried out uneventfully with PPA to furnish the tetracyclic erythrinane **28** in 90% yield. Base hydrolysis of **28** gave carboxylic acid **29**, which was then subjected to Barton decarboxylation conditions[45] using $BrCCl_3$ as the solvent. Subsequent elimination of HBr from the labile tertiary bromide afforded the known 5*H*-indolo[7*a*,1*a*]isoquinolinedione **30**.[28a] This compound was converted to 3-demethoxyerythratidinone (**1**) following the reductive method of Tsuda and co-workers.[28a]

Synthesis of Erysotramidine. As a further demonstration of the efficiency of the IMDAF/Rh(I)-catalyzed cascade of 2-imidofurans for the synthesis of erythrina alkaloids, we applied the method toward the synthesis of erysotramidine (**2**). We had previously demonstrated[29] that the reaction of azaoxabicyclohexene **5b** with catalytic $[Rh(COD)Cl]_2$ in the presence of various ammonium carboxylates afforded the dienyl alcohol **7** in 80% isolated yield according to the mechanism outlined in Scheme 8. The ready availability of **7** from cycloadduct **5b** suggested its use in a synthesis of erysotramidine (**2**). This approach was born out in the following manner. The homoallylic alcohol present in compound **7** was first protected as the TBS ether, and the Boc group was then removed with $Mg(ClO_4)_2$. Subsequent *N*-alkylation with NaH and 4-(2-bromoethyl)-1,2-dimethoxybenzene furnished **33** in 60% overall yield for the

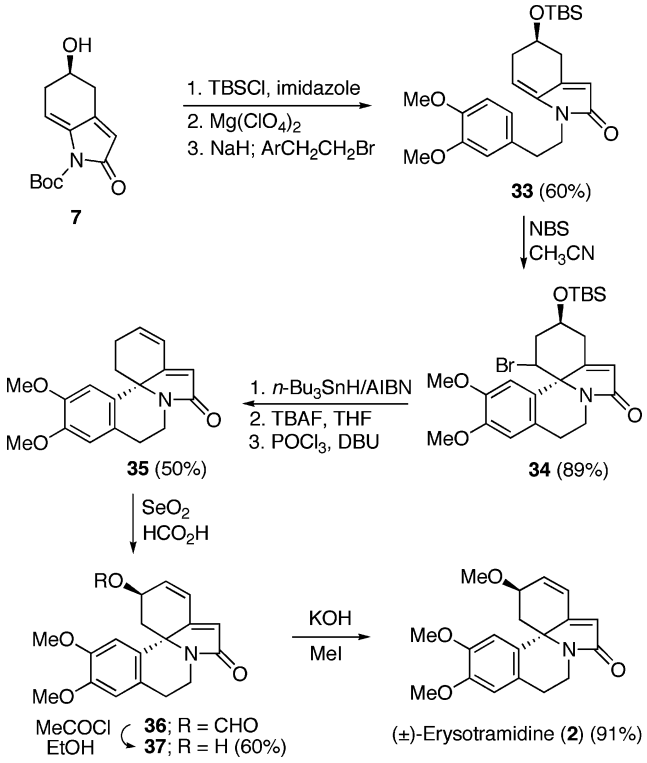
(44) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980.

(45) (a) Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507. (b) Attardi, M. E.; Taddei, M. *Tetrahedron Lett.* **2001**, *42*, 3519.

SCHEME 8. Rh(I)-Catalyzed Ring-Opening Reaction



SCHEME 9. Total Synthesis of (±)-Erysotramidine (2)



three-step sequence. Our attempts to induce an acid-promoted cyclization of **33** failed to produce any characterizable products, probably as a consequence of the antiaromatic nature of the resulting cationic intermediate. We were pleased to discover, however, that bicyclic lactam **33** underwent an extremely smooth cyclization to the desired erythrinan skeleton (i.e., **34**) in 89% yield when treated with NBS in acetonitrile. This cyclization reaction was found to be markedly dependent on the nature of the solvent; acetonitrile was the only solvent that was successful. It is not clear to us why the NBS cyclization of **33** proceeded so cleanly and why the related bicyclic lactam **20** only underwent enamido-bromination (i.e., **20** → **21**) under identical conditions. Refluxing a sample of **34** with *n*-Bu_3SnH and AIBN in benzene resulted in reduction of the secondary bromide. This was followed by deprotection of the TBS ether and subsequent dehydration of the alcohol to give **35** in 50% overall yield for the three-step process. Stereoselective allylic oxidation with selenium dioxide in the presence of formic acid gave a 1:1-

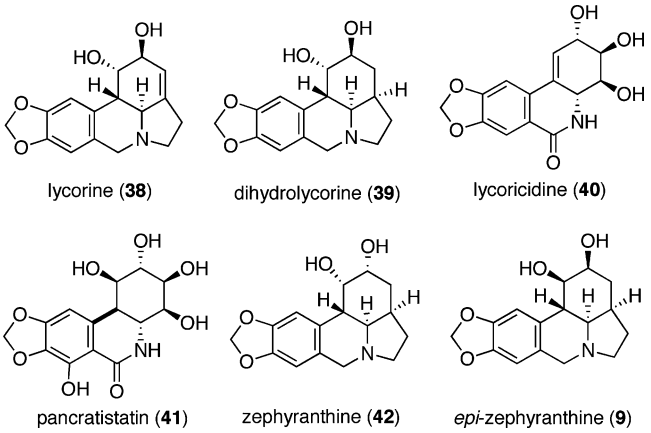


FIGURE 2. Lycorine-type alkaloids.

mixture of formate **36** and alcohol **37** 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 **36** was quantitatively transformed into alcohol **37** by treatment with acetyl chloride in ethanol.[46] Finally, compound **37** was converted into (±)-erysotramidine (**2**)[25f] in 91% yield by *O*-methylation using KOH/MeI in THF according to Tsuda's method (Scheme 9).[40a−c]

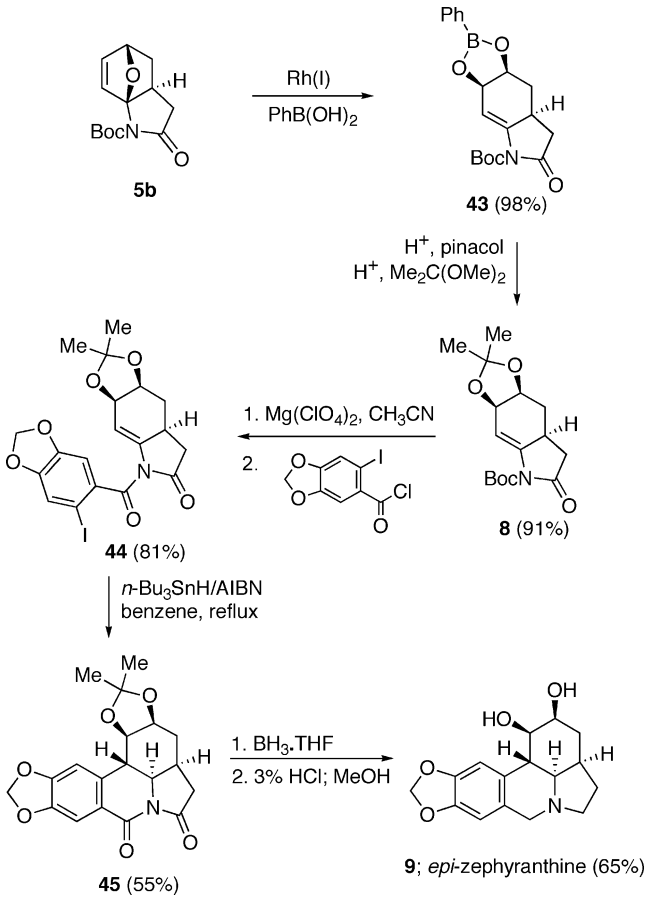
Synthesis of (±)-*epi*-Zephyranthine. To further demonstrate the wide potential of this methodology for alkaloid natural product synthesis, we opted to use dioxolane **8**, which had been previously prepared by the IMDAF/Rh(I)-catalyzed route,[29] for the synthesis of a member of the *Amaryllidaceae* family of alkaloids.[47] In contrast to other members of the lycorine (**38**) family such as dihydrolycorine (**39**), lycoricidine (**40**), pancratistatin (**41**), only a limited number of syntheses of zephranthine[48] (**42**) have been carried out and there are no reports dealing with the synthesis of the stereoisomeric *epi*-zephyrantine (**9**) (Figure 2). Dioxolane **8** was readily available from the oxabicyclic adduct **5b** via an acid-induced cleavage of boronate **43** to first produce the corresponding diol followed by a subsequent reaction with 2,2-dimethoxypropane. We were now in a position to apply the experience gained from our erythrina syntheses to the preparation of *epi*-zephyranthine (**9**). To this end, dioxolane **8** was easily converted to the corresponding benzamide **44** in 81% yield by first removing the *t*-Boc group using Mg(ClO$_4$)$_2$ in acetonitrile followed by benzoylation with the acid chloride derived from 6-iodobenzo[1,3]-dioxazole-5-carboxylic acid (Scheme 10). Exposure of **44** to *n*-Bu_3SnH in benzene at reflux in the presence of AIBN afforded the anticipated tetracyclic product **45** in 55% yield. The *trans*-B,C- and *cis*-C,D-ring fusion of the cyclized product was unambiguously assigned by an X-ray crystal structure of compound **45**. SYBYL force field calculations suggest that this stereochemistry corresponds to the most stable isomer and is also in agreement with the earlier reports

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

(47) (a) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 323−424. (b) Lewis, J. R. *Nat. Prod. Rep.* **1998**, 107−110.

(48) (a) Ozeki, S. *Chem. Pharm. Bull.* **1964**, *12*, 2533. (b) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1358. (c) Yamaki, M.; Murata, M.; Takagi, S.; Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Tanaka, H.; Irie, H.; Uyeo, S. *Heterocycles* **1976**, *5*, 163. (d) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc*. **1994**, *116*, 3139.

SCHEME 10. Total Synthesis of *epi*-Zephyranthine (9)



of Rigby[49] and Schultz.[50] Reduction of **45** with BH_3·THF followed by hydrolysis of the 1,3-dioxolane furnished (65%) *epi*-zephyranthine (**9**) in 14.5% overall yield for the seven-step sequence starting from the 2-imidofuran **4b**.

In summary, a new strategy for the synthesis of the tetrahydroindolinone core found in the erythrina and amaryllidaceae alkaloid family has been developed, which is based on an extraordinarily facile intramolecular Diels−Alder reaction of 2-imido-substituted furans. By using a Rh(I)-catalyzed ring opening of the oxabicyclic adduct, it was possible to synthesize the key tetrahydroindolinone necessary for a Pictet−Spengler cyclization. During the course of the synthesis, several novel acid-induced rearrangement reactions were encountered. The Rh(I)-catalyzed reactions proceed in high yield under very mild conditions and occur with excellent diastereoselectivity. The application of this approach to other natural product targets is currently under investigation, the results of which will be disclosed in due course.

Experimental Section

6-Oxo-2-phenyl-6,7,8,8*a*-tetrahydro-3*aH*-1,3-dioxa-5-aza-2-bora-*s*-indacene-5,7*a*-dicarboxylic Acid 5-*tert*-Butyl Ester 7*a*-Methyl Ester (6). To a solution containing 0.15 g (0.5 mmol) of 3-oxo-5-carbomethoxy-10-oxa-2-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-2-carboxylic acid *tert*-butyl ester (**5a**),[29] 7.0 mg (0.015 mmol) of [Rh(COD)Cl]$_2$, and 5.1 μL (0.03 mmol) of P(OEt)$_3$ in 2.5 mL of THF was added 0.12 g (1.0 mmol) of phenylboronic acid. The reaction mixture was heated at 65 °C for 6 h, cooled to room temperature, and quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.2 g (97%) of **6** as a white solid: mp 131−132 °C; IR (neat) 1775, 1736, 1369, 1097, and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53−1.59 (m, 1H), 1.58 (s, 9H), 2.50 (d, 1H, J = 17.2 Hz), 2.88 (dd, 1H, J = 12.8 and 6.0 Hz), 2.95 (d, 1H, J = 17.2 Hz), 3.74 (s, 3H), 5.08 (ddd, 1H, J = 10.0, 8.0 and 6.0 Hz), 5.143 (dd, 1H, J = 8.0 and 3.2 Hz), 6.38 (d, 1H, J = 3.2 Hz), 7.36 (t, 2H, J = 7.6 Hz), 7.47 (tt, 1H, J = 7.6 and 1.6 Hz), and 7.78 (dd, 2H, J = 7.6 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 36.8, 42.0, 46.2, 53.5, 73.2, 73.4, 85.0, 108.8, 128.0, 131.8, 135.0, 138.6, 148.9, 170.6, and 171.6. Anal. Calcd for $C_{21}H_{24}BNO_7$: C, 61.04; H, 5.85; N, 3.39. Found: C, 60.90; H, 5.76; N, 3.26.

2,2-Dimethyl-6-oxo-6,7,8,8*a*-tetrahydro-3*aH*-[1,3]dioxolo[4,5-f]indole-5,7*a*-dicarboxylic Acid 5-*tert*-Butyl Ester 7*a*-Methyl Ester (11). To a solution containing 0.1 g (0.38 mmol) of oxabicycle **5a** in 0.5 mL of acetone and 2 mL of CH_2Cl_2 was added 5 mg (0.03 mmol) of anhydrous stannous chloride. After the mixture was stirred at room temperature for 15 min, the solvent was removed under reduced pressure and the residue was subjected to the flash silica gel chromatography to afford 0.11 g (92%) of dioxolane **11** as a white solid: mp 131−133 °C; IR (neat) 1774, 1735, 1297, and 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.45 (s, 3H), 1.54 (s, 9H), 1.49−1.56 (m,1H), 2.49 (d, 1H, J = 17.2 Hz), 2.62 (dd, 1H, J = 12.8 and 6.0 Hz), 2.86 (d, 1H, J = 17.2 Hz), 3.69 (s, 3H), 4.52 (dt, 1H, J = 10.8 and 6.0 Hz), 4.71 (dd, 1H, J = 6.0 and 3.2 Hz), and 6.21 (d, 1H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.0, 28.1, 35.6, 42.4, 46.9, 53.4, 71.2, 71.3, 84.8, 107.6, 109.4, 139.0, 148.8, 170.9, and 171.8. Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.84; H, 6.86; N, 3.81. Found: C, 58.77; H, 6.93; N, 3.62.

5,6-Dihydroxy-2-oxo-2,3,5,6-tetrahydro-4*H*-indole-1,3*a*-dicarboxylic Acid 1-*tert*-Butyl Ester 3*a*-Methyl Ester (12). A 0.1 g (0.24 mmol) sample of boronate **6** in 10 mL of CH_2Cl_2 to which 0.14 g (1.2 mmol) of pinacol and 2.8 μL (0.05 mmol) of acetic acid had been added was stirred at room temperature for 12 h, and then the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.08 g (95%) of diol **12** as a clear oil: IR (neat) 3447, 2982, 1785, 1734, and 990 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 9H), 1.74 (t, 1H, J = 12.4 Hz), 2.44 (dd, 1H, J = 12.4 and 3.6 Hz), 2.54 (d, 1H, J = 17.2 Hz), 2.80 (d, 1H, J = 17.2 Hz), 2.81 (brs, 1H), 2.92 (brs, 1H), 3.69 (s, 3H), 3.88−3.96 (m, 1H), 4.34 (t, 1H, J = 4.4 Hz), and 6.18 (d, 1H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 34.3, 43.1, 49.0, 53.4, 65.0, 66.4, 84.8, 111.4, 139.1, 148.9, 170.7, and 172.5. HRMS Calcd for $C_{15}H_{20}NO_7$: 326.1240. Found: 326.1238.

Diol **12** could also be obtained by treating a sample of dioxolane **11** in 10 mL of methanol which contained 2 drops of aqueous HCl. The mixture was stirred at room temperature for 12 h, and then the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.08 g (93%) of the same diol **12** as was obtained from boronate **6**.

5-(*tert*-Butyl-dimethylsilanyloxy)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-2,6-dioxo-1,2,3,4,5,6-hexahydroindole-3*a*-carboxylic Acid Methyl Ester (13). To a solution 0.2 g (0.6 mmol) of the diol 12 in 10 mL of CH_2Cl_2 was added 0.62 g (12 mmol) of MnO_2. The mixture was stirred at room temperature for 3 days and filtered through Celite. The solvent was removed under reduced pressure. The black mixture was filtered through a short pad of silica, the filtrate was concentrated under reduced pressure, and the crude residue was used for the next step. The mixture was taken up in 5 mL of CH_2Cl_2, and 0.3 mL (2.7 mmol) of 2,6-lutidine and 0.24 g (0.9 mmol) of TBSOTf were added. The reaction mixture was

(49) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8795.
(50) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210.
(51) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *56*, 4823.

stirred at room temperature for 20 min. The mixture was quenched by water, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography to give 0.18 g (80%) of 5-(*tert*-butyl-dimethylsilanyloxy)-2,6-dioxo-2,3,5,6-tetrahydro-4*H*-indole-1,3*a*-dicarboxylic acid 1-*tert*-butyl ester 3*a*-methyl ester as a clear oil: IR (neat) 2954, 1804, 1734, 1629, 1299, and 862 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.05 (s, 3H), 0.12 (s, 3H), 0.86 (s, 9H), 1.53 (s, 9H), 2.03 (t, 1H, J = 12.0 Hz), 2.61 (d, 1H, J = 16.8 Hz), 2.81 (dd, 1H, J = 12.0 and 5.4 Hz), 2.85 (d, 1H, J = 16.8 Hz), 3.74 (s, 3H), 4.34 (dd, 1H, J = 12.0 and 5.4 Hz), and 6.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4, −4.4, 18.6, 25.9, 28.0, 40.5, 42.1, 48.3, 53.8, 71.0, 86.2, 111.2, 147.6, 154.9, 169.9, 170.8, and 196.5.

To a solution containing 0.52 g (1.2 mmol) of above imide in 10 mL of CH_3CN was added 0.05 g (0.24 mmol) of magnesium perchlorate. The mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.36 g (90%) of 5-(*tert*-butyl-dimethylsilanyloxy)-2,6-dioxo-1,2,3,4,5,6-hexahydroindole-3*a*-carboxylic acid methyl ester as a white solid: mp 159−161 °C; IR (neat) 3238, 1737, 1640, 1195, 1125, and 838 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.08 (s, 3H), 0.14 (s, 3H), 0.88 (s, 9H), 2.10 (t, 1H, J = 12.0 Hz), 2.61 (d. 1H, J = 16.8 Hz), 2.79 (d, 1H, J = 16.8 Hz), 2.84 (dd, 1H, J = 12.0 and 5.4 Hz), 3.76 (s, 3H), 4.30 (dd, 1H, J = 12.0 and 5.4 Hz), 5.57 (s, 1H), and 9.36 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.3, −4.3, 18.6, 25.9, 40.6, 41.5, 50.3, 53.8, 71.4, 104.1, 159.9, 171.2, 175.1, and 196.5. Anal. Calcd for $C_{16}H_{25}NO_5Si$: C, 56.61; H, 7.42; N, 4.13. Found: C, 56.80; H, 7.59; N, 4.10.

To a solution of 0.15 g (0.44 mmol) of the above amide in 5 mL of DMF was added 22 mg (0.88 mmol) of 95% NaH at 0 °C. After the mixture was stirred at 0 °C for 1 h, 0.22 g (0.89 mmol) of 4-(2-bromoethyl)-1,2-dimethoxybenzene was slowly added. The mixture was stirred for 12 h and then quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.23 g (89%) of **13** as a white solid: 150−152 °C; IR (neat) 1747, 1633, 1516, 1127, and 838 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.10 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 2.04 (t, 1H, J = 12.0 Hz), 2.53 (d. 1H, J = 16.8 Hz), 2.72−2.81 (m, 2H), 2.81 (d, 1H, J = 16.8 Hz), 2.87 (dd, 1H, J = 12.0 and 5.4 Hz), 3.51 (ddd, 1H, J = 14.4, 9.0 and 5.4 Hz), 3.67 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.93 (ddd, 1H, J = 14.4, 10.2 and 6.6 Hz), 4.31 (dd, 1H, J = 12.0 and 5.4 Hz), 5.55 (s, 1H), 6.70 (d, 1H, J = 1.8 Hz), 6.71 (dd, 1H, J = 8.4 and 1.8 Hz), and 6.77 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.3, −4.3, 18.6, 25.9, 32.2, 40.5, 40.9, 42.0, 48.7, 53.6, 56.0, 56.1, 71.5, 102.6, 111.5, 112.0, 120.8, 129.8, 148.1, 149.2, 160.6, 171.2, 172.9, and 195.7. Anal. Calcd for $C_{24}H_{36}NO_5Si$: C, 64.54; H, 8.13; N, 3.14. Found: C, 64.39; H, 8.24; N, 3.08.

10,11-Dimethoxy-1,5-dioxo-2,3,4,5,7,8-hexahydro-1*H*-benzo[4,5]azepino[3, 2,1*hi*]-indole-3*a*-carboxylic Acid Methyl Ester (16). A mixture of 0.05 g (0.1 mmol) of **13** and 0.5 mL of PPA was heated at 90 °C for 12 h, cooled to room temperature, and then quenched with water. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.03 g (80%) of **16** as a pale yellow solid: IR (neat) 2954, 1734, 1606, and 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.12 (dt, 1H, J = 13.2 and 5.4 Hz), 2.62 (ddd, 1H, J = 18.6, 13.2 and 5.4 Hz), 2.64 (d, 1H, J = 17.4 Hz), 2.68 (dd, 1H, J = 13.2 and 5.4 Hz), 2.73 (dd, 1H, J = 18.6 and 5.4 Hz), 2.84 (dd, 1H, J = 15.0 and 5.4 Hz), 2.91 (d, 1H, J = 17.4 Hz), 2.99 (dd, 1H, J = 15.0 and 12.6 Hz), 3.46 (t, 1H, J = 12.6 Hz), 3.76 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.35 (dd, 1H, J = 12.6 and 5.4 Hz), 6.61 (s, 1H), and 6.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.4, 32.3, 35.5, 41.5, 50.6, 50.9, 53.7, 56.1, 56.2, 111.5, 114.9, 116.9, 122.8, 133.9, 147.2, 148.8, 155.2, 172.1, 173.3, and 196.0. HRMS Calcd for $C_{20}H_{21}NO_6$ [M + H]: 372.1442. Found: 372.1435.

2,3-Dimethoxy-5,6-dihydroindolo[2,1-*a*]isoquinolin-9-ol (17). A solution containing 0.03 g (0.06 mmol) of **13** and 0.1 mL of TfOH in 2 mL of CH_2Cl_2 was heated at reflux for 4 h, cooled to room temperature, and quenched with water. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.02 g (80%) of lactone **18** as a yellow oil: IR (neat) 1781, 1589, 1510, and 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.52 (d, 1H, J = 11.4 Hz), 2.97 (dt, 1H, J = 16.2 and 5.4 Hz), 3.08−3.14 (m, 1H), 3.13 (dd, 1H, J = 11.4 and 5.4 Hz), 3.54 (ddd, 1H, J = 12.0, 9.6 and 5.4 Hz), 3.71 (dt, 1H, J = 12.0 and 5.4 Hz), 3.90 (s, 3H), 3.91 (s, 3H), 4.91 (dd, 1H, J = 5.4 and 1.8 Hz), 5.21 (s, 1H), 5.66 (s, 1H), 6.69 (s, 1H), and 7.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.0, 40.1, 47.8, 56.2, 60.2, 82.9, 91.4, 97.5, 108.0, 110.9, 117.9, 126.7, 146.0, 148.8, 151.1, 166.3, 173.2, and 189.1. HRMS Calcd for $C_{19}H_{19}NO_6$ [M + H]: 340.1185. Found: 340.1178.

To a sample of lactone **18** in 1 mL of MeOH was added 0.1 mL of Et_3N. The reaction mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The crude NMR spectrum showed only the presence (>95%) of phenol **17**: ^1H NMR (C_6D_6, 600 MHz) δ 2.49 (t, 2H, J = 6.6 Hz), 3.45 (s, 3H), 3.48 (s, 3H), 3.51 (t, 2H, J = 6.6 Hz), 6.41 (s, 1H), 6.54 (dd, 1H, J = 8.4 and 1.2 Hz), 6.55 (d, 1H, J = 1.2 Hz), 6.72 (s, 1H), 7.03 (brs, 2H), and 7.53 (s, 1H). HRMS Calcd for $C_{18}H_{17}NO_3$ [M + H]: 296.1281. Found: 296.1280.

4-[2-(3,4-Dimethoxyphenyl)ethyl]-9-oxa-4-aza-tricyclo[6.2.1.0^{1,5}]-undec-5-ene-3,7,10-trione (19). A solution containing 0.02 g (0.04 mmol) of **13** together with 0.01 g (0.06 mmol) of *p*-TsOH in 1 mL of toluene was heated at 100 °C for 1 h and then cooled to room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.01 g (95%) of **19** as a clear oil: IR (neat) 1790, 1754, 1673, 1606, and 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.59 (d, 1H, J = 18.0 Hz), 2.68 (d, 1H, J = 12.0 Hz), 2.79 (t, 2H, J = 7.2 Hz), 2.87 (dd, 1H, J = 12.0 and 6.0 Hz), 3.18 (d, 1H, J = 18.0 Hz), 3.61 (dt, 1H, J = 13.8 and 7.2 Hz), 3.82−3.87 (m, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 4.79 (dd, 1H, J = 6.0 and 1.8 Hz), 5.25 (d, 1H, J = 1.8 Hz), 6.62 (d, 1H, J = 1.8 Hz), 6.65 (dd, 1H, J = 8.4 and 1.8 Hz), and 6.77 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 32.3, 32.7, 42.8, 43.0, 47.6, 56.2, 81.0, 96.9, 111.7, 112.1, 121.1, 129.3, 148.4, 149.4, 162.9, 173.0, 173.1, and 189.1. HRMS Calcd for $C_{19}H_{19}NO_6$ [M + H]: 358.1285. Found: 358.1280.

Heating a sample of **19** with TfOH in CH_2Cl_2 at reflux for 4 h followed by the standard workup gave **18** in 84% yield.

5-[2-(3,4-Dimethoxyphenyl)ethyl]-2,2-dimethyl-6-oxo-3*a*,5,6,7,8,8*a*-hexahydro-[1,3]-dioxolo[4,5-*f*]indole-7*a*-carboxylic Acid Methyl Ester (20). To a solution containing 0.1 g (0.26 mmol) of acetonide 11 in 1 mL of CH_3CN was added 15 mg (0.06 mmol) of magnesium perchlorate. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford 0.06 g (84%) of 2,2-dimethyl-6-oxo-3*a*,5,6,7,8,8*a*-hexahydro-[1,3]dioxolo-[4,5-*f*]indole-7*a*-carboxylic acid methyl ester as a clear oil: IR (neat) 3198, 2985, 1727, 1699, and 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.46 (s, 3H), 1.61 (dd, 1H, J = 12.4 and 10.8 Hz), 2.48 (d, 1H, J = 16.8 Hz), 2.62 (dd, 1H, J = 12.4 and 6.0 Hz), 2.79 (d, 1H, J = 16.8 Hz), 3.71 (s, 3H), 4.49 (dt, 1H, J = 10.8 and 6.0 Hz), 4.66 (dd, 1H, J = 6.0 and 2.8 Hz), 5.21 (d, 1H, J = 2.8 Hz), and 8.42 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 28.0, 35.3, 41.4, 49.1, 53.3, 71.4, 72.1, 99.0, 109.5, 141.5, 172.4, and 175.5.

To a solution containing 0.2 g (0.74 mmol) of the above amide in 3 mL of DMF was added 0.04 g (0.97 mmol) of 60% NaH at

0 °C. After the mixture was stirred at 0 °C for 1 h, a 0.33 g (1.4 mmol) sample of 4-(2-bromoethyl)-1,2-dimethoxybenzene was added. The reaction mixture was stirred at room temperature overnight and was then quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to give 0.25 g (80%) of **20** as a white solid: mp 128−130 °C; IR (neat) 2983, 1736, 1677, 1027, and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 3H), 1.45 (s, 3H), 1.56 (dd, 1H, J = 12.4 and 10.4 Hz), 2.42 (d, 1H, J = 16.8 Hz), 2.64 (dd, 1H, J = 12.4 and 6.0 Hz), 2.71−2.85 (m, 2H), 2.78 (d, 1H, J = 16.8 Hz), 3.46 (ddd, 1H, J = 14.0, 10.0, and 6.0 Hz), 3.63 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.50 (dt, 1H, J = 10.4 and 6.0 Hz), 4.72 (dd, 1H, J = 6.0 and 2.8 Hz), 5.17 (d, 1H, J = 2.8 Hz), 6.72 (s, 1H), 6.75 (d, 1H, J = 8.0 Hz), and 6.77 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 27.9, 32.2, 35.2, 40.9, 41.6, 47.5, 53.0, 55.9, 56.0, 71.2, 72.1, 97.2, 109.3, 111.4, 112.0, 120.8, 130.6, 143.6, 147.8, 149.0, 172.5, and 172.7. Anal. Calcd for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.83; H, 6.83; N, 3.11.

4-Bromo-5-[2-(3,4-dimethoxyphenyl)ethyl]-2,2-dimethyl-6-oxo-3*a*,5,6,7,8,8*a*-hexahydro[1,3]dioxolo[4,5-*f*]indole-7*a*-carboxylic Acid Methyl Ester (21). To a solution containing 0.16 g (0.37 mmol) of the above lactam **20** in 6 mL of CH_3CN was added 0.07 g (0.37 mmol) of NBS. The reaction mixture was stirred at room temperature for 1 h and was quenched with water. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography afforded 0.18 g (97%) of **21** as a colorless oil: IR (neat) 1732, 1664, 1515, 1213, and 731 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.39 (s, 3H), 1.49 (s, 3H), 1.71 (dd, 1H, J = 12.6, 11.4 Hz), 2.50 (d, 1H, J = 16.2 Hz), 2.59 (dd, 1H, J = 12.6 and 6.0 Hz), 2.71 (td, 1H, J = 12.0 and 6.0 Hz), 2.79 (d, 1H, J = 16.2 Hz), 2.90 (td, 1H, J = 12.0 and 4.8 Hz), 3.65 (s, 3H), 3.83 (s, 3H), 3.85, (s, 3H), 4.14 (m, 2H), 4.45 (dt, 1H, J = 11.4 and 6.0 Hz), 4.74 (d, 1H, J = 6.0 Hz), and 6.78 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.6, 28.1, 34.0, 35.0, 40.9, 72.9, 51.9, 53.3, 56.0, 72.4, 77.3, 94.5, 109.5, 111.4, 112.2, 120.9, 130.6, 140.3, 147.8, 149.0, 171.6, and 173.5.

4-Bromo-5-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2,2-dimethyl-6-oxo-3*a*,5,6,7,8,8*a*-hexahydro[1,3]dioxolo[4,5-*f*]indole-7*a*-carboxylic Acid Methyl Ester (22). To a solution containing 0.047 g (0.09 mmol) of the above lactam **21** in 6 mL of CH_3CN was added 0.016 g (0.09 mmol) of NBS. The reaction mixture was stirred at room temperature for 12 h and was quenched with water. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography afforded 0.05 g (93%) of **22** as a colorless oil: IR (neat) 2950, 1737, 1738, 1506, 912, and 729 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.40 (s, 3H), 1.50 (s, 3H), 1.71 (dd, 1H, J = 12.6 and 11.4 Hz), 2.50 (d, 1H, J = 16.8 Hz), 2.60 (dd, 1H, J = 12.6 and 5.4 Hz), 2.80 (d, 1H, J = 16.0.8 Hz), 2.89 (ddd, 1H, J = 13.8, 10.2 and 6.6 Hz), 2.98 (ddd, 1H, J = 13.8, 10.2 and 4.8 Hz), 3.66 (s, 3H), 3.82 (s, 3H), 3.83, (s, 3H), 4.16 (ddd, 1H, J = 13.8, 10.2 and 4.8 Hz), 4.24 (ddd, 1H, J = 13.8, 10.2 and 6.6 Hz), 4.45 (dt, 1H, J = 11.4 and 5.4 Hz), 4.74 (d, 1H, J = 5.4 Hz), 6.84 (s, 1H), and 6.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.7, 28.2, 34.3, 35.2, 41.1, 41.4, 52.1, 53.4, 56.3, 72.5, 94.9, 109.6, 113.4, 114.6, 115.7, 129.7, 140.4, 148.5, 148.6, 171.7, and 173.7.

(7*aR*,*Z*)-Methyl 1,2-(4,5-Dimethoxy)benzo-10,10-dimethyl-6-oxo-3,4,6,7,7*a*,-8,8*a*,11a-octahydroazepino[3,2,1-*hi*][1,3]dioxolo-[4,5-*f*]indole-7*a*-carboxylate (23). To a solution of 0.13 g (0.25 mmol) of lactam **21** in 25 mL of benzene was added 8.4 mg (0.05 mmol) of AIBN followed by 0.16 mL (0.61 mmol) of Bu_3SnH. The mixture was heated at reflux for 10 h, cooled to room temperature, and poured into 10 mL of an aqueous KF solution (1 M). The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.06 g (61%) of **23** as a white solid: mp 168−170 °C; IR (neat) 2981, 1727, 1643, 1211, 1050, and 729 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.49 (s, 3H), 1.57 (s, 3H), 1.96 (t, 1H, J = 12.0 Hz), 2.59 (d, 1H, J = 16.8 Hz), 2.60 (dd, 1H, J = 12.0 and 4,8 Hz), 2.81 (d, 1H, J = 16.8 Hz), 2.92 (dd, 1H, J = 15.0 and 4.8 Hz), 3.02 (dd, 1H, J = 15.0 and 10.2 Hz), 3.41−3.50 (m, 1H), 3.73 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.29 (brs, 1H), 4.36 (dt, 1H, J = 12.0 and 4.8 Hz), 4.78 (d, 1H, J = 4.8 Hz), 6.61 (s, 1H), and 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 26.6, 29.0, 33.7, 34.9, 41.8, 48.4, 51.1, 53.4, 55.8, 56.1, 71.9, 76.2, 108.9, 109.3, 111.5, 112.3, 128.0, 133.9, 141.0, 147.9, 172.0, and 173.3. Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.06; H, 6.34; N, 3.10.

Treatment of lactam **22** under similar radical conditions also afforded **23** in 55% yield.

5-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,2-dimethyl-6-oxo-3*a*,5,6,7,8,8*a*-hexahydro[1,3]dioxolo[4,5-*f*]indole-7*a*-carboxylic Acid Methyl Ester (24). To a solution of 0.2 g (0.74 mmol) of acetonide **11** in 3 mL of DMF was added 0.04 g (0.97 mmol) 60% NaH at 0 °C. After the mixture was stirred at 0 °C for 1 h, 0.43 g (1.33 mmol) of 1-bromo-2-(2-bromoethyl)-4,5-dimethoxybenzene was added. The reaction mixture was stirred from 0 °C to room temperature overnight and then quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford 0.2 g (53%) of **24** as a clear oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.35 (s, 3H), 1.43 (s, 3H), 1.55 (dd, 1H, J = 12.6 and 10.2 Hz), 2.43 (d, 1H, J = 16.2 Hz), 2.63 (dd, 1H, J = 12.6 and 6.6 Hz), 2.77 (d, 1H, J = 16.2 Hz), 2.81 (ddd, 1H, J = 13.8, 10.2, and 6.6 Hz), 2.96 (ddd, 1H, J = 13.8, 10.2 and 6.6 Hz), 3.42−3.51 (m, 1H), 3.61 (s, 3H), 3.76−3.84 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.48 (dt, 1H, J = 10.2 and 6.6 Hz), 4.70 (dd, 1H, J = 6.6 and 3.0 Hz), 5.29 (d, 1H, J = 3.0 Hz), 6.74 (s, 1H), and 6.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.2, 28.0, 33.0, 35.1, 40.0, 41.0, 47.5, 53.1, 56.2, 60.5, 71.2, 72.1, 97.6, 109.3, 113.6, 114.3, 115.6, 129.4, 143.5, 148.5, 148.6, 172.3, and 172.8.

(7*aR*,*Z*)-Methyl 1,2-(4,5-Dimethoxy)benzo-10,10-dimethyl-6-oxo-3,4,5[1],6,7,7*a*,-8,8a,11*a*,11*b*-decahydroazepino[3,2,1-*hi*][1,3]-dioxolo[4,5-*f*]indole-7*a*-carboxylate (25). To a solution of 0.1 g (0.2 mmol) of bromo-lactam **24** in 20 mL of benzene was added 8.0 mg (0.05 mmol) of AIBN followed by 0.067 mL (0.25 mmol) of Bu_3SnH. The mixture was heated to reflux for 10 h, cooled to room temperature, and poured into 10 mL of an aqueous KF solution (1 M). The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.062 g (72%) of **25** as a white solid: mp 138−140 °C; IR (neat) 1732, 1689, 1516, 1214, and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.38 (s, 3H), 2.01 (dd, 1H, J = 13.6 and 9.2 Hz), 2.44 (d, 1H, J = 17.6 Hz), 2.52−2.60 (m, 2H), 2.71 (d, 1H, J = 17.6 Hz), 2.71−2.74 (m, 1H), 2.88−2.96 (m, 2H), 3.75 (s, 3H), 3.75−3.81 (m, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 4.42 (dt, 1H, J = 9.6 and 7.2 Hz), 4.51 (ddd, 1H, J = 13.6, 5.2 and 1.6 Hz), 4.57 (dd, 1H, J = 11.6 and 7.2 Hz), 6.67 (s, 1H), and 7.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 27.8, 34.2, 35.0, 42.1, 43.0, 44.5, 45.6, 53.2, 56.0, 56.3, 63.6, 71.2, 73.3, 109.2, 111.2, 112.7, 130.8, 133.9, 147.5, 147.6, 171.1, and 175.0. HRMS Calcd for $C_{23}H_{29}NO_7$: 431.1944. Found: 431.1943.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2,5-dioxo-1,2,3,4,5,6-hexahydroindole-3*a*-carboxylic Acid Methyl Ester (27). To a solution containing 0.38 g (0.88 mmol) of **20** in 5 mL of CH_2Cl_2 was added 1 mL of TFA. The reaction mixture was stirred at room temperature for 30 min and was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

0.34 g (93%) of **27** as a pale yellow oil: IR (neat) 2954, 1724, 1677, 1516, 1027, and 729 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 2.40 (d, 1H, J = 16.4 Hz), 2.45 (d, 1H, J = 16.4 Hz), 2.80 (t, 2H, J = 8.0 Hz), 2.97 (dd, 1H, J = 22.4 and 6.0 Hz), 3.03 (d, 1H, J = 8.8 Hz), 3.07 (d, 1H, J = 8.8 Hz), 3.12 (dd, 1H, J = 22.4 and 3.6 Hz), 3.54 (dt, 1H, J = 14.8 and 8.0 Hz), 3.68 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89 (dt, 1H, J = 14.8 and 8.0 Hz), 5.07 (dd, 1H, J = 6.0 and 3.6 Hz), 6.73 (d, 1H, J = 8.4 Hz), 6.75 (s, 1H), and 6.79 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4, 37.0, 40.1, 41.7, 46.5, 47.6, 53.4, 56.1, 56.2, 95.3, 111.4, 112.1, 120.9, 130.6, 140.4, 148.0, 149.2, 171.7, 172.7, and 205.6. HRMS Calcd for $C_{20}H_{23}NO_6$: 373.1525. Found: 373.1524.

11,12-Dimethoxy-3,6-dioxo-1,2,3,4,5,6,8,9-octahydroindolo-[7*a*,1-*a*]isoquinoline-4*a*-carboxylic Acid Methyl Ester (28). To a 0.1 g (0.26 mmol) sample of **27** was added 1.5 mL of PPA. The reaction mixture was heated at 70 °C for 2 h and then cooled to room temperature and quenched with water. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by purification of the residue by silica gel chromatography afforded 0.09 g (90%) of **28** as a clear oil: IR (neat) 1720, 1686, 1260, and 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (d, 1H, J = 18.0 Hz), 2.34 (s, 2H), 2.29−2.39 (m, 1H), 2.41−2.48 (m, 1H), 2.61 (dd, 1H, J = 15.2 and 5.2 Hz), 2.79 (d, 1H, J = 17.6 Hz), 2.84 (d, 1H, J = 18.0 Hz), 2.87 (dd, 1H, J = 15.2 and 3.2 Hz), 2.97 (dd, 1H, J = 12.8 and 3.2 Hz), 3.07 (s, 3H), 3.28 (d, 1H, J = 17.6 Hz), 3.82 (s, 6H), 4.42 (dd, 1H, J = 12.8 and 5.2 Hz), 6.55 (s, 1H), and 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 34.6, 35.2, 35.7, 42.0, 45.2, 50.8, 52.2, 56.0, 56.2, 61.1, 108.6, 111.5, 127.3, 129.7, 147.4, 148.2, 170.8, 172.7, and 208.9. HRMS Calcd for $C_{20}H_{23}NO_6$: 373.1525. Found: 373.1516.

11,12-Dimethoxy-1,2,8,9-tetrahydro-5*H*-indolo[7*a*,1-*a*]isoquinoline-3,6-dione (30). To a mixture containing 0.2 g (0.56 mmol) of **28** in 6 mL of MeOH was added 2 mL of 2 M NaOH. The mixture was heated at 90 °C for 12 h, cooled to room temperature, and acidified to pH = 3 with HCl. The mixture was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give 0.14 g (75%) of 11,12-dimethoxy-3,6-dioxo-1,2,3,4,5,6,8,9-octahydroindolo-[7*a*,1*a*]isoquinoline-4*a*-carboxylic acid (**29**) as a pale yellow oil: IR (neat) 2935, 1718, 1635, and 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.18 (d, 1H, J = 18.0 Hz), 2.24−2.34 (m, 1H), 2.31 (s, 2H), 2.57 (dd, 1H, J = 15.6 and 3.2 Hz), 2.74 (d, 1H, J = 18.0 Hz), 2.78 (d, 1H, J = 17.6 Hz), 2.84 (ddd, 1H, J = 15.6, 12.8 and 5.2 Hz), 2.97 (td, 1H, J = 12.8 and 3.2 Hz), 3.22 (d, 1H, J = 17.6 Hz), 3.77 (s, 3H), 3.79 (s, 3H), 4.33 (dd, 1H, J = 12.8 and 5.2 Hz), 6.51 (s, 1H), and 6.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 34.9, 35.2, 35.9, 42.2, 45.0, 50.7, 56.0, 66.3, 108.6, 111.7, 127.4, 129.7, 147.4, 148.3, 171.6, 174.9, and 209.1. HRMS Calcd for $C_{19}H_{21}NO_6$: 359.1369. Found: 359.1363.

To a solution of 0.04 g (0.1 mmmol) of the above acid in 3 mL of CH_2Cl_2 was added 10 μL (0.12 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The crude residue was taken up in 2 mL of $CBrCl_3$, and 18 mg (0.12 mmol) of 3-mercapto-pyridine-1-oxide sodium salt and 2 mg of AIBN were added. The mixture was heated at reflux for 2 h, cooled to room temperature, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 0.02 g (75%) of **30** as a pale yellow oil: IR (neat) 2935, 1689, 1684, and 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30−2.37 (m, 1H), 2.45−2.58 (m, 3H), 2.89 (ddd, 1H, J = 16.8, 8.0 and 4.0 Hz), 3.12 (dt, 1H, J = 16.8 and 8.0 Hz), 3.42 (dt, 1H, J = 13.2 and 8.0 Hz), 3.77 (s, 3H), 3.86 (s, 3H), 4.34 (ddd, 1H, J = 13.2, 8.0 and 4.0 Hz), 6.25 (s, 1H), 6.55 (s, 1H), and 6.70 (s, 1H). HRMS Calcd for $C_{18}H_{19}NO_4$: 313.1314. Found: 313.1310.

3-Demethoxyerythratidinone (1). A 0.02 g sample of **30**, 0.5 mL of ethylene glycol, and a catalytic amount of *p*-TsOH in 5 mL of benzene were heated at reflux for 7 h. The cooled mixture was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography and immediately used in the next step. A 0.02 g sample of sublimed $AlCl_3$ in 0.4 mL of ether was added to a solution of 0.02 g of $LiAlH_4$ in 5 mL of THF at −15 °C, and the mixture was stirred at this temperature for 30 min. The resulting solution was added to a stirred solution of the acetonide derived from **30** in 3 mL of THF. After being stirred for 1 h at 25 °C, the mixture was diluted with ether, and the excess $LiAlH_4$ was decomposed by the addition of 5% aqueous NH_4OH. The ether layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was taken up in 1 mL of acetone, 0.5 mL of 5% HCl was added, and the mixture was heated at reflux for 1 h. The cooled mixture was washed with 10% NaOH, extracted into $CHCl_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was crystallized from benzene−hexane to give 0.01 g of 3-demethoxyerythratidinone (**1**) as a colorless solid, mp 100−101 °C (lit.[28a] 101−102 °C) and whose NMR spectrum matched that reported in the literature.[28a]

5-(*tert*-Butyl-dimethylsilanyloxy)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-1,4,5,6-tetrahydroindol-2-one (33). To a solution containing 0.04 g (0.17 mmol) of dienyl alcohol **7**[29] in 1 mL of DMF was added 0.03 g (0.38 mmol) of imidazole at 0 °C followed by 0.03 g (0.19 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was heated at 50 °C for 2 h and was then diluted with EtOAc. The mixture was washed by water, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography to give 0.06 g (92%) of 5-(*tert*-butyl-dimethyl-silanyloxy)-2-oxo-2,4,5,6-tetrahydro-indole-1-carboxylic acid *tert*-butyl ester as a white solid: mp 118−119 °C; IR (neat) 2960, 1777, 1736, 1322, 1080, and 866 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 6H), 0.86 (s, 9H), 1.56 (s, 9H), 2.34 (ddd, 1H, J = 17.5, 8.3 and 3.4 Hz), 2.54 (ddd, 1H, J = 16.2, 10.3 and 1.8 Hz), 2.56−2.61 (m, 1H), 2.86 (dd, 1H, J = 16.2 and 4.4 Hz), 4.00 (ddt, 1H, J = 10.3, 8.3 and 4.4 Hz), 5.73 (s, 1H), and 6.54 (ddd, 1H, J = 6.4, 3.4 and 1.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.5, 18.2, 25.9, 28.3, 34.7, 34.8, 67.5, 83.7, 115.8, 116.5, 136.1, 149.6, 150.7, and 168.2. Anal. Calcd for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.50; H, 8.59; N, 3.97.

To a solution containing 0.05 g (0.13 mmol) of the above imide in 1 mL of CH_3CN was added 5.6 mg (0.03 mmol) of magnesium perchlorate. The mixture was heated at 50 °C for 2 h and was then cooled to 25 °C. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.04 g (87%) of 5-(*tert*-butyl-dimethylsilanyloxy)-1,4,5,6-tetrahydro-indol-2-one as a white solid: mp 97−99 °C; IR (neat) 3716, 2950, 1678, 1095, and 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 2.31 (ddd, J = 17.2, 8.4 and 3.2 Hz), 2.50 (dt, 1H, J = 17.2 and 4.4 Hz), 2.52 (ddd, 1H, J = 16.0, 10.2 and 2.0 Hz), 2.87 (dd, 1H, J = 16.0 and 4.4 Hz), 4.03 (ddt, 1H, J = 10.2, 8.4 and 4.4 Hz), 5.58 (ddt, 1H, J = 4.4, 3.2 and 2.0 Hz), 5.78 (s, 1H), and 8.61 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.5, 18.2, 30.0, 34.3, 34.4, 68.7, 109.1, 117.7, 138.3, 148.3, and 173.5; FAB HRMS Calcd for $[(C_{14}H_{23}NO_2Si) + Li]^+$: 272.1658. Found: 272.1658.

To a solution containing 0.06 g (0.24 mmol) of the above amide in 3 mL of DMF was added 0.02 g (0.54 mmol) of NaH (60%) at 0 °C. The mixture was stirred at 0 °C for 1.5 h, and then 0.22 g (0.9 mmol) of 4-(2-bromoethyl)-1,2-dimethoxybenzene was added. The reaction mixture was stirred at 25 °C for 12 h and was then quenched by the addition of water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.07 g (85%) of **33** as a white solid: mp 117−118 °C; IR (neat) 2955, 1687, 1513, 1260, and 861 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 2.24

(ddd, J = 17.2, 8.8 and 3.2 Hz), 2.42−2.52 (m, 2H), 2.78 (t, 2H, J = 7.6 Hz), 2.85 (dd, 1H, J = 16.0 and 4.4 Hz), 3.71 (t, 2H, J = 7.6 Hz), 3.84 (s, 6H), 5.27 (m, 1H), 5.77 (s, 1H), 6.67 (s, 1H), 6.71 (d, 1H, J = 8.0 Hz), and 6.77 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.5, 18.2, 25.9, 34.3, 34.5, 34.9, 41.0, 56.0, 56.1, 68.7, 106.7, 111.4, 112.2, 117.1, 120.9, 131.5, 139.7, 146.4, 147.8, 149.1, and 170.5. Anal. Calcd for $C_{24}H_{35}NO_4Si$: C, 67.10; H, 8.21; N, 3.26. Found: C, 67.06; H, 8.16; N, 3.27.

1-Bromo-3-(*tert*-butyl-dimethylsilanyloxy)-11,12-dimethoxy-1,2,3,4,8,9-hexahydroindolo[7*a*,1-*a*]isoquinolin-6-one (34). To a solution containing 0.05 g (0.12 mmol) of **33** in 5 mL of CH_3CN was added 0.02 g (0.12 mmol) of *N*-bromo-succinimide (NBS). The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by purification by flash silica gel chromatography afforded 0.05 g (89%) of **34** as a white solid: mp 189−190 °C; IR (neat) 2950, 1674, 1508, 1094, and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 2.24−2.33 (m, 2H), 2.86 (ddd, 1H, J = 14.4, 10.2, 1.8 Hz), 2.98 (t, 2H, J = 6.6 Hz), 3.28 (dd, 1H, J = 14.4 and 5.4 Hz), 3.94 (dt, 1H, J = 13.2 and 6.6 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 3.91 (dt, 1H, J = 13.2 and 6.6 Hz), 4.39 (tt, 1H, J = 10.2 and 5.4 Hz), 4.56 (t, 1H, J = 3.0 Hz), 6.14 (d, 1H, J = 1.8 Hz), 6.74 (s, 1H), and 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −4.4, −4.5, 18.2, 26.0, 27.7, 36.2, 38.5, 39.5, 55.7, 56.1, 56.5, 67.8, 68.0, 110.2, 112.7, 126.2, 127.3, 128.1, 147.2, 149.1, 156.2, and 169.6. Anal. Calcd for $C_{24}H_{34}BrNO_4Si$: C, 56.69; H, 6.74; N, 2.75. Found: C, 56.65; H, 6.70, N, 2.75.

11,12-Dimethoxy-1,2,8,9-tetrahydroindolo[7*a*,1-*a*]isoquinolin-6-one (35). To a 0.05 g (0.1 mmol) sample of bromide **34** in 5 mL of benzene were added 3 mg of AIBN and 43 μL (0.16 mmol) of *n*-Bu_3SnH. The reaction mixture was heated at reflux for 12 h and then cooled to room temperature. Concentration under reduced pressure followed by purification by silica gel chromatography afforded 0.03 g (70%) of 3-(*tert*-butyl-dimethylsilanyloxy)-11,12-dimethoxy-1,2,3,4,8,9-hexahydroindolo[7*a*,1*a*]isoquinolin-6-one as a colorless oil: IR (neat) 2950, 1687, 1513, 1258, 1092, and 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.47−1.51 (m, 1H), 1.81−1.87 (m, 2H), 2.31 (dt, 1H, J = 13.0 and 3.5 Hz), 2.83 (dd, 1H, J = 22.6 and 9.6 Hz), 2.87 (dd, 1H, J = 22.6 and 10.5 Hz), 2.96 (dd, 1H, J = 15.6 and 7.6 Hz), 3.15 (dd, 1H, J = 13.7 and 5.7 Hz), 3.38 (ddd, 1H, J = 13.0, 7.9 and 5.7 Hz), 3.76−3.43 (m, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 4.09 (ddd, 1H, J = 13.0, 6.7, 5.4 Hz), 5.91 (d, 1H, J = 1.6 Hz), 6.68 (s, 1H), and 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.4, 18.2, 26.0, 28.6, 31.1, 36.4, 37.1, 39.7, 56.1, 56.5, 65.7, 72.6, 110.2, 112.6, 122.9, 127.1, 129.6, 146.9, 148.3, 161.9, and 170.1.

To a solution of 0.04 g (0.10 mmol) of the above compound in 1 mL of THF was added 0.14 mL (0.14 mmol) of TBAF (1 M). The reaction mixture was stirred at 25 °C for 1 h and was then quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.03 g (100%) of 3-hydroxy-11,12-dimethoxy-1,2,3,4,8,9-hexahydroindolo[7*a*,1-*a*]isoquinolin-6-one as a colorless oil: IR (neat) 3378, 2936, 1663, 1079, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53, (td, 1H, J = 13.6 and 4.0 Hz), 1.69 (brs, 1H), 1.83 (tdd, 1H, J = 13.6, 11.2 and 3.6 Hz), 1.96 (dd, 1H, J = 13.6 and 3.6 Hz), 2.36 (dt, 1H, J = 12.8 and 3.6 Hz), 2.45 (d, 1H, J = 3.6 Hz), 2.83−3.00 (m, 3H), 3.29 (ddd, 1H, J = 13.2, 5.6 and 1.6 Hz), 3.42 (dt, 1H, J = 13.2 and 6.4 Hz), 3.85 (s, 3H), 3.88 (s, 3H), 4.05 (dt, 1H, J = 12.8 and 6.4 Hz), 5.96 (d, 1H, J = 1.6 Hz), 6.70 (s, 1H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 30.7, 36.7, 37.2, 39.1, 56.1, 56.6, 65.8, 72.0, 110.0, 112.7, 123.3, 127.2, 129.6, 147.0, 148.4, 161.5, and 170.1. HRMS Calcd for $C_{18}H_{21}NO_4$: 315.1471. Found: 315.1476.

To a solution containing 0.024 g (0.08 mmol) of the above alcohol in 1.5 mL of CH_2Cl_2 were added 8.4 μL (0.09 mmol) of $POCl_3$ and 56 μL (0.38 mmol) of DBU. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with a saturated NH_4Cl aqueous solution. The aqueous layer was extracted with EtOAc, and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.016 g (72%) of **35** as a colorless oil: IR (neat) 2929, 1687, and 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (dt, 1H, J = 12.0 and 5.6 Hz), 2.14−2.26 (m, 1H), 2.32 (dd, 1H, J = 12.0 and 4.6 Hz), 2.41 (dt, 1H, J = 19.2 and 5.6 Hz), 2.97 (t, 2H, J = 6.8 Hz), 3.55 (dt, 1H, J = 12.8 and 6.8 Hz), 3.76 (s, 3H), 3.84 (s, 3H), 4.03 (dt, 1H, J = 12.8 and 6.8 Hz), 5.88 (s, 1H), 6.28 (ddd, 1H, J = 9.6, 5.6, and 2.0 Hz), 6.69 (s, 1H), 6.81 (dd, 1H, J = 9.6 and 2.8 Hz), and 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, and 158.0. HRMS Calcd for $[(C_{18}H_{19}NO_3) + Li]^+$: 304.1525. Found: 304.1516.

Formic Acid 11,12-Dimethoxy-6-oxo-2,6,8,9-tetrahydro-1*H*-indolo[7*a*,1*a*]-isoquinolin-2-yl Ester (36). To a solution containing 0.55 g (1.8 mmol) of **35** in 7 mL of 1,4-dioxane at 25 °C were 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 the mixture was cooled to room temperature, 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 flash silica gel chromatography provided 0.09 g (14%) of formate **36** as a yellow pale oil: IR (neat) 2933, 1720, 1686, and 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (dd, 1H, J = 11.2 and 10.4 Hz), 2.84 (dd, 1H, J = 11.2 and 5.2 Hz), 2.93−3.103 (m, 2H), 3.58 (dt, 1H, J = 12.8 and 6.4 Hz), 3.77 (s, 3H), 3.85 (s, 3H), 4.00 (dt, 1H, J = 12.8 and 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 and 2.4 Hz), and 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 and 170.6. HRMS Calcd for $C_{19}H_{19}NO_5$: 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-[7*a*,1*a*]isoquinolin-6-one (**37**) which was isolated as a tan solid: mp 230−232 °C; IR (KBr) 3419, 2927, 1680, and 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (dd, 1H, J = 11.6 and 10.0 Hz), 2.11 (brs, 1H), 2.81 (dd, 1H, J = 11.6 and 4.8 Hz), 2.90−3.12 (m, 2H), 3.60 (ddd, 1H, J = 12.8, 6.8 and 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), and 6.87 (dd, 1H, J = 10.0 and 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, and 171.0. HRMS Calcd for $C_{18}H_{19}NO_4$: 313.1314. Found: 313.1305.

Alcohol **37** could also be obtained from the solvolysis of formate **36**. To a solution containing 0.002 g (0.064 mmol) of **36** in 3 mL of EtOH was added 0.1 mL of acetyl chloride at 25 °C. The reaction mixture was stirred for 1 h at 25 °C. Removal of the solvent under reduced pressure afforded 0.002 g (100%) of **37** as the exclusive product.

(±)-Erysotramidine (2). To a mixture containing 0.09 g (0.27 mmol) of alcohol **37** in 7 mL of THF and 4 mL of methyl iodide were 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 25 °C. The solution was poured into ice−water, and the resulting mixture was extracted with $CHCl_3$. The combined organic layer was 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 **19a**: IR (neat) 2930, 1666, and 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (dd, 1H, J = 11.6 and 10.4 Hz), 2.80 (dd, 1H, J = 11.6 and 4.4 Hz), 2.90−3.24 (m, 2H), 3.34 (s, 3H), 3.61 (ddd,

1H, J = 12.8, 7.2 and 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 and 7.2 Hz), 6.02 (s, 1H), 6.33 (d, 1H, J = 10.0 Hz), 6.72 (s, 1H), 6.80 (s, 1H), and 6.90 (dd, 1H, J = 10.0 and 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, and 170.8. HRMS Calcd for $[(C_{19}H_{21}NO_4) + Li]^+$: 334.1631. Found: 334.1633.

Preparation of (3*aR*,7*aS*,8*aS*)-5-(6-Iodobenzo[*d*][1,3]dioxole-5-carbonyl)-2,2-dimethyl-7,7*a*,8,8*a*-tetrahydro-3*aH*-[1,3]dioxolo-[4,5-*f*]indol-6(5*H*)-one (44). To a solution containing 0.05 g (0.17 mmol) of *tert*-butyl-2,3,3*a*,4,5,6-hexahydro-5,6-acetonide-2-oxoindole-1-carboxylate (**8**)[29] in 1 mL of CH_3CN was added 8 mg (0.034 mmol) of magnesium perchlorate. The reaction mixture was heated at 40 °C for 2 h and cooled to room temperature. Concentration under reduced pressure and purification by silica gel chromatography provided the deprotected amide as a white solid: mp 151−153 °C; IR (neat) 3170, 1683, 1324, and 876 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 3H), 1.52 (q, 1H, J = 11.6 Hz), 1.48 (s, 3H), 2.15 (dt, 1H, J = 11.6 and 5.0 Hz), 2.24 (dd, 1H, J = 16.8 and 9.6 Hz), 2.56 (dd, 1H, J = 16.8 and 9.2 Hz), 2.72−2.81 (m, 1H), 4.23 (dt, 1H, J = 11.6 and 5.0 Hz), 4.61−4.64 (m, 1H), 5.11 (t, 1H, J = 3.2 Hz), and 8.29 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0, 28.6, 32.4, 34.0, 36.0, 71.7, 74.0, 94.9, 109.2, 145.8, and 177.7. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.02; H, 7.21; N, 6.62.

To a solution of 0.03 g (0.12 mmol) of the above amide in 1 mL of CH_2Cl_2 were added 1.5 mg (0.001 mmol) of (dimethylamino)pyridine, 0.08 mL (0.58 mmol) of Et_3N, and 6-iodobenzo[*d*]-[1,3]dioxole-5-carbonyl chloride[51] in 1 mL of CH_2Cl_2. The reaction mixture was stirred for 2 h, quenched with water, and washed with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 0.06 g (98%) of **44** as a white solid: mp 82−84 °C; IR (neat) 1770, 1698, 1240, and 876 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 3H), 1.52 (q, 1H, J = 11.6 Hz), 1.51 (s, 3H), 2.24 (dt, 1H, J = 11.6 and 4.8 Hz), 2.36 (dd, 1H, J = 17.2 and 10.6 Hz), 2.70 (dd, 1H, J = 17.2 and 8.8 Hz), 2.79−2.88 (m, 1H), 4.29 (dt, 1H, J = 11.6 and 4.8 Hz), 4.75−4.78 (m, 1H), 6.02 (s, 2H), 6.57 (t, 1H, J = 3.2 Hz), 6.75 (s, 1H), and 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 28.5, 32.3, 33.8, 36.8, 71.4, 73.0, 81.3, 102.4, 106.2, 109.0, 118.9, 134.9, 142.5, 148.5, 150.0, 168.2, and 173.7. Anal. Calcd for $C_{19}H_{18}INO_6$: C, 47.22; H, 3.75; N, 2.90. Found: C, 47.05; H, 3.79; N, 2.98.

Preparation of (3*aS*,4*aS*,4*a*1*R*,13*bS*,13*cR*)-2,2-Dimethyl-4*a*,5,-13*b*,13*c*-tetrahydro-3*aH*-bis[1,3]dioxolo[4,5-*a*:4′,5′-*j*]pyrrolo-[3,2,1-*de*]phenanthridine-6,8(4*H*,4*a*1*H*)-dione (45). To a solution of containing 0.1 g (0.2 mmol) of imide **44** in 40 mL of benzene was added 0.017 g (0.1 mmol) of AIBN and 0.11 mL (0.4 mmol) of *n*-Bu_3SnH. The solution was heated at reflux for 3 h and cooled to room temperature. Concentration under reduced pressure followed by purification using silica gel chromatography provided 0.04 g (55%) of the major product **45** as a white solid, mp 217−220 °C; IR (neat) 1758, 1481,1275, 927, and 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 3H), 1.53 (s, 3H), 1.60−1.69 (m,-1H), 2.28 (dt, 1H, J = 12.4 and 5.2 Hz), 2.44 (dd, 1H, J = 17.2 and 7.2 Hz), 2.46 (m, 1H), 2.94 (dd, 1H, J = 17.2 and 10.0 Hz), 3.13 (dd, 1H, J = 13.2 and 8.8 Hz), 3.97 (dd, 1H, J = 13.2 and 10.0 Hz), 4.24−4.39 (m, 2H), 6.04 (d, 1H, J = 1.2 Hz), 6.05 (d, 1H, J = 1.2 Hz), 7.27 (s, 1H), and 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4, 25.3, 27.2, 32.8, 38.2, 41.5, 58.5, 73.8, 75.0, 102.3, 106.8, 109.3, 123.4, 137.7, 147.7, 152.7, 161.5, and 172.7. FAB HRMS Calcd for $[(C_{19}H_{19}NO_6) + Li]^+$: 364.1372. Found: 364.1382.

***epi*-Zephyranthine (9).** To a solution containing 0.02 g (0.055 mmol) of compound **45** was added 0.82 mL (0.82 mmol) of BH_3 (1.0 M in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h and was then quenched with 3 mL of MeOH. Concentration of the solution under reduced pressure followed by purification using silica gel chromatography provided 0.012 g (72%) of the expected aminodioxolane as a white solid: mp 170 °C (dec); IR (neat) 1483, 1166, and 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.44 (s, 3H), 1.50 (s, 3H), 1.53 (q, 1H, J = 12.6 Hz), 1.70−1.76 (m, 1H), 2.16 (dt, 1H, J = 12.6 and 6.0 Hz), 2.50−2.58 (m,1H), 2.61 (dd, 1H, J = 12.6 and 9.6 Hz), 2.84 (dd, 1H, J = 12.6 and 9.0 Hz), 3.02 (dt, 1H, J = 11.4 and 7.2 Hz), 3.47 (p, 1H, J = 6.0 Hz), 3.59 (d, 1H, J = 12.6 Hz), 4.14 (d, 1H, J = 12.6 Hz), 4.25 (ddd, 1H, J = 11.4, 7.2 and 4.8 Hz), 4.31 (dd, 1H, J = 9.6 and 7.2 Hz), 5.93 (d, 1H, J = 1.2 Hz), 5.94 (d, 1H, J = 1.2 Hz), 6.74 (s, 1H), and 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4, 27.2, 31.2, 31.8, 33.4, 38.7, 62.2, 62.7, 68.9, 73.2, 75.0, 101.3, 106.1, 108.5, 109.3, 127.1, 131.0, 146.5, and 147.9. FAB HRMS Calcd for $[(C_{19}H_{23}NO_4) + Li]^+$: 336.1787. Found: 336.1780.

A 0.01 g (0.03 mmol) sample of the above dioxolane in 2 mL of a 3% HCl−MeOH mixture was stirred at 0 °C for 1 h and was then concentrated under reduced pressure. Purification by silica gel chromatography provided 0.008 g (90%)of **9** as a white solid: mp 215−218 °C; IR (neat) 3365, 1483, and 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.90 (ddd, 1H, J = 15.0, 6.6 and 3.0 Hz), 2.07 (dt, 1H, J = 12.6 and 6.6 Hz), 2.20 (dt, 1H, J = 15.0 and 3.0 Hz), 2.28 (d, 1H, J = 3.0 Hz), 2.32 (d, 1H, J = 6.6 Hz), 2.60 (qd, 1H, J = 12.6 and 7.8 Hz), 2.68 (dqd, 1H, J = 12.6, 6.6 and 3.0 Hz), 2.85 (dd, 1H, J = 10.8 and 6.6 Hz), 3.08 (dd, 1H, J = 12.6 and 7.8 Hz), 3.15 (t, 1H, J = 10.8 Hz), 3.63 (d, 1H, J = 13.2 Hz), 3.74 (td, 1H, J = 12.6 and 6.6 Hz), 4.04 (ddd, 1H, J = 10.8, 6.6 and 3.0 Hz), 4.15 (p, 1H, J = 3.0 Hz), 4.63 (d, 1H, J = 13.2 Hz), 5.96 (d, 1H, J = 1.8 Hz), 5.97 (d,1H, J = 1.8 Hz), 6.79 (s, 1H), and 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.3, 30.7, 34.8, 36.6, 58.3, 62.4, 69.4, 70.4, 71.0, 101.3, 105.6, 109.2, 126.7, and 130.5. HRMS Calcd for $C_{16}H_{19}NO_4$: 289.1314. Found: 289.1312.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of various key compounds lacking CHN analyses, together with an ORTEP drawing for compounds **16** and **45**, as well as the corresponding CIFs for these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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