Applications of Vinylogous Mannich Reactions. Asymmetric Synthesis of the Heteroyohimboid Alkaloids (−)-Ajmalicine, (+)-19-*epi*-Ajmalicine, and (−)-Tetrahydroalstonine

Stephen F. Martin,* Cameron W. Clark, and Jeffrey W. Corbett

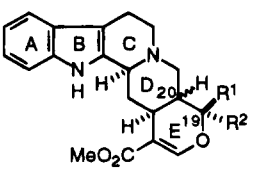
Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

Received January 31, 1995[⊗]

The vinylogous Mannich additions of 1-[(trialkylsilyl)oxy]butadienes to the acyl iminium salt derived from **7** proceeded with a modest degree of stereoselectivity to give a mixture (1.8:1) of **8** and **9**. The triene **8** underwent an intramolecular hetero Diels–Alder reaction to give the pentacyclic intermediate **10**. Decarboxylation of **10** according to the Barton protocol led to **13**, which was then elaborated to (−)-tetrahydroalstonine (**1**) by a straightforward sequence of reactions. This asymmetric synthesis of **1** required only 10 steps from readily available L-tryptophan. On the other hand, the related vinylogous Mannich addition of a vinyl ketene acetals to **16** were highly stereoselective giving the corresponding trans-substituted hydrocarboline as the only detectable product. Subsequent reaction of this adduct with methyl vinyl ketone followed by cyclization of the intermediate **18** gave the key tetracyclic intermediate **19**. Removal of the carboxyl group from the C(5) position of **19** following the Barton procedure gave the ketone **20**, which was converted into (−)-ajmalicine (**2**) in three steps by a known procedure. Alternatively, hydride reduction of the tetracyclic amine **19** gave the alcohol **22**, which was subjected to a modified Mitsunobu reaction; selective hydrolysis of the intermediate triester led to the lactone **24**. Radical decarboxylation via the Barton procedure gave an intermediate lactone that was converted into (+)-19-*epi*-ajmalicine (**3**) in two steps. Removal of the carboxyl presented pathways to both (−)-ajmalicine (**2**) and (+)-19-*epi*-ajmalicine (**3**). Thus, the asymmetric syntheses of **2** and **3** were completed by concise sequences of reactions requiring only 11 and 13 steps, respectively, from D-tryptophan.

Introduction

The structurally diverse members of the indole alkaloid family have elicited numerous scientific investigations because of their important and interesting physiological, biological, and structural properties.[1] The heteroyohimboid alkaloids constitute a prominent subgroup of indole alkaloids, and a number of these alkaloids including (−)-tetrahydroalstonine (**1**), (−)-ajmalicine (**2**), which is used clinically, and (+)-19-*epi*-ajmalicine (**3**) exhibit interesting pharmacological effects such as adrenergic blocking and vasodilation.[2–4] The total syntheses of ajmalicine,[5,6] 19-*epi*-ajmalicine,[5c,6b,d,e,7] and tetrahydroalstonine[5a,8,9] in racemic and optically pure form have been reported.



1: α-H_{20}; R^1 = H; R^2 = Me
2: β-H_{20}; R^1 = H; R^2 = Me
3: β-H_{20}; R^1 = Me; R^2 = H

The most common synthetic entry to the heteroyohimboid alkaloids is based on a ABDE → ABCDE construction in which the C ring is formed late in the synthesis. This type of approach requires the initial preparation of various DE bicyclics, followed by their attachment to a suitable tryptophyl synthon, and stereoselective formation of the C ring. However, depending upon the nature of the ABDE ring precursor, there may be questions

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1995.

(1) For a review of the monoterpenoid, indole alkaloids, see: (a) Stockigt, J. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: New York, 1980. (b) Cordell, G. A. *Introduction to Alkaloids, A Biogenetic Approach*; Wiley-Interscience: New York, 1981. (c) Saxton, J. E. *Specialist Periodical Reports, The Alkaloids*; The Royal Society of Chemistry, Burlington House: London, 1983; Vol. 13. (d) Dalton, D. R. *The Alkaloids-A Biogenetic Approach*; M. Dekker: New York, 1979. (e) Brown, R. T. In *Indoles. The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 4. (f) *The Alkaloids, Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1975, Vol. 14. (g) Szántay, C.; Blaskó, C.; Honty, K.; Dörnyei, G. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 27. (h) Ban, Y.; Murakami, Y.; Iwasawa, Y.; Tsuchiya, M.; Takano, N. *Med. Res. Rev.* **1988**, *8*, 231.

(2) Neuss, N. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: New York, 1980.

(3) Bories, J.; Merland, J.-J.; Thiebot, J. *Neurobiology* **1977**, *14*, 33 and references cited therein. Anand, N. In *Comprehensive Medicinal Chemistry*; Hansch, C., Ed.; Pergamon Press: Oxford, 1990, Vol. 1.

(4) Neuman, J.; Engel, A. M. F.; Neuman, M. P. *Arzneim. Fortsch.* **1986**, *36*, 1394.

(5) (a) Gutzwiller, J.; Pizzolato, G.; Uskokovic, M. *J. Am. Chem. Soc.* **1971**, *93*, 5907. (b) Winterfeldt, E.; Radunz, H. E.; Korth, T. *Chem. Ber.* **1968**, *101*, 3172. (c) Winterfeldt, E.; Gaskell, A. J.; Korth, T.; Radunz, H. E.; Walkowiak, M. *Chem. Ber.* **1969**, *102*, 3558.

(6) (a) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1984**, 715. (b) Hanessian, S.; Faucher, A.-M. *J. Org Chem.* **1991**, *56*, 2947. (c) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 517. (d) Honda, T.; Haze, N.; Ishige, H.; Masuda, K.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 539. (e) Djakoure, L. A.; Jarreau, F.-X.; Goutarel, R. *Tetrahedron* **1975**, *31*, 2695. (f) Takano, S.; Satoh, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 59. (g) van Tamelen, E. E.; Placeway, C.; Schiemenz, G. P.; Wright, I. G. *J. Am. Chem. Soc.* **1969**, *91*, 7359.

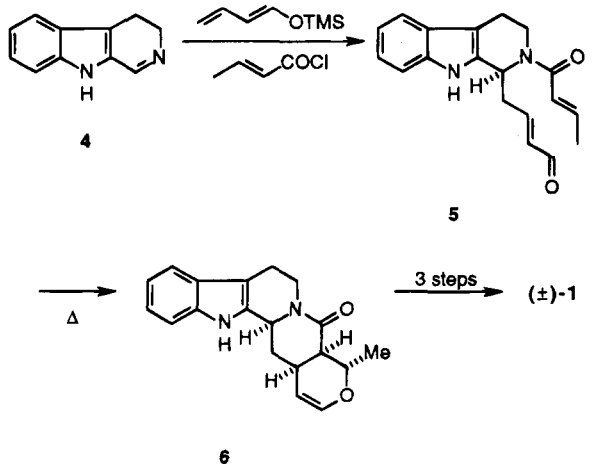
(7) (a) Baggiolini, E. G.; Pizzloato, G.; Uskokovic, M. R. *Tetrahedron* **1988**, *44*, 3203. (b) Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 923.

(8) (a) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015. (b) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (c) Uskokovic, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742.

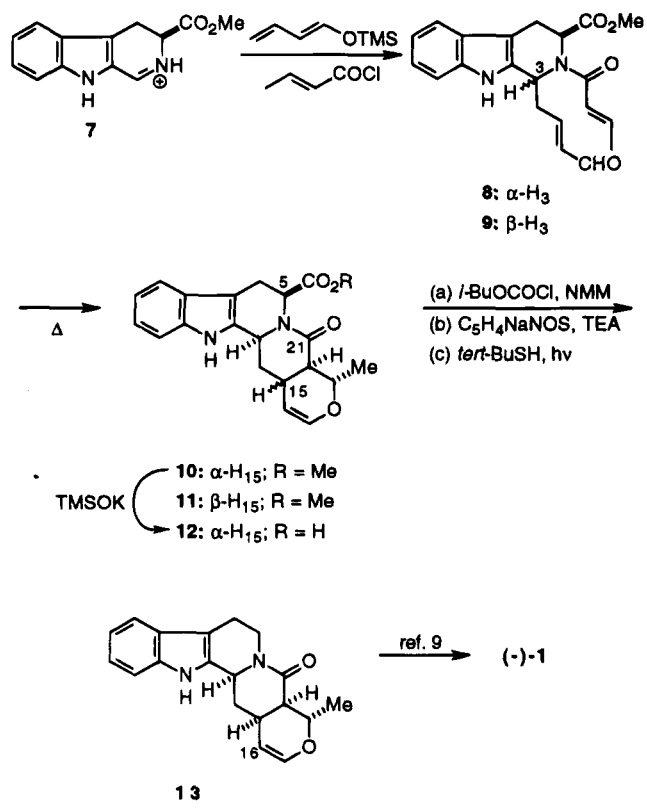
(9) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161 and references therein.

0022-3263/95/1960-3236$09.00/0

Scheme 1



Scheme 2



regarding the regioselectivity and stereoselectivity of the cyclization reaction that forms the C ring. In a unified approach to the heteroyohimboid and other classes of indole alkaloids, we developed a general solution to these problems that features the synthesis of the pentacyclic nucleus via a ABC → ABCDE approach.[9] In a key construction, the vinylogous Mannich reaction of 1-[(trimethylsilyl)oxy]butadiene with the acyl iminium salt that was generated *in situ* by *N*-acylation of the carboline **4** with crotonyl chloride delivered **5** (Scheme 1). This triene then underwent a hetero Diels–Alder reaction to produce the pentacyclic nucleus **6** characteristic of the hetereoyohimboid alkaloids. The cycloadduct **6** was transformed into racemic tetrahydroalstonine completing a total synthesis that required only seven steps from commercially available starting materials. We have recently developed a variant of this strategy in which the chirality present in L- and D-tryptophan is efficiently transferred to the stereocenters in the pentacyclic nucleus of representative heteroyohimboid alkaloids.[10] We now disclose the details of these investigations that culminated in the concise asymmetric syntheses of (−)-tetrahydroalstonine (**1**), (−)-ajmalicine (**2**), and (+)-19-*epi*-ajmalicine (**3**).

Results and Discussion

The original plan for the asymmetric synthesis of the heteroyohimboid alkaloids was based upon the expectation that vinylogous Mannich reactions involving the carboline **7**, which may be prepared from L-tryptophan by a known procedure,[11] would proceed with reasonable levels of stereoselectivity. In the event, the imine ester **7** was treated with 1-[(trimethylsilyl)oxy]butadiene in the presence of crotonyl chloride to afford a diastereomeric mixture (1.8:1) of the aldehydes **8** (34%) and **9** (19%), the structures of which were determined by X-ray crystallographic analysis (Scheme 2).[12] Activation of the carbon–nitrogen double bond of **7** by *in situ* formation of an *N*-acyl iminium salt is apparently necessary as the [(trimethylsilyl)oxy]butadiene did not add to **7** in the absence of crotonyl chloride. The chemical shift of the proton at C(3) of these adducts was diagnostic appearing at lower field (δ 5.74 ppm) in the cis-isomer **8** relative to the trans-isomer **9** (δ 4.85). When the major adduct **8** was heated in mesitylene at 170 °C (sealed tube) for 48 h, a mixture (5:1) of the cycloadducts pentacycles **10** and **11** was obtained in 81% combined yield. The structure of pentacycle **10** was determined by single crystal X-ray analysis.[13]

The remaining steps in the synthesis of tetrahydrohydroalstonine required removal of the carboxyl group at C(5), reduction of the lactam carbonyl group at C(21), and introduction of a carbomethoxy group at C(16). Owing to an interest in extending this approach to the synthesis of indole alkaloids bearing a carbomethoxy group at C(5), protocols for the selective reduction of the lactam carbonyl group in **10** were first explored. Unfortunately, standard methods using various hydride reducing agents (*e.g.*, Me_3OBF_4, $NaBH_4$, AlH_3, DIBAL-H) were ineffective returning either starting material or mixtures of the desired amine together with overreduced products. Efforts to convert the lactam to a thiolactam using Lawesson's or Belleau's reagents were also unavailing.[14]

Having been unable to reduce the lactam group, attention was then turned to decarboxylation of the ester function at C(5). Although base-induced saponification of the ester could not be effected under the mild condi-

(10) For other uses of tryptophan in the asymmetric syntheses of indole alkaloids, see: (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 786. (c) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1989**, *30*, 6421. (d) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220. (e) Baily, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895.

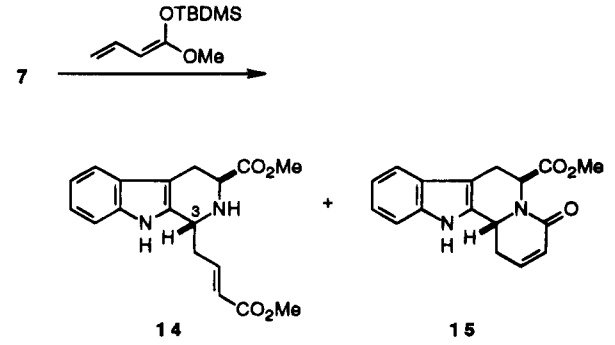
(11) (a) Previero, A.; Coletti-Previero, M.-A.; Barry, L.-G. *Can. J. Chem.* **1968**, *46*, 3404. (b) Previero, A.; Barry, L.-G.; Torreilles, J.; Fleury, B.; Letellier, S.; Maupas, B. *Tetrahedron* **1984**, *40*, 221.

(12) The author has deposited atomic coordinates for compounds **8** and **9** with the Cambridge Crystallographic Data Centre. These coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(13) Lynch, V. M.; Corbett, J. W.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1991**, *C47*, 464.

(14) (a) Pederson, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. (b) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815.

Scheme 3

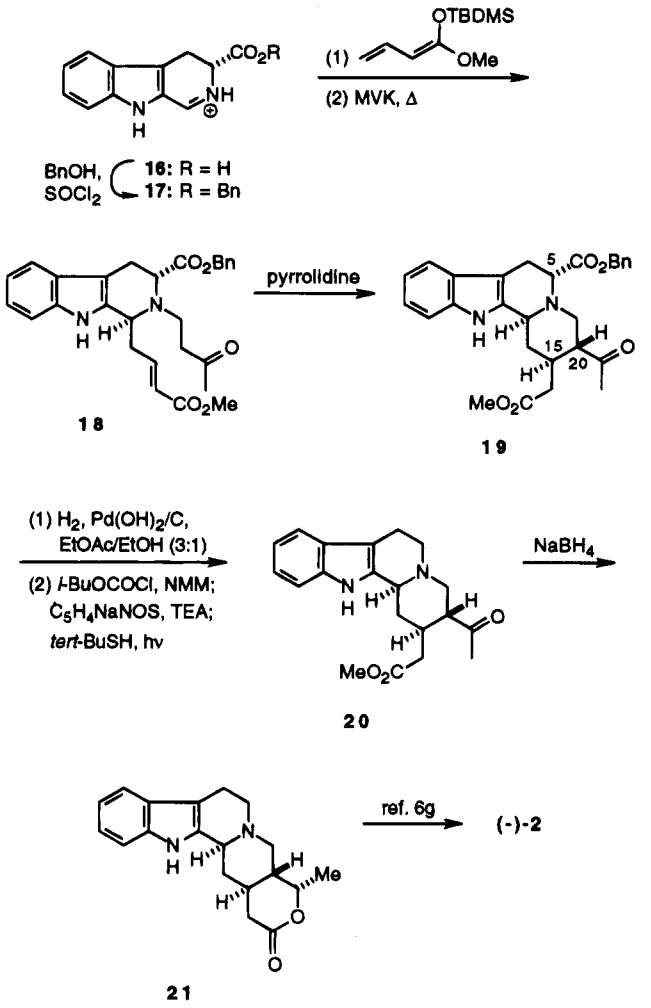


tions required to avoid β-elimination of the hydropyran oxygen group, treatment of **10** with potassium trimethylsilanoate (TMSOK) gave the desired carboxylic acid **12** in 60% yield.[15] Radical decarboxylation of **12** via the procedure of Barton provided the desired intemediate **13** in 63% yield.[16] Carboxymethylation of **13** followed by selective reduction of the lactam moiety was achieved according to procedures previously developed in our laboratories,[9] thereby completing a total, asymmetric synthesis of (−)-tetrahydroalstonine (**1**) in 10 steps from readily available L-tryptophan. The ^{1}H and ^{13}C NMR, mp, and optical rotation {$[\alpha]^{20}_D$ = −107° (*c* = 0.50, $CHCl_3$), lit.[17] $[\alpha]^{27}_D$ = −110° (*c* = 0.50, $CHCl_3$)} of the synthetic (−)-**1** thus obtained were identical in all respects with published data.[6f,9]

Owing to the modest diastereofacial selectivity observed for the vinylogous Mannich reaction of **7** to give a mixture of **8** and **9**, other related additions were examined to explore whether enhanced stereoselectivity might be obtained. In one experiment, we found that vinyl ketene acetals, which are more nucleophilic than 1-[(trimethylsilyl)oxy]butadiene, added to the iminium salt **7** in a highly stereoselective fashion producing the *trans*-adduct **14** as the major product (45−50%) together with small amounts (<5%) of the lactam **15** (Scheme 3). Although this discovery might be exploited in devising a stereochemically-improved route to the key hetero Diels−Alder substrate **8**, we were unable to develop a concise and efficient sequence of reactions to effect this transformation. Rather than belabor the problem, it occurred to us that a more intriguing prospect lay in the application of this process to the development of a novel entry to the related heteroyohimboid alkaloids (−)-ajmalicine (**2**) and (+)-19-*epi*-ajmalicine (**3**) as detailed in Schemes 4 and 5, respectively.

The direct utilization of the enantiomer of **14** in the synthesis of hetereoyohimboid alkaloids appeared problematic owing to the presence of the two methyl ester functions that must be selectively manipulated. The simple expedient of differentiating the two carboxyl functions at the outset of the sequence thus had obvious merit. The addition of several vinyl ketene acetals to the

Scheme 4



acid **16** was problematic, so the corresponding benzyl ester **17** was prepared in 97% yield by treating **16** with thionyl chloride in neat benzyl alcohol (Scheme 4). Reaction of the imine ester **17** with the silyl ketene acetal obtained from methyl crotonate[18] proceeded with essentially complete diastereofacial selectivity as expected to give the *trans*-product that was alkylated with methyl vinyl ketone to furnish **18** in 65% overall yield. Treatment of **18** with pyrrolidine in the presence of 4 Å molecular sieves then afforded the tetracyclic amine **19** in 94% yield. The relative *trans*-stereochemistry at C(15) and C(20) of **19** was assigned based upon the observed coupling constant for the protons at the ring juncture ($J_{15,20}$ = 9.8 Hz) that correlates well with similar compounds.[19-21] The stereochemistry of **19** is also the same as that observed by Massiot, who executed a related cyclization in his synthesis of (−)-ajmalicine.[6a]

Selective deprotection of the benzyl ester in **19** was readily accomplished by hydrogenolysis using $Pd(OH)_2/C$ (1 atm H_2) in ethyl acetate/ethanol (3:1) to provide an amino acid in 98% yield. The ratio of ethyl acetate and ethanol was found to be critical in this transformation

(15) (a) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831. (b) Hwu, J. R.; Gilbert, B. A. *Tetrahedron* **1989**, *45*, 1233.

(16) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939. (b) Barton, D. H. R.; Kretzschmar, G. *Tetrahedron Lett.* **1983**, *24*, 5889. (c) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (d) Barton, D. H. R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985**, *41*, 4347. (e) Barton, D. H. R.; Crich, D.; Kretzschman, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39. (f) Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951.

(17) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1972**, 1081.

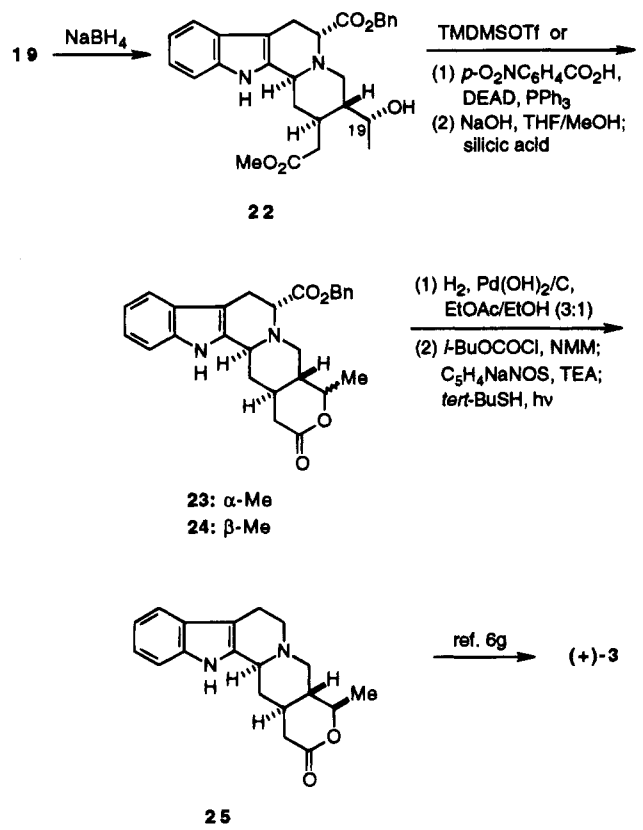
(18) (a) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3205. (b) Lombardo, L. *Tetrahedron Lett.* **1985**, *26*, 381.

(19) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509.

(20) For the X-ray structure of the corresponding dimethyl ester of **19**, see: Lynch, V. M.; Corbett, J. W.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1992**, *C48*, 1878.

(21) Lounasmaa, M. *Tetrahedron* **1980**, *36*, 1607.

Scheme 5



since too much ethanol led to overreduction and too much ethyl acetate gave no reaction. The α-amino acid was then decarboxylated according to the Barton protocol[16] to furnish the known ketone **20** in 55% yield. Van Tamelen and others have converted **20** to ajmalicine in three steps,[6g] and repetition of this sequence gave (−)-ajmalicine (**2**) in a total of only nine steps from the known acid **16** and in an overall yield of 15.3%. The ^{1}H NMR, ^{13}C NMR, mp, and optical rotation {$[\alpha]^{20}_D$ −59° (c = 0.50, $CHCl_3$), lit.[22] $[\alpha]^{24}_D$ −60° (c = 0.50, $CHCl_3$)} obtained for synthetic **2** were identical in all respects with published data.[21,22]

Toward the goal of improving the overall efficiency of the synthesis, an alternate sequence of reactions was examined in which the decarboxylation step was postponed to a later stage. The reduction of **19** with $NaBH_4$ afforded the tetracyclic, secondary alcohol **22** rather than the expected lactone that would be obtained upon cyclization of **22** (Scheme 5). Because the related reduction of **20** produced exclusively the lactone **21** under identical conditions (*vide supra*),[5b,c,23] the stereochemistry of the hydroxyl group at C(19) secondary alcohol was initially questioned. However, **22** underwent cyclization to the lactone **23** in 85% yield by the action of *tert*-butyldimethylsiloxy triflate. The stereochemistry of **23** was confirmed by its subsequent conversion via radical decarboxylation by the Barton procedure to give the lactone **21** in 35% yield.

Although the yield in the decarboxylation of **23** could not be improved, the serendipitous isolation of alcohol **22** suggested a possible approach to (+)-19-*epi*-ajmalicine (**3**), another member of the heteroyohimboid family. In the event, inversion of the C(19) hydroxyl group in **22** was achieved under modified Mitsunobu conditions[24] to give an intermediate triester that underwent hydrolysis with concomitant lactonization to give the lactone **24** in 75% overall yield (Scheme 5). Selective hydrolysis of the methyl ester in **22** provided an intermediate hydroxy acid that did not cyclize to give **24** by an intramolecular Mitsunobu inversion. Debenzylation of **24** by catalytic hydrogenolysis followed by radical decarboxylation as before afforded the known lactone **25** in 46% overall yield. The conversion of **25** into (+)-19-*epi*-ajmalicine (**3**) was performed according to the procedure of van Tamelen.[6g] The ^{1}H and ^{13}C NMR, mp, and optical rotation {$[\alpha]^{20}_D$ +56° (c = 0.50, $CHCl_3$), lit.[7a] $[\alpha]^{25}_D$ +58.2° (c = 1.40, $CHCl_3$)} obtained for a sample of synthetic **3**, which was thus obtained in only 11 steps from the acid **11**, were virtually identical to that published.[5c,7]

Conclusion

A general strategy for the concise, asymmetric syntheses of various members of the heteroyohimboid family has been developed. The key step in the approach is the stereoselective addition of vinyl enol ethers and ketene acetals to the enantiomerically pure imine esters **7** and **17**, which are readily derived from L- and D-tryptophan, respectively, via vinylogous Mannich reactions. Incorporation of the α-amino ester not only imparts diastereoselectivity upon the alkylation, but it also provides a functional handle at C(5) of the heteroyohimboid nucleus that might also prove useful in the regiospecific generation of iminium ions leading to indole alkaloids of the sarpagine and ajmaline families.[25] Such studies are the subjects of current investigations.

Experimental Section

General Procedures. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl immediately prior to use. Methanol (MeOH) was distilled from magnesium methoxide immediately prior to use. Triethylamine (TEA), *N*-methylmorpholine, pyrrolidine, acetonitrile (CH_3CN), mesitylene, and methylene chloride were distilled from calcium hydride immediately prior to use. Thionyl chloride was freshly distilled from (+)-limonene prior to use. Benzyl alcohol and methyl vinyl ketone were freshly distilled prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that had been oven and/or flame dried. IR spectra were recorded on an FTIR instrument. The ^{1}H and ^{13}C NMR spectra were determined unless otherwise indicated as solutions in $CDCl_3$ at the indicated field; chemical shifts are expressed in parts per million (δ units) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad.

Preparation of Hetero Diels–Alder Precursors. To a suspension of iminium salt **7** (2.11 g, 7.97 mmol) in dry CH_2Cl_2 (130 mL) at rt was added 1-(trimethylsiloxy)butadiene (5.63

(22) (a) Klohs, M. W.; Draper, M. D.; Keller, F.; Malish, W.; Petracek, F. J. *J. Am. Chem. Soc.* **1954**, *76*, 1332. (b) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito. K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (c) Töke, L.; Honty, K.; Szabó, L.; Blaskó, G.; Szántay, C. *J. Org. Chem.* **1973**, *38*, 2496.

(23) (a) Naito, T.; Kojima, N.; Miyata, O.; Ninomiya, I.; Inoue, M.; Doi, M. *J. Chem Soc., Perkin Trans. 1* **1990**, 1271. (b) References 5b,c and 6b.

(24) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. For reviews of the Mitsunobu reaction, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(25) For a discussion about the possible role of an α-amino acid as a precursor to an iminium ion, see: (a) Brown, R. T.; Row, L. R. *J. Am. Chem. Soc., Chem. Commun.* **1967**, 453. (b) Kompis, I.; Hesse, M.; Schmid, H. *Lloydia* **1971**, *34*, 269. (c) van Tamelen, E. E.; Dorschel, C. *Bioorg. Chem.* **1979**, *28*, 2615.

g, 7.0 mL, 39.9 mmol) and crotonyl chloride (1.67 g, 1.5 mL, 16.0 mmol) under an argon atmosphere with vigorous stirring. The resulting yellow mixture was stirred until all of the solid material dissolved (about 3 h). The solution was poured into EtOAc (100 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL). The organic phase was dried (Na_2SO_4), and excess solvents were removed under reduced pressure to give a crude mixture of the diastereomeric aldehydes **5** and **6** as a thick yellow oil. The aldehydes were partially purified by flash chromatography (50% EtOAc–hexane), and then the diastereomers were separated by preparative HPLC (60% EtOAc–hexane) using two recycles to give 0.98 g (34%) of **8** and 0.56 g (19%) of **9**.

Methyl [3*S-(3α,5α)]-3,4,5,6-Tetrahydro-3-(4′-oxo-2′-butenyl)-4-crotonyl-1*H*-pyrido[3,4-*b*]indole-5-carboxylate (8):** mp 68–69 °C; $[\alpha]^{20}_D$ +57.2° (*c* = 1.00, CH_3OH); ^1H NMR (500 MHz, DMSO-d_6) δ 10.53 (br s, 1 H), 9.52 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.11–7.04 (comp, 2 H), 7.01 (t, *J* = 7.4 Hz, 1 H), 6.79–6.72 (m, 1 H), 6.58 (dd, *J* = 15.0, 1.6 Hz, 1 H), 6.16 (dd, *J* = 15.6, 7.7 Hz, 1 H), 5.74 (br s, 1 H), 5.56 (br s, 1 H), 3.63 (s, 3 H), 3.40 (dd, *J* = 15.8, 1.6 Hz, 1 H), 3.00–2.94 (comp, 2 H), 2.83–2.77 (m, 1 H), 1.88 (dd, *J* = 6.8, 1.6 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 193.2, 171.3, 166.4, 153.7, 140.8, 136.1, 133.4, 131.8, 125.6, 122.4, 120.9, 118.2, 117.3, 110.7, 104.5, 51.5, 49.2, 38.2, 21.5, 17.0; IR ($CHCl_3$) 3420, 3000, 1690 cm^{-1}; mass spectrum (CI) *m*/*z* 366.1570 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 367, 297 (base). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.64. Found: C, 67.92; H, 6.41; N, 7.05.

Methyl [3*R-(3β,5α)]-3,4,5,6-Tetrahydro-3-(4′-oxo-2′-butenyl)-4-crotonyl-1*H*-pyrido[3,4-*b*]indole-5-carboxylate (9):** mp 224 °C; $[\alpha]^{20}_D$ −41.6° (*c* = 1.00, CH_3OH); ^1H NMR (500 MHz, DMSO-d_6) δ 10.65 (br s, 1 H), 9.46 (d, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.07 (dt, *J* = 7.9, 0.7 Hz, 1 H), 7.01 (t, *J* = 7.9 Hz, 1 H), 6.97–6.87 (m, 1 H), 6.73–6.66 (m, 1 H), 6.43 (dd, *J* = 15.0, 1.6 Hz, 1 H), 6.07–6.02 (m, 1 H), 5.41 (t, *J* = 5.8 Hz, 1 H), 4.88–4.83 (m, 1 H), 3.52 (s, 3 H), 3.28 (dd, *J* = 15.7, 5.9 Hz, 1 H), 3.17–3.12 (m, 1 H), 3.03 (dd, *J* = 15.7, 5.1 Hz, 1 H), 3.00–2.95 (m, 1 H), 1.85 (dd, *J* = 6.8, 1.6 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 193.0, 170.4, 167.3, 152.3, 140.7, 135.9, 134.8, 133.5, 125.6, 122.7, 120.7, 118.3, 117.2, 110.8, 105.9, 54.2, 51.6, 51.2, 37.3, 22.3, 17.9; IR ($CHCl_3$) 3530, 3000, 1690 cm^{-1}; mass spectrum (CI) *m*/*z* 366.1581 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 367, 297 (base).

Procedure for the Hetero Diels–Alder Cycloaddition. A solution of **8** (400 mg, 1.09 mmol) in mesitylene (110 mL) was degassed by three freeze-thaw cycles and heated in a sealed ampule. The reaction was heated at 180 °C for 48 h before cooling to rt and concentrating to dryness. The dark brown solid was purified by flash chromatography using 50% EtOAc–hexane to afford a mixture (5:1) of 270 mg (62%) of **10** and 54 mg (19%) of **11**.

Methyl [3*S-(3α,5α,15α,19β,20α)]-1,3,5,6,14,15,20,21-Octahydro-19-methyl-21-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine-5-carboxylate (10):** mp 180–183 °C; $[\alpha]^{20}_D$ −88.2° (*c* = 1.11, CH_3OH); ^1H NMR (500 MHz) δ 8.19 (s, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.17 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.11 (dt, *J* = 7.8, 1.0 Hz, 1 H), 6.20 (dd, *J* = 6.2, 2.0 Hz, 1 H), 4.90 (dd, *J* = 9.2, 4.7 Hz, 1 H), 4.60 (dd, *J* = 5.1, 2.1 Hz, 1 H), 4.58–4.54 (m, 1 H), 4.49 (dd, *J* = 6.2, 3.1 Hz, 1 H), 3.67 (s, 3 H), 3.37 (ddd, *J* = 15.6, 7.2, 1.5 Hz, 1 H), 3.03 (ddd, *J* = 15.6, 5.1, 1.7 Hz, 1 H), 2.92–2.89 (m, 1 H), 2.63–2.58 (comp, 2 H), 2.07 (dt, *J* = 13.5, 9.2 Hz, 1 H), 1.33 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz) δ 170.7, 170.2, 142.8, 136.2, 132.6, 126.6, 120.0, 118.4, 118.4, 111.1, 108.0, 101.5, 68.6, 56.1, 52.9, 52.3, 44.1, 33.1, 25.6, 23.0, 18.8; IR ($CHCl_3$) 3450, 2900, 1650 cm^{-1}; mass spectrum (EI) *m*/*z* 366.1588 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 366 (base), 307, 292, 279, 169.

Methyl [3*S-(3α,5α,15β,19β,20α)]-1,3,5,6,14,15,20,21-Octahydro-19-methyl-21-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine-5-carboxylate (11):** mp 121–123 °C; $[\alpha]^{20}_D$ −134° (*c* = 1.06, $CHCl_3$); ^1H NMR (500 MHz, acetone-d_6/DMSO-d_6 (1:1)) δ 10.85 (br s, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.35 (dd, *J* = 8.9, 0.8 Hz, 1 H), 7.07 (dt, *J* = 7.1, 1.1, 1 H), 7.00 (ddd, *J* = 7.1, 1.0, 0.8 Hz, 1 H), 6.38 (dd, *J* = 6.1, 1.6 Hz, 1 H), 5.18–5.13 (comp, 2 H), 4.78 (dd, *J* = 6.1, 0.8 Hz, 1 H), 4.05–4.02 (m, 1 H), 3.55 (s, 3 H), 3.43 (ddd, *J* = 15.6, 4.0, 0.6 Hz, 1 H), 3.00 (ddd, *J* = 15.6, 6.0, 1.9 Hz, 1 H), 2.58–2.53 (comp, 2 H), 2.49–2.43 (m, 1 H), 2.23–2.18 (m, 1 H), 1.49 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, acetone-d_6/DMSO-d_6 (1:1)) δ 172.7, 172.1, 143.4, 137.5, 133.9, 127.0, 121.8, 119.5, 118.3, 111.9, 105.8, 72.7, 53.0, 52.2, 51.3, 46.4, 34.3, 30.9, 23.0, 20.5; IR ($CHCl_3$) 3450, 2900, 1650 cm^{-1}; mass spectrum (EI) *m*/*z* 366.1588 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 366 (base), 307, 292, 279, 169.

[3*S-(3α,5α,15α,19β,20α)]-1,3,5,6,14,15,20,21-Octahydro-19-methyl-21-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine-5-carboxylate (12).** To ester **10** (25 mg, 68 μmol) in dry THF (0.2 mL) was added potassium trimethylsilanoate (TMSOK) (30 mg, 0.23 μmol). The mixture was stirred at rt for 0.5 h before diluting with CH_2Cl_2 (20 mL) and washed with 1 N NaOH (1 × 20 mL). The aqueous phase was acidified by the addition of 2 N HCl (1 × 20 mL). The resulting aqueous layer was then extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to afford 14 mg (60%) of **12** as a yellow white solid: mp 244–247 °C; $[\alpha]^{20}_D$ −18.2° (*c* = 1.19, CH_3OH); ^1H NMR (250 MHz, methanol-d_4) δ 10.41 (s, 1 H), 7.39 (d, *J* = 7.7 Hz, 1 H), 7.25 (d, *J* = 7.7 Hz, 1 H), 7.06–6.92 (comp, 2 H), 6.63–6.59 (m, 1 H), 5.65 (d, *J* = 6.0 Hz, 1 H), 4.90–4.77 (m, 1 H), 4.76–4.72 (m, 1 H), 4.50–4.42 (m, 1 H), 3.43 (d, *J* = 15.5 Hz, 1 H), 2.99 (ddd, *J* = 15.5, 6.0, 1.7 Hz, 1 H), 2.71–2.62 (comp, 2 H), 1.84 (d, *J* = 7.2 Hz, 3 H), 1.71–1.52 (comp, 2 H); ^{13}C NMR (62 MHz, methanol-d_4) δ 174.4, 171.5, 138.3, 136.4, 133.9, 127.9, 120.1, 118.8, 112.2, 112.0, 106.2, 97.7, 52.8, 51.3, 44.1, 37.9, 37.6, 30.6, 23.9, 14.3; mass spectrum (EI) *m*/*z* 352.1427 ($C_{20}H_{20}N_2O_4$ requires 352.1423), 352, 334, 263, 182, 168 (base).

[3*S-(3α,15α,19β,20α)]-1,3,5,6,14,15,20,21-Octahydro-19-methyl-21-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine (13).** To a suspension of **12** (15 mg, 41 μmol) in dry THF (0.8 mL) and CH_3CN (0.4 mL) at 0 °C were added isobutyl chloroformate (6 mg, 6 μL, 45 μmol) and *N*-methylmorpholine (4 mg, 5 μL, 41 μmol). The cooling bath was removed, and the mixture was stirred until the solution became clear yellow (about 15 min). The reaction was recooled to 0 °C before addition of the sodium salt of *N*-hydroxypyridinethione (7 mg, 45 μmol) and triethylamine (5 mg, 6 μL, 45 μmol). The mixture was stirred at 0 °C for 5 min, 1,1-dimethylethanethiol (38 mg, 48 μL, 0.42 mmol) was added, and the solution was irradiated with a 450 W lamp for 10 min. The clear yellow solution was concentrated under reduced pressure to give a yellow oil which was dissolved in EtOAc (20 mL) and washed with 1 N NaOH (20 mL). The aqueous phase was extracted with EtOAc (10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow solid that was purified by flash chromatography (35% EtOAc–hexane) to afford 8 mg (63%) of **13** as a white solid: mp 254–256 °C; $[\alpha]^{20}_D$ −178° (*c* = 0.39, $CHCl_3$); ^1H NMR (250 MHz) δ 7.90 (br s, 1 H), 7.51 (d, *J* = 8.3 Hz, 1 H), 7.34 (d, *J* = 7.4 Hz, 1 H), 7.23–7.10 (comp, 2 H), 6.43 (d, *J* = 6.1 Hz, 1 H), 5.22–5.15 (m, 1 H), 4.79–4.73 (comp, 2 H), 4.00–3.94 (m, 1 H), 2.91–2.78 (comp, 3 H), 2.67–2.63 (comp, 2 H), 2.50–2.44 (m, 1 H), 1.81–1.71 (m, 1 H), 1.45 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (62 MHz) δ 167.6, 144.8, 136.2, 132.9, 126.8, 122.3, 120.0, 118.4, 110.9, 109.5, 102.2, 69.9, 53.6, 46.6, 40.4, 34.4, 28.4, 21.1, 19.7; mass spectrum (CI) *m*/*z* 308.1521 ($C_{19}H_{20}N_2O_2$ requires 308.1525) 309, 154 (base).

Benzyl (5*R)-5,6-Dihydro-1*H*-pyrido[3,4-*b*]indol-4-ium-5-carboxylate (17).** Thionyl chloride (11.4 g, 95.8 mmol) was added to benzyl alcohol (100 mL) at 0 °C over a 10 min period. The acid **16**[11] (3.01 g, 12.0 mmol) was added, and the resulting slurry was stirred at rt for approximately 72 h, at which time the reaction was a clear, bright yellow solution. Et_2O (400 mL) was added, and the resulting yellow-green solid was collected by vacuum filtration, washed with Et_2O until the filtrate was clear (ca 100 mL), and dried *in vacuo* to afford 3.98 g (97%) of **17** as a yellow solid, which was recrystallized from MeOH: mp 150–152 °C dec; $[\alpha]^{24}D$ −266° (*c* = 1.00, CH_3OH); ^1H NMR (300 MHz, methanol-d_4) δ 8.96 (s, 1 H), 7.73 (d,

J = 8.6 Hz, 1 H), 7.53–7.47 (comp, 2 H), 7.34–7.20 (comp, 6 H), 5.27 (d, J = 4.7 Hz, 2 H), 5.17 (t, J = 8.4 Hz, 1 H), 3.74 (dd, J = 8.4, 2.1 Hz, 2 H); ^{13}C NMR (75 MHz, methanol-d_4) δ 169.2, 156.6, 131.6, 129.6, 129.4, 129.3, 128.0, 126.0, 125.6, 123.6, 123.1, 116.2, 114.6, 69.4, 65.2, 56.2, 23.9; IR ($CHCl_3$) 3066, 2968, 1752, 1629 cm^{-1}; mass spectrum (FAB) m/z 305.1297 ($C_{19}H_{17}N_2O_2$ requires 305.1298), 305 (base), 215, 169.

Benzyl [3S*-(3α,5β)]-3,4,5,6-Tetrahydro-3-[3′-(methoxycarbonyl)-2′-propenyl]-1*H*-pyrido[3,4-*b*]indole-5-carboxylate. To a slurry of the imine **17** (3.96 g, 11.6 mmol) in dry CH_2Cl_2 (60 mL) at 0 °C was added 1-(*tert*-butyldimethylsiloxy)-1-methoxy-1,3-butadiene (7.50 g, 35.0 mmol). After 15 min the reaction was allowed to warm to rt and stirred for 3 h to give a clear yellow-orange solution. The solution was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford an orange solid, which was purified by flash chromatography (30% EtOAc–hexane) to yield 3.18 g (69%) of the adduct as a light yellow solid: mp 43–45 °C; $[\alpha]^{24}_D$ −6.2° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.31 (br s, 1 H), 7.44 (d, J = 7.4 Hz, 1 H), 7.27–7.21 (comp, 6 H), 7.09 (comp, 2 H), 6.98 (dt, J = 15.7, 7.3 Hz, 1 H), 5.91 (d, J = 15.7 Hz, 1 H), 5.12 (s, 2 H), 4.30 (t, J = 6.1 Hz, 1 H), 3.94 (dt, J = 6.8, 5.3 Hz, 1 H), 3.69 (s, 3 H), 3.03 (ddd, J = 15.3, 6.8, 5.3 Hz, 2 H), 2.58–2.48 (comp, 3 H); ^{13}C NMR (75 MHz) δ 173.3, 166.6, 145.5, 135.9, 135.6, 133.8, 128.4, 128.0, 127.7, 126.8, 123.5, 121.7, 119.3, 118.0, 110.8, 107.3, 66.5, 52.6, 51.4, 49.2, 38.3, 24.7; IR ($CHCl_3$) 3470, 3366, 2950, 1730, 1657 cm^{-1}; mass spectrum (CI) m/z 405.1822 ($C_{24}H_{25}N_2O_4$ requires 405.1814), 405, 305 (base), 242, 169.

Benzyl [3S*-(3α,5β)]-3,4,5,6-tetrahydro-3-[3′-(methoxycarbonyl)-2′-propenyl]-(3′′-oxobutyl)-1*H*-pyrido[3,4-*b*]indole-5-carboxylate (18). A solution of the amine (3.18 g, 7.9 mmol) and methyl vinyl ketone (50 mL) was heated at 60 °C overnight. The excess methyl vinyl ketone was removed under reduced pressure, and the resulting dark brown residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with saturated aqueous $NaHCO_3$ (1 × 50 mL), and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a brown oil, which was purified by flash chromatography (30% EtOAc–hexane) to afford 3.50 g (94%) of **18** as a white solid: mp 104–105 °C; $[\alpha]^{24}_D$ −8.2° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.28 (s, 1 H), 7.40 (d, J = 7.0 Hz, 1 H), 7.26–7.18 (comp, 6 H), 7.14–7.05 (comp, 2 H), 6.94 (dt, J = 15.6, 7.2 Hz, 1 H), 5.85 (d, J = 15.6 Hz, 1 H), 5.11 (d, J = 3.0 Hz, 2 H), 4.18 (t, J = 5.7 Hz, 1 H), 3.95 (dd, J = 7.4, 5.1 Hz, 1 H), 3.68 (s, 3 H), 3.18–2.65 (comp, 4 H), 2.63–2.51 (comp, 4 H), 2.06 (s, 3 H); ^{13}C NMR (75 MHz) δ 208.3, 172.5, 166.7, 145.8, 136.2, 135.6, 133.5, 128.3, 127.9, 127.7, 126.7, 122.8, 121.6, 119.3, 118.0, 110.8, 107.3, 66.1, 57.4, 56.4, 51.3, 45.1, 43.1, 36.6; IR ($CHCl_3$) 3469, 2948, 1717, 1653 cm^{-1}; mass spectrum (CI) m/z 475.2220 ($C_{28}H_{31}N_2O_5$ requires 475.2233), 475, 417, 405, 375 (base), 305, 234, 169.

Benzyl [3S*-(3α,5β,15α,16β)]-1,3,5,6,14,15,16,17-Octahydro-16-acetyl-15-[(methoxycarbonyl)methyl]indolo[2,3-*a*]quinolizine-5-carboxylate (19). To a suspension of activated 4-Å molecular sieves (2.5 g) in dry CH_3CN (25 mL) was added ketone **18** (0.93 g, 1.96 mmol) and pyrrolidine (0.17 g, 0.20 mL, 2.3 mmol). The suspension was shaken at rt for 48 h, whereupon a second portion of pyrrolidine (84 mg, 0.10 mL, 1.2 mmol) was added and shaking continued for 24 h. The reaction was diluted with CH_2Cl_2 (100 mL), filtered, and washed with saturated $NaHCO_3$ (1 × 50 mL). The aqueous phase was extracted with additional CH_2Cl_2 (1 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford a dark brown oil, which was purified by flash chromatography (25% acetone–hexane) to give 0.91 g (98%) of **19** as an off-white solid: mp 125–127 °C; $[\alpha]^{24}_D$ −41.3° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.81 (br s, 1 H), 7.46 (d, J = 7.4 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.25–7.08 (comp, 7 H), 5.02 (d, J = 12.5 Hz, 2 H), 4.30 (dd, J = 11.4, 1.3 Hz, 1 H), 3.89 (dd, J = 5.4, 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.23–3.21 (m, 2 H), 3.12 (m, 2 H), 2.74 (dt, J = 9.8, 6.6 Hz, 1 H), 2.48–2.15 (comp, 4 H), 2.20 (s, 3 H), 1.33–1.21 (m, 1 H); ^{13}C NMR (125 MHz) δ 209.1, 172.4, 172.1, 136.2, 135.7, 134.0, 128.4, 128.0, 127.7, 127.0, 121.6, 119.5, 118.0, 110.8, 105.6, 66.0, 61.5, 55.7, 54.8, 53.2, 51.6, 38.4, 36.7, 34.1, 29.9, 25.2; IR (CCl_4) 3479, 3056, 2939, 1737, 1717 cm^{-1}; mass spectrum (CI) m/z 475.2221 ($C_{28}H_{31}N_2O_5$ requires 475.2233), 475 (base), 384, 340, 183, 169.

[3S*-(3α,5β,15α,16β)]-1,3,5,6,14,15,16,17-Octahydro-16-acetyl-15-[(methoxycarbonyl)methyl]indolo[2,3-*a*]quinolizine-5-carboxylate. To a solution of the ester **19** (260 mg, 0.549 mmol) in EtOAc (12 mL) and EtOH (4 mL) at rt was added 20% $Pd(OH)_2$/C (26 mg, 37.3 μmol). The solution was stirred under H_2 (1 atm) for 1 h. The solution was filtered and the catalyst washed with hot MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford 206 mg (98%) of the acid as a white solid, which was used without further purification: mp 145–147 °C; $[\alpha]^{24}$D −52.8° (c = 1.00, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.12 (br s, 1 H), 7.67 (d, J = 7.6 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.35–7.30 (m, 1 H), 7.27–7.22 (m, 1 H), 4.42 (d, J = 10.7 Hz, 1 H), 4.13 (d, J = 5.2 Hz, 1 H), 3.93 (s, 3 H), 3.53 (dd, J = 11.2, 3.2 Hz, 1 H), 3.40–3.16 (comp, 3 H), 3.04–2.98 (m, 1 H), 2.81–2.53 (comp, 3 H), 2.49 (s, 3 H), 2.46–2.40 (m, 1 H), 1.44–1.32 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 209.7, 174.4, 172.0, 136.1, 135.1, 126.6, 120.4, 118.2, 117.4, 110.9, 104.3, 60.5, 54.6, 54.1, 52.8, 51.3, 38.1, 35.8, 34.1, 30.2, 24.8; IR ($CHCl_3$) 3469, 2952, 1728, 1712, 1624 cm^{-1}; mass spectrum (EI) m/z 384.1676 ($C_{21}H_{24}N_2O_5$ requires 384.1685), 384, 339, 311, 195, 182, 168 (base).

[3S*-(3α,15α,16β)]-1,3,5,6,14,15,16,17-Octahydro-16-acetyl-15-[(methoxycarbonyl)methyl]indolo[2,3-*a*]quinolizine (20). To a solution of acid (200 mg, 0.521 mmol) in THF (10 mL) and CH_3CN (5 mL) at 0 °C were added isobutyl chloroformate (79 mg, 75 μL, 0.58 mmol) and *N*-methylmorpholine (54 mg, 75 μL, 0.53 mmol). The cooling bath was removed and the mixture stirred at rt until the solution turned clear yellow (about 20 min). The solution was recooled to 0 °C, whereupon the sodium salt of *N*-hydroxypyridinethione (85 mg, 0.571 mmol) and triethylamine (59 mg, 80 μL, 0.58 mmol) were added. The solution was stirred at 0 °C for 5 min, whereupon 2-methyl-2-propanethiol (0.48 g, 0.61 mL, 5.4 mmol) was added and the mixture was irradiated with a 450 W lamp for 20 min. The resultant clear yellow solution was concentrated under reduced pressure, taken up in EtOAc (25 mL), and washed with 1 N NaOH (1 × 25 mL). The aqueous phase was back extracted with EtOAc (1 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow solid, which was purified by flash chromatography (30% EtOAc–hexane) to afford 97 mg (55%) of **20** as a white solid: mp 150–151 °C; $[\alpha]^{24}$D −15.8° (c = 0.50, $CHCl_3$) {lit.[6b] $[\alpha]_D$ −16° (c = 0.50, $CHCl_3$)}. The ^{1}H and ^{13}C NMR spectra correspond to that previously reported.[21,22b]

Benzyl [3S*-(3α,5β,15α,16β)]-1,3,5,6,14,15,16,17-Octahydro-16-(1′(*R*)-hydroxyethyl)-15-[(methoxycarbonyl)methyl]indolo[2,3-*a*]quinolizine-5-carboxylate (22). To a solution of the ketone **19** (0.50 g, 1.06 mmol) in dry MeOH (80 mL) at −10 °C was added $NaBH_4$ (0.20 g, 5.3 mmol). The reaction was stirred at −10 °C for 45 min before adding a second portion of $NaBH_4$ (0.12 g, 3.2 mmol). The mixture was stirred at −10 °C for 30 min, saturated aqueous $NaHCO_3$ (25 mL) was slowly added, and the mixture was allowed to warm slowly to rt. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 25 mL). The aqueous phase was back extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow solid, which was purified by flash chromatography (50% acetone–hexane) to afford 0.46 g (92%) of **22** as a white solid: mp 62–64°; $[\alpha]^{20}_D$ −41° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.12 (s, 1 H), 7.41–7.39 (m, 1 H), 7.26–7.20 (comp, 8 H), 5.22 (s, 2 H), 4.30 (d, J = 10.6 Hz, 1 H), 3.97–3.89 (comp, 2 H), 3.69 (s, 3 H), 3.23–3.07 (comp, 3 H), 3.01–2.96 (dd, J = 11.5, 3.9 Hz, 1 H), 2.68–2.59 (m, 1 H), 2.32–2.15 (comp, 3 H), 2.03 (s, 1 H), 1.49–1.43 (m, 1 H), 1.33–1.25 (m, 1 H), 1.21 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.4, 172.4, 136.1, 135.7, 134.5, 128.4, 127.9, 127.6, 127.0, 121.2, 119.1, 117.8, 110.7, 105.1, 65.7, 61.4, 60.3, 53.3, 51.8, 51.5, 47.7, 38.2, 38.0, 33.6, 25.2,

20.2; IR ($CHCl_3$) 3471, 3400, 2932, 1728 cm^{-1}; mass spectrum (CI) m/z 476.2307 ($C_{28}H_{32}N_2O_5$ requires 476.2311), 477 (base), 429, 341.

Benzyl [3S*-(3α,5β,15α,19β,20β)]-1,3,5,6,14,15,16,17,20,-21-Decahydro-19-methyl-17-oxo-19*H*-indolo[2,3-*a*]pyrano-[3,4-*g*]quinolizine-5-carboxylate (23). To a solution of alcohol **22** (118 mg, 0.25 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C was added *tert*-butyldimethylsiloxy triflate (0.28 g, 0.25 mL, 1.1 mmol). The reaction was stirred at 0 °C for 30 min, warmed to rt, and stirred for an additional 3 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 15 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow solid, which was purified by flash chromatography (3% MeOH–CH_2Cl_2) to afford 93.6 mg (85%) of **23** as a white solid: mp 248–250 °C; $[\alpha]^{20}_D$ −124° (c = 1.00, $CHCl_3$); ^1H NMR (500 MHz) δ 7.74 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.31 (dd, J = 8.0, 0.7 Hz, 1 H), 7.25–7.08 (comp, 7 H), 5.04 (s, 2 H), 4.68 (dq, J = 6.8, 4.6 Hz, 1 H), 4.31 (dd, J = 11.4, 1.8 Hz, 1 H), 3.89 (dd, J = 6.0, 2.0 Hz, 1 H), 3.25 (t, J = 1.8 Hz, 1 H), 3.23 (dd, J = 6.0, 2.1 Hz, 1 H), 3.01 (t, J = 4.9 Hz, 1 H), 2.91 (dd, J = 11.2, 3.1 Hz, 1 H), 2.75 (m, 1 H), 2.22 (m, 1 H), 2.19–2.08 (comp, 3 H), 1.31 (d, J = 6.8 Hz, 3 H), 1.29–1.23 (m, 1 H); ^{13}C NMR (125 MHz) δ 172.3, 169.9, 136.2, 135.7, 133.7, 128.4, 128.1, 127.6, 127.1, 121.8, 119.6, 118.1, 110.8, 106.0, 77.4, 66.0, 61.8, 53.7, 53.0, 40.7, 38.2, 36.4, 29.2, 25.2, 17.6; IR ($CHCl_3$) 3469, 2928, 2860, 1722 cm^{-1}; mass spectrum (CI) m/z 444.2036 ($C_{27}H_{28}N_2O_4$ requires 444.2049), 445 (base), 268, 242, 221.

Benzyl [3S*-(3α,5β,15α,16β)]-1,3,5,6,14,15,16,17-Octahydro-16-[1′(*S*)-[[*p*-nitrophenyl)carbonyl]oxy]ethyl]-15-[(methoxycarbonyl)methyl]indolo[2,3-*a*]quinolizine-5-carboxylate. To a solution of alcohol **22** (0.50 g, 1.05 mmol) in dry THF (20 mL) at 0 °C was added *p*-nitrobenzoic acid (0.70 g, 4.2 mmol) and triphenylphosphine (1.39 g, 4.2 mmol). Diethyl azodicarboxylate (0.73 g, 4.2 mmol) was added slowly over a period of 10 min. The mixture was stirred at 0 °C for 1 h and then overnight at rt. CH_2Cl_2 (100 mL) was added, and the mixture was washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (1 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow-orange liquid that was purified by flash chromatography (25% EtOAc–hexane) to furnish 0.57 g (88%) of product as a yellow solid: mp 111 °C; $[\alpha]^{20}_D$ −36° (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz) δ 8.29 (d, J = 8.8 Hz, 2 H), 8.19 (d, J = 8.8 Hz, 2 H), 7.87 (s, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.29 (d, J = 7.7 Hz, 1 H), 7.25–7.06 (m, 7 H), 5.45 (dq, J = 6.6, 3.3 Hz, 1 H), 5.05 (s, 2 H), 4.32 (br d, J = 10.5 Hz, 1H), 3.90 (dd, J = 5.4, 2.1 Hz, 1 H), 3.72 (s, 3 H), 3.31–3.23 (m, 3 H), 3.12 (dd, J = 11.4, 3.1 Hz, 1 H), 2.74 (dd, J = 15.3, 3.2 Hz, 1 H), 2.30–2.22 (m, 2 H), 2.12–2.02 (m, 2 H), 1.35 (d, J = 6.6 Hz, 3 H), 1.32–1.26 (m, 1 H); ^{13}C NMR (75 MHz) δ 172.8, 172.4, 163.8, 150.5, 136.2, 135.8, 135.7, 134.1, 130.6, 128.4, 128.0, 127.6, 127.0, 123.5, 121.5, 119.4, 118.0, 110.7, 105.7, 71.8, 65.9, 61.6, 53.3, 52.3, 51.8, 44.8, 37.9, 37.7, 34.8, 25.1, 14.6; IR ($CHCl_3$) 3470, 2953, 1727, 1530 cm^{-1}; mass spectrum (CI) m/z 626.2485 ($C_{35}H_{36}N_3O_8$ requires 626.2502), 626 (base), 205, 154, 117, 102.

Benzyl [3S*(3α,5β,15α,19α,20β)]-1,3,5,6,14,15,16,17,20,-21-Decahydro-19-methyl-17-oxo-19*H*-indolo[2,3-*a*]pyrano-[3,4-*g*]quinolizine-5-carboxylate (24). A mixture of the above *p*-nitro triester (0.20 g, 0.32 mmol) in dry THF (10 mL) containing MeOH (0.5 mL) and powdered NaOH (26 mg, 0.65 mmol) was stirred until the ester had been consumed as judged by TLC (approximately 1 h). Silicic acid (0.50 g) was added, and the solvent was removed under reduced pressure. The residual solid was purified by flash chromatography (2% MeOH–CH_2Cl_2) to yield 0.12 g (86%) of **24** as a white solid: mp 107 °C; $[\alpha]^{20}_D$ −89° (c = 0.50, $CHCl_3$); ^1H NMR (300 MHz) δ 7.96 (br s, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.25–7.09 (comp, 7 H), 5.03 (s, 2 H), 4.29 (br d, J = 10.6 Hz, 1 H), 4.16 (dq, J = 10.3, 6.3 Hz, 1 H), 3.90 (dd, J = 5.4, 2.0 Hz, 1 H), 3.25–3.23 (comp, 2 H), 3.01 (dd, J = 11.2, 4.6 Hz, 1 H), 2.92 (t, J = 10.4 Hz, 1 H), 2.67 (dd, J = 18.0, 5.0 Hz, 1 H), 2.17–2.04 (comp, 2 H), 1.79 (qt, J = 11.5, 4.3 Hz, 1 H), 1.56 (qd, J = 10.3, 4.5 Hz, 1 H), 1.36 (d, J = 6.3 Hz, 3 H), 1.17 (q, J = 11.7 Hz, 1 H); ^{13}C NMR (125 MHz) δ 172.2, 169.9, 136.2, 135.6, 133.8, 128.4, 128.0, 127.6, 127.0, 121.7, 119.5, 118.0, 110.9, 105.7, 79.7, 65.9, 61.7, 54.0, 53.0, 43.8, 37.4, 36.5, 34.9, 25.1, 19.8; IR ($CHCl_3$) 3472, 2912, 1727 cm^{-1}; mass spectrum (CI) m/z 445.2129 ($C_{27}H_{28}N_2O_4$ requires 445.2127), 445, 383, 254, 154.

[3S*(3α,5β,15α,19α,20β)]-1,3,5,6,14,15,16,17,20,21-Decahydro-19-methyl-17-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine-5-carboxylate. A solution of the ester **24** (200 mg, 0.45 mmol) in EtOAc (12 mL) and EtOH (4 mL) containing 20% $Pd(OH)_2$/C (20 mg, 28 μmol) was stirred under H_2 (1 atm). Upon completion of the reaction (approximately 1.5 h), the solution was filtered and the catalyst was washed with hot MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford 156 mg (98%) of the acid as a white solid: mp 212 °C; $[\alpha]^{20}_D$ −4° (c = 0.35, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 10.75 (br s, 1 H), 7.36 (d, J = 7.4 Hz, 1 H), 7.25 (d, J = 7.4 Hz, 1 H), 7.00 (t, J = 7.4 Hz, 1 H), 6.92 (t, J = 7.4 Hz, 1 H), 4.27–4.17 (comp, 2 H), 3.84 (dd, J = 5.0, 1.3 Hz, 1 H), 3.32 (m, 1 H), 3.16–2.94 (comp, 2 H), 2.83 (t, J = 11.0 Hz, 1 H), 2.56 (dd, J = 17.7, 4.8 Hz, 1 H), 2.30–2.19 (comp, 2 H), 1.97–1.89 (m, 1 H), 1.50 (qd, J = 10.6, 3.8 Hz, 1 H), 1.26 (d, J = 6.2 Hz, 3 H), 1.13 (q, J = 11.9 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.1, 169.5, 136.1, 135.0, 126.5, 120.5, 118.3, 117.4, 110.9, 104.1, 78.8, 60.5, 53.2, 52.8, 43.0, 36.7, 36.1, 34.2, 24.8, 19.6; IR ($CHCl_3$) 3668, 2984, 1720, 1616 cm^{-1}; mass spectrum (CI) m/z 355.1645 ($C_{20}H_{23}N_2O_4$ requires 355.1658), 355, 307, 218 (base).

[3S*-(3α,15α.19α,20β)]-1,3,5,6,14,15,16,17,20,21-Decahydro-19-methyl-17-oxo-19*H*-indolo[2,3-*a*]pyrano[3,4-*g*]quinolizine (25). To a solution of the above acid (25 mg, 71 μmol) in a mixture of THF (1.0 mL) and CH_3CN (0.5 mL) at 0 °C were added isobutyl chloroformate (11 mg, 10 μL, 78 μmol) and *N*-methylmorpholine (7 mg, 10 μL, 73 μmol). The cooling bath was removed and the mixture stirred until the solution turned clear yellow (about 20 min). The solution was recooled to 0 °C, and the sodium salt of *N*-hydroxypyridinethione (23 mg, 156 μmol) and triethylamine (8 mg, 11 μL, 79 μmol) were added. The solution was stirred at 0 °C for 15 min, warmed to rt, and stirred until formation of the thioester was complete (about 30 min). The solution was filtered through a small cotton plug. 2-Methyl-2-propanethiol (65 mg, 83 μL, 740 μmol) was added, and the mixture was irradiated with a 450 W lamp for 30 min. The resultant clear yellow solution was concentrated under reduced pressure, and the residue was dissolved in EtOAc (20 mL) and washed with 1 N NaOH (1 × 10 mL). The aqueous phase was back extracted with EtOAc (1 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow solid, which was purified by flash chromatography (3% MeOH–CH_2Cl_2) to afford 10 mg (46%) of **25** as a white solid: mp 291 °C dec; $[\alpha]^{20}_D$ −127° (c = 1.00, pyridine) {lit.[6e] mp > 280 °C; $[\alpha]_D$ −131° (c = 1.46, pyridine)}. ^1H and ^{13}C NMR spectra correspond to that previously reported.[5c,6e]

Acknowledgment. We thank the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation for their generous support of this research program.

Supplementary Material Available: ^1H NMR spectra for all new compounds including **8–13**, **17–19**, and **22–24** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950194E