Mannich Biscyclizations. Total Synthesis of (−)-Ajmalicine†

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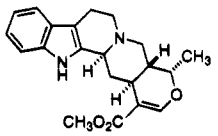
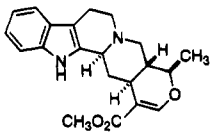
Abstract: A concise enantioselective total synthesis of the cardiovascular agent (−)-ajmalicine and an approach toward the synthesis of (+)-19-epiajmalicine are described. The key step of the (−)-ajmalicine synthesis is a carboxylate-terminated *N*-acyliminium ion biscyclization (**74** → **67**), which assembles the D and E rings of this heteroyohimbine alkaloid in one step. A related carboxylate-terminated iminium ion biscyclization (**28** → **29**) is the central step in the approach to (+)-epiajmalicine.

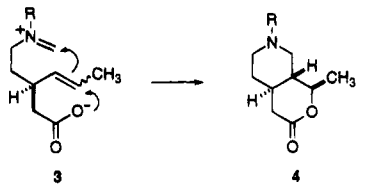
The indole alkaloids[3] have received much attention over the years because of their important pharmacological properties.[4] (−)-Ajmalicine (**1**, also called raubasine and δ-yohimbine), a member of the general family of the heteroyohimbine alkaloids, is prescribed widely in the treatment of cardiovascular diseases.





It is a potent peripheral vasodilating agent and increases muscle caliber for short periods.[5] Ajmalicine also reduces platelet aggregation in patients at risk due to complications of atherosclerosis,[6] and also has been prescribed for the treatment of Raynaud's disease.[7] Ajmalicine exhibits few side effects and does not cause acute hypotension even at relatively high doses (2 mg/kg).[5,8] The isolation of ajmalicine from the roots of commercially grown *Catharanthus roseus* has been highly optimized, and there has been considerable recent attention directed toward the production of ajmalicine by cell culture techniques.[9,10] Heteroyohimbine alkaloids related to ajmalicine are selective α-adrenoreceptor blocking agents.[11]

Although ajmalicine was first prepared in racemic form by van Tamelen and Placeway in 1961,[12] only within the last 10 years have asymmetric total syntheses been described.[13] Important asymmetric approaches to other classes of the heteroyohimbine alkaloids have also been developed.[11,14] In this paper, we describe the development of a stereospecific carboxylate-terminated Mannich biscyclization reaction (**3** → **4**) for constructing the D and E rings of heteroyohimbine alkaloids in one step (eq 1). Exploitation of this strategy to realize a notably efficient total synthesis of (−)-ajmalicine (**1**) and to define a concise route to (+)-19-epiajmalicine (**2**) is specifically detailed.



(1)

The intramolecular Mannich reaction is arguably the most powerful reaction extant for the synthesis of azacyclic rings, and not surprisingly Mannich cyclizations have been employed in the synthesis of a wide variety of alkaloids.[15] In the vast

† We dedicate this paper to Professor James A. Marshall in honor of his 60th birthday.

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(13) (a) From L-tryptophanamide in 13 steps and 3.8% overall yield: Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1984**, 715. (b) From ethyl L-lactate in 21 steps and 1.1% overall yield: Hatakeyama, S.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 865. (c) From diethyl L-tartrate in 17 steps and <6% overall yield (no yield is reported for four steps): Takano, S.; Satoh, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 59. (d) From α-D-glucose pentaacetate in 25 steps and 1.3% overall yield: Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947. (e) From *N*-benzyltrifluoroacetamide in 15 steps and 1.3% overall yield: Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509, 517. (f) Multistep preparation of an intermediate in the Hanessian synthesis from (−)-carvone: Honda, T.; Haze, N.; Ishige, H.; Masuda, K.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 539. (g) From D-tryptophan in 11 steps and ~10% overall yield: Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236.

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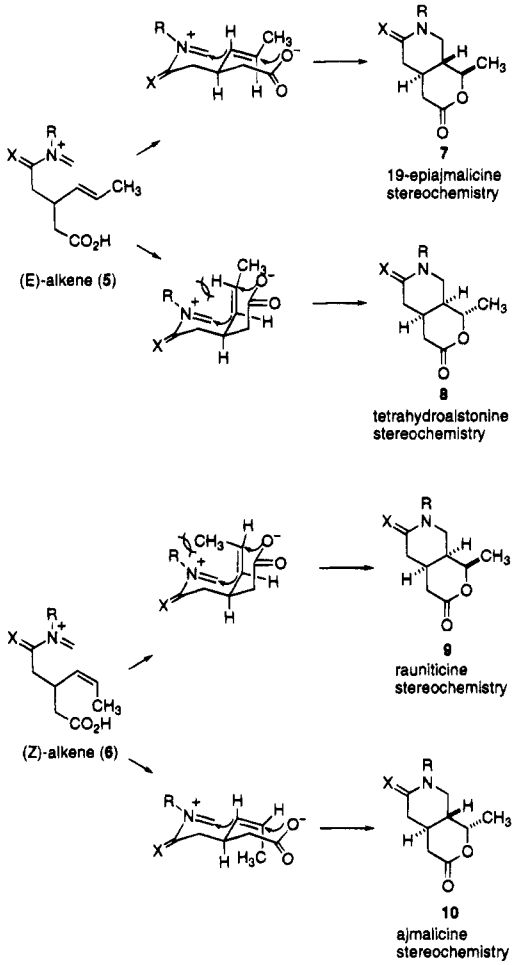
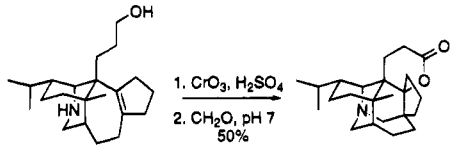


Figure 1. Chair transition states for biscyclization (X = O or H, H).

majority of applications a single azacyclic ring is formed. The use of the Mannich reaction to form polycycles is much rarer. A notable example is due to Grieco and Fobare who utilized an allylsilane-terminated Mannich biscyclization to prepare *trans*-hydroisoquinolines.[16] More directly related to our studies, Heathcock and co-workers employed a carboxylate-terminated iminium ion biscyclization in their striking synthesis of (±)-daphnilactone (eq 2).[17]



(2)

Results

Synthesis Plan. The potential use of Mannich biscyclizations to prepare the D,E bicyclic moiety of heteroyohimbine alkaloids is outlined in Figure 1. In this approach the relative stereochemistry between the C(19)-methyl and the ring junction would be controlled by the alkene geometry. Of the possible chair–chair transition states depicted,[15] those giving the *trans* ring fusion should be favored due to the minimization of A(1,3) interactions in transition structures in which the terminal *Z*

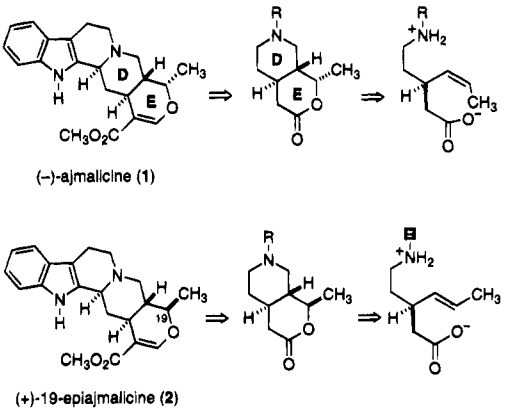


Figure 2. Plan for the synthesis of (−)-ajmalicine and (+)-19-epiajmalicine.

substituent of the diene eclipses the methine hydrogen.[18] Thus, the (*E*)-alkene **5** should lead to a bicyclic product, **7**, having the 19-epiajmalicine stereochemistry, whereas the (*Z*)-alkene **6** should afford **10** having the ajmalicine stereochemistry.

The synthesis plan that emerges from these considerations is summarized in Figure 2. At least three issues must be addressed experimentally. Firstly, can the biscyclization be accomplished, and if so can either iminium ion (X = H, H) or acyliminium ion (X = O) electrophiles be employed? Secondly, will the (*Z*)-alkene, with its enhanced A(1,3) control element, be required to achieve high stereocontrol of the D/E ring fusion? Finally, can the biscyclization be conducted in the presence of a nucleophilic indole (R = indolylethyl)?

Iminium Ion Biscyclizations. Biscyclizations To Form Octahydro-1-methyl-3-oxo-1*H*-pyrano[3,4-*c*]pyridines. A Direct Enantioselective Approach to (+)-19-Epiajmalicine. To test the key biscyclization reaction, amino acid **15** was synthesized as summarized in Scheme 1. The benzyl-protected carbamate **12** was first prepared from 3-amino-1-propanol (**11**) by standard transformations (80% overall yield). The unpurified aldehyde resulting from Swern oxidation[19] of alcohol **12** was condensed with methyl (triphenylphosphoranylidene)acetate, according to Ireland and Norbeck,[20] to yield the Wittig condensation product **13** with high (*E*)-selectivity (*E*:*Z* > 9:1). Trimethylsilyl chloride-catalyzed conjugate addition of (*Z*)-propenyl cuprate[21] to the α,β-unsaturated ester **13** proceeded cleanly and gave the desired (*Z*)-hexenoate **14** in high yield and isomeric purity (*Z*:*E* > 98:2). Upon treatment of **14** with 6 M HCl, both the ester and the carbamate functionalities were hydrolyzed to deliver the δ-amino acid hydrochloride quantitatively. Purification of the hydrochloride salt through a column of the cation exchange resin AG 50W-X8 and elution with 1 M NH_4OH[22] gave amino acid **15** in 93% yield. An attempt to neutralize the hydrochloride salt with propylene oxide in chloroform at 55–60 °C yielded lactam **16** as the major product.[23]

When amino acid **15** and excess formalin were heated to 85–90 °C for 4 h in 2:1 H_2O–THF, the desired biscyclization occurred to afford oxooctahydropyranopyridine **17** in 81–95% yield and >98:2 diastereoselectivity. Attempts to cyclize **15** under anhydrous conditions (CH_3CN, 70–100 °C) with $(CH_2O)_n$ gave predominantly lactam **16** (68–73%) along with a minor

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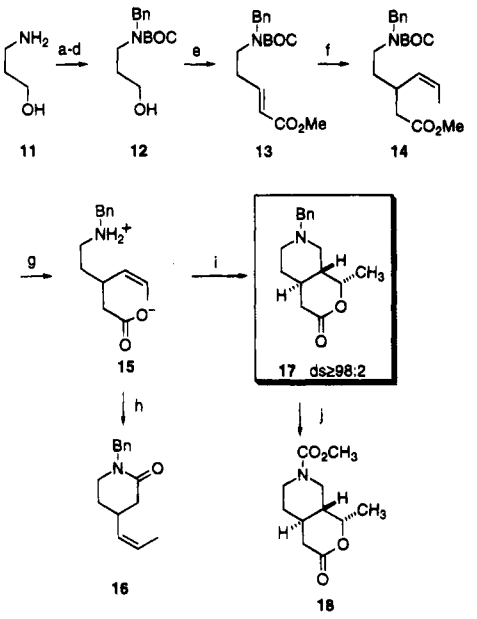
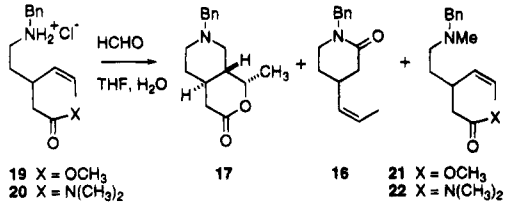
Scheme 1[a]



[a] Conditions: (a) $(t\text{-}BuO_2C)_2$, 1 M NaOH; (b) (TBS)Cl, imidazole; (c) NaH, BnCl; (d) AcOH, H_2O, THF (80% from **11**); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; $Ph_3P{=}CHCO_2CH_3$ (87%); (f) (*Z*)-$(CH_3CH{=}CH)_2$-CuLi, (TMS)Cl, CH_2Cl_2, −78 → +20 °C (90%); (g) 6 M HCl, 23 °C; cation exchange resin (93%); (h) propylene oxide, $CHCl_3$ 55−60 °C; (i) HCHO, 2:1 H_2O−THF, 85−90 °C (81−95%); (j) $ClCO_2CH_3$, PhH, 60 °C (84%).

Table 1. Biscyclizations with an Ester or Amide Nucleophile



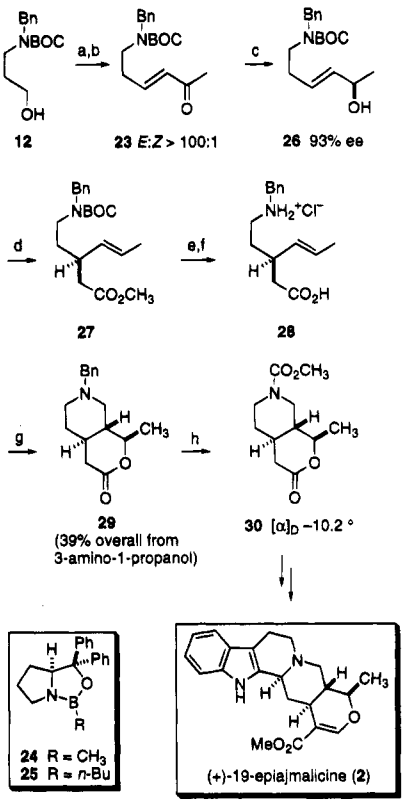
sub-strate	temp (°C)	time (h)	yield (%) 17	16	21/22
19	90	4	0	58	24
20	90	4	11	0	66

amount of the biscyclization product **17** (21−22%). Confirmation that biscyclization had occurred to provide the bicyclic product with the ajmalicine stereochemistry was readily obtained by converting **17** to the known methyl carbamate **18**.[24]

The key biscyclization was examined also with substrates having tethered ester and amide nucleophiles. Treatment of ester **19** with formalin, however, provided not **17**, but lactam **16** (58% yield) and the Eschweiler−Clarke reduction product **21** (24%, Table 1). Subjection of dimethyl amide **20** to the same conditions provided a minor amount of the desired pyranopiperidine **17** (11%) as well as the reduction product **22** (66%). These studies demonstrate that the carboxylate anion is the preferred nucleophile for terminating the biscyclization.

Having shown that Mannich biscyclization in the (*Z*)-propenyl series is an effective method for the formation of octahydro-1-methyl-3-oxo-1*H*-pyrano[3,4-*c*]pyridines, we next examined related cyclizations of enantioenriched (*E*)-propenyl substrates as summarized in Scheme 2. Swern oxidation of alcohol **12** and treatment of the unpurified aldehyde with (triphenylphosphoranylidene)-2-propanone[20] gave enone **23** as an unsatisfactory 4.4:1 *E*:*Z* mixture of alkene stereoisomers. However, reaction of the same aldehyde with dimethyl (2-oxopropyl)-phosphonate[25] in the presence of lithium bromide and Et_3N[26] proceeded with excellent diastereoselection (*E*:*Z* > 100:1) to provide enone **23** in 84% overall yield. Enantioselective reduction[27] of **23** with catecholborane in the presence of (*S*)-oxazaborolidine catalyst **24**[28] provided the corresponding (*R*)-hexenol **26** in 81% ee and 96% yield. By employing the *n*-butyloxazaborolidine catalyst **25**, alcohol **26** was obtained in slightly higher enantiopurity (93% ee) and 91% yield. The enantiomeric purity of **26** was determined by HPLC analysis on Chiralcel OD (hexane−*i*-PrOH, 9:1).

Scheme 2[a]



[a] Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (97%); (b) LiBr, Et_3N, $(MeO)_2P(O)CH_2COMe$ (84%); (c) **25**, catecholborane (91%); (d) $EtCO_2H$ (cat.), $CH_3C(OCH_3)_3$, $PhCH_3$, 115 °C (86%); (e) LiOH, THF, H_2O (98%); (f) 6 M HCl (94%); (g) NaOH (1 equiv); HCHO (aq), pH 6.5, 60 °C (82%); (h) $ClCO_2CH_3$, PhH (82%).

Orthoester Claisen rearrangement of allylic alcohol **26** in the presence of trimethyl orthoacetate gave the enantioenriched ester **27**. Hydrolysis of **27** with LiOH and subsequent cleavage of the carbamate with 6 M HCl afforded the amino acid hydrochloride **28**. This salt was neutralized with 1 equiv of NaOH, and the resulting unpurified δ-amino acid was heated to 80 °C in a sealed tube with excess formalin in THF−H_2O at pH 6.5 to afford oxooctahydropyranopyridine **29** in 82% yield. Reduced yields of **29** were realized at lower pH, *e.g.*, with non-neutralized formalin (54% yield) or from direct cyclization of

(24) (a) Takano, S.; Satoh, S.; Ogasawara, K.; Aoe, K. *Heterocycles* **1990**, *30*, 583. (b) Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958 and supplementary material referenced therein.

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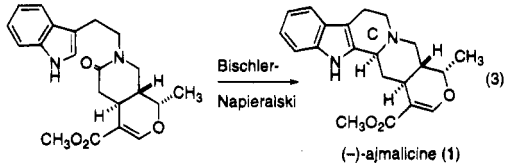
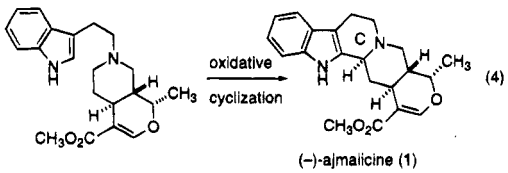
the hydrochloride salt **28** (42%, together with 34% of the δ-lactam). Similar yields of **29** (65−85%) could be obtained using the isolated amino acid; however, formation of the zwitterionic δ-amino acid from **28** was not quantitative, and the overall yields of pyranopiperidine **29** from **28** were lower. Benzylamine **29** was converted to the known methyl carbamate **30**, whose rotation $[\alpha]^{25}_D$ −10.2° (*c* 0.46, MeOH) was in accordance with the data reported for its enantiomer, $[\alpha]^{22}_D$ +10.8° (*c* 1.02, MeOH).[24a]

Analysis of the unpurified cyclization product by GC−MS indicated that three additional isomers were formed in small amounts. One of these isomers was confirmed to be the C(19)-epimer **17** by GC analysis (**29**:**17** = 97.6:2.4). The remaining two isomers are assumed to be the *cis*-fused products, suggesting that stereoselectivity in formation of the ring junction was indeed slightly less (96.5:3.5) in the cyclization of an (*E*)-propenyl substrate.

In summary, methyl carbamate **30** was prepared from 3-amino-1-propanol in 12 steps and 32% overall yield. Although not pursued in this study, carbamate **30** should be converted in five steps to (+)-19-epiajmalicine following the general sequence employed by Momose and co-workers in their synthesis of (−)-ajmalicine.[13e]

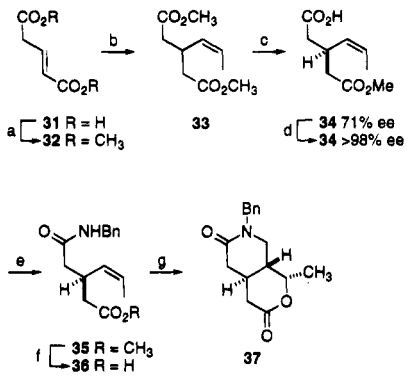
Acyliminium Ion Biscyclizations. Biscyclizations To Form the D and E Rings of (−)-Ajmalicine. Having shown that iminium ion biscyclizations were synthetically useful, we next investigated related biscyclizations with *N*-acyliminium ion electrophiles. In the context of heteroyohimbine alkaloid total synthesis, the lactam products of these cyclizations would have the advantage of allowing the higher yielding Bischler−Napieralski reaction to be employed to form the C ring (eq 3), rather than an oxidative cyclization that would be required for ring closure of products arising from iminium ion biscyclizations (eq 4).[11−14,29]





For the asymmetric synthesis of (−)-ajmalicine (**1**), we chose to start with commercially available *trans*-glutaconic acid (**31**), which was first esterified to give dimethyl glutaconate (**32**) (Scheme 3).[30] Copper-catalyzed addition of (*Z*)-propenylmagnesium bromide[22] to diester **32** in the presence of (TMS)Cl, using conditions that we had earlier optimized for this transformation,[31] provided propenylglutarate **33** in 83% yield. Enzymatic resolution of this *meso*-diester with pig liver esterase afforded the enantioenriched acid **34** in quantitative yield, albeit in modest ee (71%, determined by chiral GLC analysis on Cyclodex B).[32] Several modified reaction conditions and other esterases and lipases were surveyed, yet no conditions examined delivered **34** with improved enantiopurity.[32b] However, the (*R*)-methylbenzylamine salt of **34** could be selectively crystallized from 10% chloroform−hexanes. After acidification to regenerate the free acid, **34** was obtained in 98% ee (60% yield). Since the half ester of lower isomeric purity that remained in chloroform−hexanes was readily recovered and re-esterified to diester **33**, this enrichment of enantiopurity by resolution was highly efficient. Conversion of acid **34** to the acyl chloride and subsequent condensation with excess benzylamine provided ester amide **35**. Selective hydrolysis of the methyl ester was accomplished with lithium hydroxide, affording, after acidification, acid **36** in 84% yield from **34**.[33]

Scheme 3 [a]



[a] Conditions: (a) CH_3OH, $(CH_3O)_3CH$, H_2SO_4, 80 °C (100%); (b) (*Z*)-CH_3CH=$CHMgBr$ (3 equiv), CuI (0.3 equiv), (TMS)Cl (5 equiv THF, −78 °C → rt (84%); (c) pig liver esterase, pH 7.5, rt (100%); (d) crystallize with (R)-methylbenzylamine; acidic workup (60%); (e) $(COCl)_2$, CH_2Cl_2; $BnNH_2$, Et_3N, THF (93%); (f) LiOH, THF, H_2O; HCl (90%); (g) $(CH_2O)_n$, TFA, CH_3NO_2 (85%).

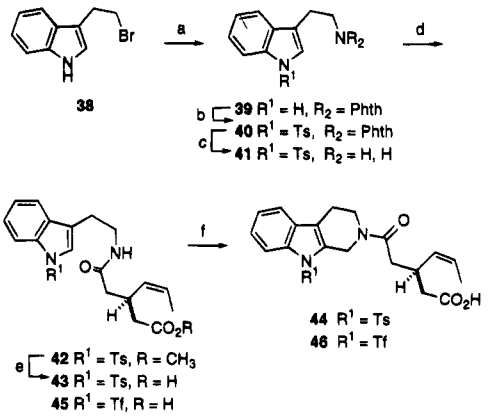
Several conditions were investigated to affect biscyclization of the acyl iminium ion formed from formaldehyde and amide **36**. Under the aqueous conditions that proved effective for biscyclization of formaldiminium ions, no cyclization was observed. In these reactions, **36** was recovered in moderate yield even after prolonged reaction times (26 h, 60 °C). Anhydrous conditions, however, facilitated the biscyclization. Treatment of amide **36** with paraformaldehyde and trifluoroacetic acid (TFA) in nitromethane at room temperature afforded the desired lactone−lactam **37** in 85% yield. Analysis by GC−MS indicated a diastereoselectivity of 96.5:3.5, slightly lower than that observed for related iminium ion cyclizations (*vide supra*).

Biscyclizations with Substrates Containing an Indole or Indoline Fragment. Having established the effectiveness of acyliminium ion biscyclizations in this series, we next investigated the possibility of performing the Mannich biscyclization on a substrate containing an indole moiety. Anticipating that the nucleophilicity of the indole could be problematic, we chose to deactivate the indole as its *N*-tosyl derivative. 1-(4-Tolylsulfonyl)tryptamine (**41**) was prepared from (1*H*-indol-3-yl)ethyl bromide (**38**) using standard transformations[34] in an unoptimized three-step sequence (Scheme 4). Coupling of the acyl chloride derived from acid **34** with amine **41** gave amide

(29) Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 1903.
(30) Kohler, E. P.; Reid, G. H. *J. Am. Chem. Soc.* **1925**, *47*, 2803.
(31) Leotta, G. J., III; Overman, L. E.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 1946.

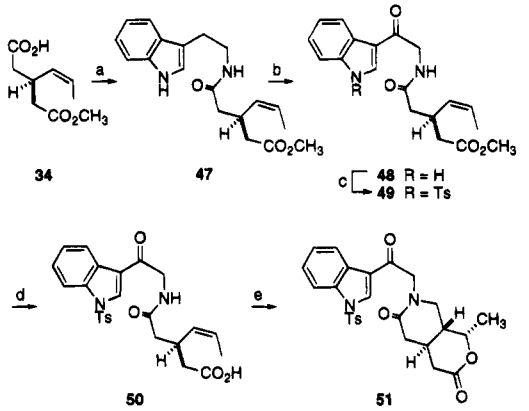
(32) (a) For reviews of enzymatic resolutions with pig liver esterase, see: Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, pp 309−344. (b) *Porcine pancreas* lipase, *Rhizopus arrhizus* lipase, *Pseudomonas sp.* lipase, and *Candida cylindracea* lipase were examined.
(33) Extensive racemization occurred during the base-catalyzed hydrolysis (see Experimental Section). Racemization presumably occurs as suggested in eq 5.
(34) (a) Gabriel synthesis: Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1671. (b) Phthalimide cleavage: Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786.

Scheme 4 [a]



[a] Conditions: (a) potassium phthalimide, $PhCH_3$, 100 °C (75%); (b) NaH, $(n\text{-}Bu)_4NHSO_4$, TsCl, THF (44%); (c) $N_2H_4{\cdot}H_2O$, EtOH, reflux (76%); (d) $(COCl)_2$, **34**, then **41**, THF (86%); (e) LiOH, H_2O, THF (96%); (f) HCHO, HCO_2H, THF or $(CH_2O)_n$, TFA, CH_3NO_2 or $CHCl_3$ (~70%).

Scheme 5 [a]



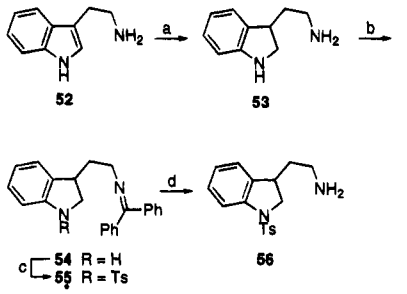
[a] Conditions: (a) $(COCl)_2$, CH_2Cl_2; tryptamine, Et_3N, THF (94%); (b) DDQ (2 equiv), 9:1 THF−H_2O (93%); (c) TsCl, Et_3N, CH_2Cl_2 (94%); (d) LiOH, H_2O, THF (84%); (e) $(CH_2O)_n$, TFA, $CHCl_3$ (74%).

42 in 86% yield. Hydrolysis of **42** then provided amide−acid **43**. However, cyclization of **43** under a variety of conditions (*e.g.*, formalin, HCO_2H, THF or paraformaldehyde, TFA, CH_3NO_2) led to the formation of tetrahydro-β-carboline **44**. Even when the powerfully electron-withdrawing (trifluoromethyl)sulfonyl group[35] was substituted for tosyl, tetrahydro-β-carboline **46** was formed in 72% yield (Scheme 4).

Since an *N*-sulfonyl group alone proved to be ineffective in deactivating the indole toward electrophilic attack, we prepared the *N*-tosyl ketoacid **50** in the expectation that the combination of the tosylate and ketone would successfully mask the nucleophilicity of the indole unit (Scheme 5). Acid **34** was again converted to its corresponding acyl chloride and then coupled with tryptamine to afford amide **47** (94%). Oxidation of amide **47** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in THF−H_2O gave ketone **48**.[36] Protection of the indole by treatment with *p*-toluenesulfonyl chloride and Et_3N in THF and hydrolysis of ester delivered the cyclization precursor **50**.

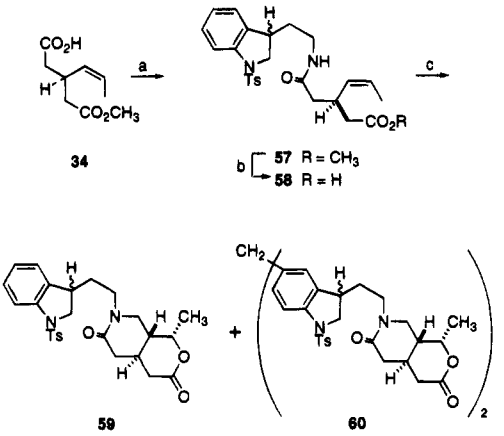
When ketoacid **50** was subjected to anhydrous Mannich cyclization conditions, the desired tetracycle **51** was obtained in 74% yield; this product appeared to be a single stereoisomer by ^1H NMR analysis. However, all attempts to reductively remove the ketone carbonyl group of **51** provided complex product mixtures. Although this problem might have been solved through further experimentation, we chose instead to focus on cyclizations of substrates possessing an indoline functionality and then after biscyclization oxidize this unit to the indole.[37]

Scheme 6 [a]



[a] Conditions: (a) $BH_3{\cdot}THF$, TFA; (b) Ph_2CO, $PhCH_3$, reflux; (c) TsCl, Et_3N, THF; (d) $H_2NOH{\cdot}HCl$, H_2O−THF (35−40% overall).

Scheme 7 [a]



[a] Conditions: (a) $(COCl)_2$, CH_2Cl_2; **56**, Et_3N, THF (92%); (b) LiOH, H_2O, THF; (c) $(CH_2O)_n$, 1:1 TFA−CH_2Cl_2 (~55% from **57**).

To test this idea, it was necessary to prepare the requisite amines (Scheme 6). Following the procedure of Maryanoff *et al.*, tryptamine (**52**) was reduced with $BH_3{\cdot}THF$ in TFA, affording indoline **53** in 74% yield.[38] Selective protection of the primary amine with BOC_2O was complicated by competitive alkoxycarbonylation of the secondary amine, and only a 64% yield of the desired carbamate could be realized. To avoid this complication, the primary amine was protected as a benzophenone imine. Tosylation of the indoline nitrogen of imine **54** under standard conditions then provided **55**, which upon treatment with hydroxylamine hydrochloride at pH 4−6 yielded amine **56**.[39] This four-step sequence provided **56** in overall yields of 35−40%.

Condensation of amine **56** with the acyl chloride derivative of glutarate monoester **34** provided **57**, which was hydrolyzed to yield acid **58** (Scheme 7). Biscyclization of acid **58** with $(CH_2O)_n$ in TFA−$CHCl_3$ afforded a complex mixture from which two products could be identified: the desired lactam **59** (minor) and the bisadduct **60** (major). Even when only 1 equiv of paraformaldehyde was employed, the bisadduct **60** was

(35) For the successful deactivation of indoles with (trifluoromethyl)sulfonyl, see: Conway, S. C.; Gribble, G. W. *Synth. Commun.* **1992**, *22*, 2987.

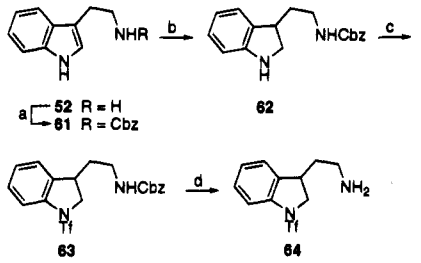
(36) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457.

(37) For a review on the oxidation of indolines to indoles, see: Preobrazhenskaya, M. N. *Russ. Chem. Rev.* **1967**, *36*, 753.

(38) Maryanoff, B. E.; McComsey, D. F.; Nortey, S. O. *J. Org. Chem.* **1981**, *46*, 355; Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733.

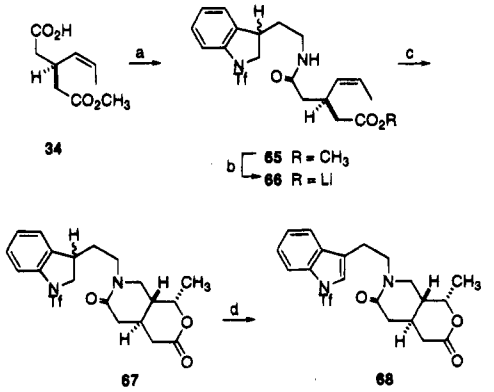
(39) Fasth, K.-J.; Antoni, G.; Langström, B. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3081.

Scheme 8 [a]



[a] Conditions: (a) CbzCl, 1 M NaOH, THF (97%); (b) BH_3·THF, TFA (88%); (c) Tf_2O, Et_3N, CH_2Cl_2, −78 °C (88%); (d) 1,4-cyclohexadiene, 10% Pd/C, EtOH (89%).

Scheme 9 [a]



[a] Conditions: (a) $(COCl)_2$, CH_2Cl_2; **64**, Et_3N, THF (89%); (b) LiOH, H_2O, THF; (c) $(CH_2O)_n$, 1:1 TFA−CH_2Cl_2; (d) DDQ, PhH, 140 °C, sealed tube (49% over three steps).

produced as the major characterized product. Unfortunately, by reducing the indole to the indoline to prevent nucleophilic engagement of the indole with the *N*-acyliminium ion, the aromatic ring had been rendered more susceptible to electrophilic aromatic substitution.

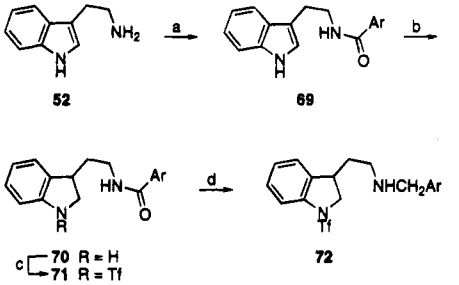
To circumvent this undesired Friedel−Crafts process, the indoline nitrogen was protected as a triflamide. The requisite indoline **64** was accessed from tryptamine as summarized in Scheme 8. Protection of the indole nitrogen of tryptamine followed by reduction[38] readily provided indoline **62**. Triflation and subsequent hydrogenolysis of **63** afforded the desired primary amine **64**.[40] This sequence was more efficient and convenient than the related procedure described in Scheme 6 and provided **64** in 75% overall yield from tryptamine.

Treatment of the glutarate monoester **34** with oxalyl chloride, followed by coupling of the unpurified acyl chloride with amine **64**, provided amide **65** in 89% yield (Scheme 9). Hydrolysis of **65** with lithium hydroxide provided lithium salt **66**, which was cyclized under standard conditions to give the tetracyclic product **67**. No bisadducts were detected, even when a large excess (10 equiv) of paraformaldehyde was used. Although the triflyl group was successful in preventing electrophilic aromatic substitution, this powerful electron-withdrawing group also significantly deactivated indoline **67** toward oxidation. As a result, a temperature of 140 °C was required to induce aromatization to yield indole **68**. Nonetheless, the overall conversion of ester **65** to tetracyclic indole **68** could be accomplished in 49% overall yield.

Total Synthesis of (−)-Ajmalicine. Having found conditions for the preparation of tetracycle **68**, we were now positioned to synthesize (−)-ajmalicine. In earlier experiments, it was noticed

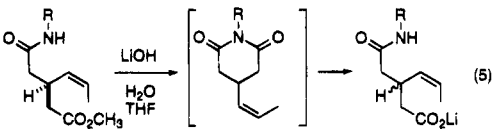
(40) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.

Scheme 10 [a]



[a] Conditions: (a) 2,4-$(CH_3O)_2C_6H_3COCl$, Et_3N, THF (98%); (b) BH_3·THF, TFA (71%); (c) Tf_2O, Et_3N, CH_2Cl_2, −78 °C (87%); (d) BH_3·THF, THF, reflux (87%). Ar = 2,4-dimethoxyphenyl.

that the hydrolysis of glutarate amide esters with lithium hydroxide proceeded to a significant extent through the symmetrical imide (eq 5). Such an event would lead to partial, or complete, racemization of this key intermediate!



To avoid any possibility of racemization, the secondary amine **72** was prepared as summarized in Scheme 10. The 2,4-dimethoxybenzyl protecting group was chosen because it is easily removed from an amide with trifluoroacetic acid.[41] Coupling of tryptamine (**52**) with 2,4-dimethoxybenzoyl chloride provided amide **69** in 98% yield. Reduction of the indole[38] yielded indoline **70**, which was converted to its triflyl derivative **71**. Finally reduction of amide **71** with BH_3·THF in refluxing THF for 1 h gave the secondary (2,4-dimethoxybenzyl)amine **72**.[42] This reduction had to be carefully controlled, since prolonged exposure (>3 h) of **71** to BH_3·THF in refluxing THF led to cleavage of the triflyl group.

Coupling of amine **72** with the acyl chloride derived from acid **34** afforded the desired amide **73** in 91% yield (Scheme 11). Hydrolysis of **73** with lithium hydroxide in aqueous THF required a temperature of 50 °C for 3 h, indicating that significant amide assistance, as proposed in eq 5, had occurred in earlier hydrolyses of related intermediates containing primary amide functionality (*e.g.*, complete hydrolysis of **65** in 1 h at ambient temperature). Treatment of carboxylate **74** with paraformaldehyde in TFA−$CHCl_3$ at room temperature cleaved the 2,4-dimethoxybenzyl protecting group and effected Mannich biscyclization, delivering tetracycle **67** in ~85% yield. Oxidation of **67** to indole **68** then was accomplished with DDQ in benzene at 140 °C for 5 h. The overall yield for this three-step conversion of **73** to the tetracyclic indole **68** was 40%.

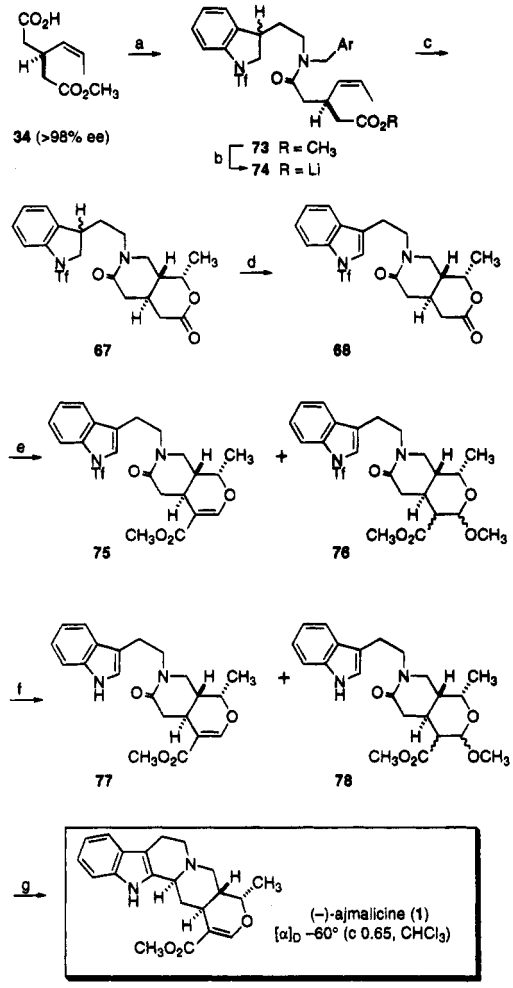
The vinylogous carbonate functionality next was installed by the general method of Uskoković and co-workers;[43] lactone **68** was treated with Brederick's reagent, and the resulting unpurified vinylogous carbamate was heated with HCl−MeOH to give an inseparable mixture of the desired vinylogous carbonate **75** and its methanol adduct **76** (6:1 ratio). Removal of the triflyl protecting group was achieved by treating this mixture with K_2CO_3 in refluxing methanol to provide a mixture of indoles **77** and **78**. This mixture was then subjected to the Bischler−Napieralski cyclization conditions ($POCl_3$ in refluxing

(41) (a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777. (b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219.

(42) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

(43) Uskoković, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Preuss, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742.

Scheme 11 [a]



[a] Conditions: (a) $(COCl)_2$, CH_2Cl_2; **72**, Et_3N, THF (91%); (b) LiOH, H_2O, THF; (c) $(CH_2O)_n$, 1:1 TFA−$CHCl_3$; (d) DDQ, PhH, 140 °C, sealed tube (40% over three steps); (e) *t*-BuOCH(NMe_2)$_2$; HCl, MeOH, 120 °C, sealed tube; (f) K_2CO_3, MeOH, ↑↓; (g) $POCl_3$, PhH, ↑↓; $NaBH_4$, MeOH (37% over three steps). Ar = 2,4-dimethoxyphenyl.

benzene) followed by direct reduction of the pentacyclic iminium ion product ($NaBH_4$ in methanol) to afford (−)-ajmalicine (**1**). This three-step conversion of indole **68** to (−)-ajmalicine proceeded in 37% overall yield.

The optical rotation and melting point of synthetic (−)-ajmalicine compared well with those of the natural alkaloid: $[\alpha]^{24}_D$ −60.1° (*c* 0.65, $CHCl_3$) (lit.[13e] $[\alpha]^{25}_D$ −60° ($CHCl_3$), lit.[44] $[\alpha]^{20}_D$ −63° (*c* 0.5, $CHCl_3$));[44] mp 232−234 °C (lit.[12b] mp 222−225 °C, lit.[13e] 236−239 °C). Synthetic (−)-ajmalicine was also identical in all respects (TLC, IR, 500 MHz ^1H NMR, and 125 MHz ^{13}C NMR) with a natural specimen.[44]

Conclusion

The utility of Mannich biscyclizations to assemble the D and E rings of heteroyohimbine alkaloids with high stereocontrol has been demonstrated. The total synthesis of (−)-ajmalicine proceeds in 11 steps and 6.8% overall yield from commercially available *trans*-glutaconic acid. This sequence and the one recently reported by Martin and co-workers[13g] are the most efficient total synthesis routes to (−)-ajmalicine reported to date.

Experimental Section[45]

Methyl (Z)-3-[2-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]ethyl]-4-hexenoate (14). Dry, freshly recrystallized CuI (2.9 g, 15 mmol) was suspended in dry ether (50 mL) under argon and cooled to −78 °C. A 0.83 M solution of (*Z*)-1-propenyllithium in ether (36 mL, 30 mmol) was added dropwise over 60 min, and the mixture was allowed to warm to −38 °C until all the CuI had dissolved (about 60 min). The black solution was cooled to −78 °C, and chlorotrimethylsilane (1.9 mL, 15 mmol) and a solution of **13** (2.0 g, 6.0 mmol) in dry ether (6 mL) were added, sequentially. The reaction mixture then was allowed to slowly warm to room temperature (rt) (over 2 h) and after 4 h was quenched with saturated aqueous NH_4Cl/concentrated NH_4OH (1:1, 600 mL). Extraction with CH_2Cl_2 (800 mL), drying (Na_2SO_4), and concentration gave a yellow oil that was further purified on silica gel (100 g, gradient elution, 1:10 → 1:4 EtOAc−hexanes) to yield 2.0 g (90%) of **14** (97% pure by GLC analysis) as a colorless oil:[46] ^1H NMR ($CDCl_3$) δ 7.20−7.38 (m, 5H), 5.50 (dq, *J* = 6.8, 10.8 Hz, 1H), 5.02−5.06 (m, 1H), 4.43−4.60 (m, 2H), 3.63 (s, 3H), 2.90−3.36 (m, 2H), 2.69−2.94 (m, 1H), 2.25−2.41 (m, 1H), 2.19 (dd, *J* = 8.4, 14.7 Hz, 1H), 1.5−1.8 (m, 2H), 1.58 (dd, *J* = 1.7, 6.9 Hz, 3H), 1.44 and 1.48 (2 br s, br, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6 155.7, 155.8, 138.5, 132.3, 128.3, 127.0, 125.6, 79.5, 51.3, 49.9, 50.6, 44.7, 40.2, 33.4, 31.6, 32.9, 28.3, 13.0; IR (film) 1740, 1694, 1416, 770, 700 cm^{-1}; HRMS (CI, isobutane) *m/z* 362.2298 (362.2331 calcd for $C_{21}H_{32}NO_4$, MH).

(Z)-3-[2-(*N*-Benzylamino)ethyl]-4-hexenoic Acid (15). Carbamate ester **14** (150 mg, 0.42 mmol) was suspended in 6 M HCl (10 mL) and THF (2.5 mL) and stirred for 24 h at 20 °C. The solution was then loaded onto an AG 50W-X8 cation exchange resin (4 mL resin bed, prewashed with 25 mL of 1 M HCl) and rinsed with H_2O (50 mL) until the washings were pH 6. The amino acid was eluted with 1 M NH_4OH (100 mL) and then concentrated at 50−60 °C to afford 100 mg (93%) of **14** as a colorless solid:[46] mp 106−111 °C; ^1H NMR (CD_3OD) δ 7.35−7.2 (m, 5H), 5.51 (dq, *J* = 6.8, 10.8 Hz, 1H), 5.17 (ddd, *J* = 1.7, 11, 11 Hz, 1H), 3.30 (m, 2H), 2.97 (d, *J* = 8 Hz, 1H), 2.9−3.0 (m, 1H), 2.19 (dd, *J* = 5.5, 14.2 Hz, 1H), 2.15 (dd, *J* = 8.1, 14.2 Hz, 1H), 1.9−1.8 (m, 1H), 1.63 (dd, *J* = 1.7, 7.1 Hz, 3H), 1.52−1.62 (m, 1H); ^{13}C NMR (CD_3OD) δ 180.0, 134.1, 133.0, 130.9, 130.4, 130.2, 126.2, 52.2, 47.0, 44.2, 33.4, 32.3, 13.4; IR (KBr) 3430 (br), 3008, 2945, 2922, 1654, 1521, 1440, 1047, 736, 699 cm^{-1}; HRMS (CI, isobutane) *m/z* 248.1634 (248.1650 calcd for $C_{15}H_{22}NO_2$, MH). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.73; H, 8.56.

1-Benzyl-4-[(Z)-1-propenyl]-2-piperidone (16) was isolated as the major byproduct of attempted biscyclizations of **15** and **19** (see Scheme 1 and Table 1): ^1H NMR ($CDCl_3$) δ 7.4−7.2 (m, 5H), 5.51 (dq, *J* = 7, 10.5 Hz, 1H), 5.25 (dt, *J* = 2, 10.5 Hz, 1H), 4.54 and 4.75 (2d, *J* = 14.5 Hz, 2H), 3.27 (dd, *J* = 4, 8 Hz, 2H), 2.95−2.8 (m, 1H), 2.59 (dd, *J* = 5.5, 17.5 Hz, 1H), 2.23 (dd, *J* = 10.5, 17.5 Hz, 1H), 1.9−1.8 (m, 1H), 1.66 (dd, *J* = 2.0, 7.0 Hz, 3H), 1.7−1.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.4, 137.3, 132.6, 128.7, 128.2, 127.4, 124.9, 50.1, 46.2, 38.6, 31.2, 29.4, 13.1; IR (film) 3029, 2946, 2924, 2883, 1645, 1585, 1496, 1343, 1260, 1029 cm^{-1}; HRMS (CI, isobutane) *m/z* 230.1525 (230.1544 calcd for $C_{15}H_{20}NO$, MH).

***rel*-(1*R*,4a*S*,8a*S*)-Octahydro-7-benzyl-1-methyl-3-oxo-1*H*-pyrano-[3,4-*c*]pyridine (17).** In a sealed tube, a solution of amino acid **15** (15 mg, 0.061 mmol), formalin (37% HCHO in H_2O) (0.15 mL, 1.8 mmol), H_2O (2 mL), and THF (1.3 mL) was maintained for 4 h at 90 °C. Saturated aqueous $NaHCO_3$ (1 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 10 mL). After drying (Na_2SO_4) and concentration, 15 mg (95%) of **17** (98% pure by GLC analysis) was obtained as a yellow oil that could be further purified by crystallization from methyl *t*-butyl ether: mp 99.5−100 °C; ^1H NMR (C_6D_6) δ 7.30 (br d, *J* = 7.3 Hz, 2H), 7.23 (br t, *J* = 7.4, 2H), 7.13 (br t, *J* = 7.1 Hz, 1H), 3.87 (app quintet, *J* = 6.1 Hz, 1H), 3.25 and 3.15 (2d, *J* = 13.3, 2H), 1.66 (dd, *J* = 11.3, 17.9 Hz, 1H), 1.5−1.4 (m, 2H), 1.12 (t, *J* = 10.8 Hz, 1H), 0.95−1.1 (m, 3H), 0.75−0.90 (m, 1H), 0.74 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (C_6D_6) δ 168.4, 139.2, 128.9, 128.6, 127.4, 76.7, 63.3, 54.6, 53.3, 39.9, 36.8, 32.3, 28.7, 17.3; IR (KBr) 2978, 2935, 2915, 1730, 1375, 1203, 1109, 1058, 749, 702 cm^{-1}; HRMS (CI, isobutane) *m/z* 260.1645 (260.1650 calcd for $C_{16}H_{22}NO_2$, MH).

Methyl *rel*-(1*R*,4a*S*,8a*S*)-Octahydro-1-methyl-3-oxo-1*H*-pyrano-[3,4-*c*]pyridine-7-carboxylate (18). A solution of benzylamine **17** (21

(44) Obtained from Fluka Chemika-BioChemika.

(45) For general experimental details, see: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

(46) NMR spectra of this intermediate were complicated by the presence of amide (or carbamate) rotational isomers.

mg, 0.079 mmol), dry benzene (2.5 mL), and methyl chloroformate (18 μl, 0.24 mmol) was maintained at 60 °C for 6 h. The residue obtained after concentration was purified on silica gel (5 g, elution with 60% EtOAc−hexanes containing 0.5% Et_3N) to yield 15 mg (84%) of known **18**[24] as a viscous oil that slowly crystallizes: ^1H NMR ($CDCl_3$) δ 4.70 (quintet, J = 6.3 Hz, 1H), 4.03−4.39 (m, 2H), 3.71 (s, 3H), 2.67−2.83 (m, 1H), 2.73 (dd, J = 5.4, 18.0 Hz, 1H), 2.42−2.58 (m, 1H), 2.12 (dd, J = 11.3, 18.0 Hz, 1H), 1.73−2.04 (m, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.16−1.37 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.5, 155.7, 76.7, 52.8, 45.0, 43.5, 39.6, 36.2, 31.8, 29.0, 17.2.

(*E*)-6-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]-3-hexen-2-one (23). To a solution of oxalyl chloride (0.99 mL, 11 mmol) in dry CH_2Cl_2 (80 mL) at −78 °C was added DMSO (0.91 mL, 13 mmol) over 20 min followed by a solution of alcohol **12** (2.0 g, 7.5 mmol) in dry CH_2Cl_2 (6 mL).[19] After stirring at −78 °C for another 25 min, Et_3N (3.9 mL, 28 mmol) was added over 1 min. The resulting mixture was maintained for 60 min at −78 °C and then allowed to warm to rt over 1 h. With cooling in an ice bath, the reaction was carefully hydrolyzed by addition of 40 mL of 1 M HCl. Extraction of the aqueous phase with CH_2Cl_2 (80 mL), washing of the combined organic phases with saturated aqueous $NaHCO_3$, drying (Na_2SO_4), and concentration afforded 1.9 g (97%) of the unpurified aldehyde, which was used without further purification: ^1H NMR ($CDCl_3$) δ 9.71−9.81 (m, 1H), 7.20−7.42 (m, 5H), 4.49 and 4.45 (2 br s, 2H), 3.47−3.56 (m, 2H), 2.55−2.76 (m, 2H), 1.49 (br s, 9H).

A 100 mL flask containing LiBr (0.79 g, 9.1 mmol) slurried in dry THF (40 mL) under N_2 was charged with dimethyl (2-oxopropyl)-phosphonate (1.0 mL, 7.5 mmol), and the resulting mixture was stirred for 5 min at rt.[26] After addition of Et_3N (1.1 mL, 7.5 mmol), a white precipitate formed and stirring was continued for 10 min. A solution of the thoroughly dried, unpurified aldehyde described above (1.9 g, 7.3 mmol) in dry THF (4 mL) was added, and the mixture was stirred overnight at rt. After quenching with 60 mL of saturated aqueous NH_4Cl, hexanes (20 mL) and ether (20 mL) were added and the phases were separated. Extraction of the aqueous phase with ether, drying of the combined organic phases (Na_2SO_4), and concentration gave a yellow oil, which was further purified on silica gel (40 g, elution with 1:5 EtOAc−hexanes containing 0.05% Et_3N) to yield 1.9 g (84%) of **23** as a colorless oil (99% pure by GLC analysis):[46] ^1H NMR ($CDCl_3$, 50 °C) δ 7.35−7.2 (m, 5H), 6.75−6.65 (m, 1H), 6.01 (d, J = 15.9 Hz, 1H), 4.42 (s, 2H), 3.4−3.3 (br s, 2H), 2.45−2.2 (m, 2H), 2.17 (s, 3H), 1.46 (br s, 9H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 197.6, 155.4, 144.3, 138.1, 132.4, 128.3 (2C), 127.1, 79.8, 50.6, 45.3, 31.3, 28.2, 26.5; IR (film) 3065, 3031, 3006, 2979−2931, 1700, 1635, 1457, 1157, 801 cm^{-1}; HRMS (CI, isobutane) m/z 304.1893 (304.1912 calcd for $C_{18}H_{26}NO_3$, MH).

(*E*)-(*R*)-6-[*N*-benzyl-*N*-(*tert*-butoxycarbonyl)amino]-3-hexen-2-ol (26). To enone **23** (1.2 g, 4.0 mmol, dried by azeotroping 2× with toluene) in dry toluene (30 mL) at −78 °C was added a 1.1 M solution of oxazaborolidine **25** (0.54 mL, 0.59 mmol). After 5 min a 1.0 M solution of catecholborane in toluene (7.9 mL, 7.9 mmol) was added over 20 min, and the solution was maintained at −78 °C for 21 h. The resulting solution was quenched with H_2O, warmed to rt, and successively washed with 0.5 M NaOH (3×), 0.5 M HCl (1×), and brine (1×). After drying ($MgSO_4$) and concentration, 1.3 g of a slightly yellow oil (95% pure by ^1H NMR) was obtained, which was purified on silica gel (40 g, elution with 1:5 EtOAc−hexane containing 0.05% Et_3N) to give 1.1 g (91%) of **26** as a colorless oil:[46] 93% ee (HPLC analysis on Chiralcel OD, 25 cm × 0.46 cm, 9:1 hexane−2-propanol 9, 0.5 mL/min; k_1' 0.85, α 1.17, R_S 1.14); $[\alpha]^{25}_D$ + 2.76° (c 1.0, methanol), $[\alpha]^{25}_{Hg^{435}}$ +2.68°; ^1H NMR (toluene-d_8, 80 °C) δ 7.4−7.2 (m, 5H), 5.42−5.37 (m, 2H), 4.31 (br s, 2H), 4.04−3.97 (m, 1H), 3.17 (br t, J = 6.8 Hz, 2H), 2.14−2.08 (m, 2H), 1.41 (s, 9H), 1.08 (d, J = 6.4 Hz, 3H); ^{13}C NMR (toluene-d_8, 80 °C) δ 155.8, 139.6, 137.4, 128.7, 128.3, 127.4, 126.9, 79.4, 68.4, 51.3, 47.2, 31.7, 28.6, 23.7; IR (film) 3400, 3031, 2974, 2929, 1685, 1417, 1366, 1247, 969, 771, 734, 700 cm^{-1}; HRMS (CI, isobutane) m/z 288.2031 (288.1963 calcd for $C_{18}H_{26}NO_2$, M − OH).

(*E*)-(*R*)-Methyl 3-[2-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]ethyl]-4-hexenoate (27). A solution of allylic alcohol **26** (3.0 g, 9.8 mmol), trimethyl orthoacetate (13 mL, 98 mmol), and a catalytic amount of propionic acid (73 μL, 0.98 mmol) in dry toluene (50 mL) was heated at 115 °C for 3 h. The mixture was cooled to rt and, after addition of 0.05 M NaOH (30 mL), was extracted with ether (3 × 50 mL). Concentration afforded a yellow oil that was further purified by chromatography on silica gel (50 g, elution with 1:6 EtOAc−hexanes containing 0.05% Et_3N) to yield 2.7 g (75%; 86% based on consumed starting material) of the desired methyl ester **27** as a colorless oil along with 390 mg of starting material. Methyl ester **27** could only be obtained in 90% purity; attempts at further purification failed:[46] ^1H NMR ($CDCl_3$) δ 7.38−7.15 (m, 5H), 5.43 (dq, J = 15.1, 6.3 Hz, 1H), 5.25−5.12 (m, 1H), 4.55−4.3 (m, 2H), 3.63 (s, 3H), 3.35−2.95 (m, 4H), 2.45−2.15 (m, 3H), 1.61 (dd, J = 1.1, 6.3 Hz, 3H), 1.48 and 1.44 (2 br d, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 155.4, 138.4, 132.7, 128.3 (2C), 127.0, 126.2, 79.5, 51.3, 49.9 (br), 44.6 (br), 40.2, 37.1 (br), 32.7 (br), 28.3, 17.8; IR (film) 3089, 3064, 3031, 2978−2920, 1739, 1720, 1496, 1436, 1168, 771, 741, 701 cm^{-1}; HRMS (CI, isobutane) m/z 362.2329 (362.2331 calcd for $C_{21}H_{32}NO_4$, MH).

(*E*)-(*R*)-3-[2-(*N*-Benzylamino)ethyl]-4-hexenoic Acid Hydrochloride (28). A solution of ester **27** (2.0 g, 5.6 mmol) and $LiOH·H_2O$ (0.94 g, 22 mmol) in THF−H_2O-methanol (3:3:1, 35 mL) was stirred at rt for 40 h. The solution then was acidified with 6 M HCl to pH 2 and extracted with ether (3 × 30 mL). After drying of the organic phases ($MgSO_4$) and concentration, the acid was obtained as a yellow oil, which could be purified on silica (10 g, gradient elution, 1:5 → 1:2 EtOAc−hexanes) to yield 1.7 g (98%) of the acid as a colorless oil.

A mixture of THF (2 mL), 6 M HCl (6 mL), and a portion of the unpurified acid (820 mg, 2.4 mmol) was stirred at 40−45 °C for 135 min until the acid had dissolved. Concentration provided the amino acid hydrochloride, which was crystallized from $CHCl_3$−hexane to yield 630 mg (94%) of **28** as colorless needles: mp 136 °C; $[\alpha]^{25}_D$ +5.2° (c 1.0, methanol), $[\alpha]^{25}_{Hg^{405}}$ +12.4°, $[\alpha]^{25}_{Hg^{435}}$ +11.6°, $[\alpha]^{25}_{Hg^{546}}$ +8.7°, $[\alpha]^{25}_{Hg^{577}}$ +8.4°; ^1H NMR ($CDCl_3$) δ 9.28 (br s, 1H), 9.08 (br s, 1H), 8.58 (br s, 1H), 7.62−7.52 (m, 2H), 7.4−7.3 (m, 3H), 5.45 (dq, J = 15.0, 6.5 Hz, 1H), 5.10 (dd, J = 8.6, 15.0 Hz, 1H), 4.2−4.0 (m, 2H), 2.95−2.67 (m, 2H), 2.55−2.40 (m, 1H), 2.27 (d, J = 6.5 Hz, 2H), 2.07-1.9 (m, 1H), 1.82−1.63 (m, 1H), 1.53 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.5, 131.4, 130.4, 130.2, 129.3, 128.9, 127.5, 50.9, 44.8, 39.8, 36.7, 29.9, 17.7; IR (KBr) 3100 (br), 3050, 2998−2832, 2733, 2561, 2476, 2366, 1729, 1583, 1456, 1214, 1162, 971, 761, 709 cm^{-1}; HRMS (CI, isobutane) m/z 248.1662 (248.1650 calcd for $C_{15}H_{22}NO_2$, M − Cl). Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81. Found C, 63.59; H, 7.89.

(1*R*,4a*R*,8a*R*)-Octahydro-7-benzyl-1-methyl-3-oxo-1*H*-pyrano[3,4-*c*]pyridine (29). In a sealed tube, amino acid hydrochloride **28** (16 mg, 0.056 mmol) was dissolved in THF−H_2O (1:2, 3 mL) and neutralized with 0.56 mL of 0.1 M NaOH. After addition of formalin (153 μL neutralized to pH 6.5 with 0.1 M NaOH) the solution was heated at 80 °C for 150 min. After addition of a small amount of Na_2CO_3, the mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to yield 12 mg (82%) of the biscyclization product **29** as colorless crystals: mp 136 °C; isomeric purity 96.5:3.5 (capillary GLC analysis); $[\alpha]^{25}_D$ −11.8°, $[\alpha]^{25}_{Hg^{435}}$ −23.1°, $[\alpha]^{25}_{Hg^{546}}$ −12.1°, $[\alpha]^{25}_{Hg^{577}}$ −10.4° (c 1.0, acetone); ^1H NMR (C_6D_6) δ 7.27 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 3.50 (dq, J = 6.3, 10.1 Hz, 1H), 3.28 and 3.19 (2d, J = 13.3 Hz, 2H), 2.53 (dt, J = 3.0, 10.5 Hz, 2H), 2.27 (dd, J = 5.0, 17.6 Hz, 1H), 1.66 (dd, J = 12.4, 17.6 Hz, 1H), 1.48 (dt, J = 2.2, 11.6 Hz, 1H), 1.11 (t, J = 10.6 Hz, 1H), 1.03 (ddd, J = 6.9, 10.3, 21.0 Hz, 1H), 0.98−1.04 (m, 1H), 0.88 (d, J = 6.3 Hz, 3H), 0.82 (ddd, J = 3.8, 12.1, 24.2 Hz, 1H), 0.67−0.87 (m, 1H); ^{13}C NMR (C_6D_6) δ 168.2, 139.0, 128.9, 128.6, 127.4, 79.1, 63.3, 55.2, 52.8, 43.3, 36.9, 34.8, 31.6, 19.6; IR (KBr) 2975, 2931, 1730, 1560, 1457, 754, 702 cm^{-1}; HRMS (CI, isobutane) m/z 260.1626 (260.1650 calcd for $C_{16}H_{22}NO_2$, MH).

Methyl (1*R*,4a*R*,8a*R*)-Octahydro-1-methyl-3-oxo-1*H*-pyrano[3,4-*c*]pyridine-7-carboxylate (30). To a solution of **29** (39 mg, 0.15 mmol) in dry benzene (3 mL) was added methyl chloroformate (69 μL, 0.90 mmol), and the resulting solution was maintained at 60 °C for 4 h. The residue obtained after concentration was purified on silica gel (7 g, elution with 1:1 EtOAc−hexanes containing 0.5% Et_3N) to yield 28 mg (82%) of known **30**[24a] as a viscous oil: $[\alpha]^{25}_D$ −10.2° (c 0.46, MeOH); ^1H NMR ($CDCl_3$) δ 4.4−4.1 (m, 2H), 4.12 (dq, J = 6.3, 10.3 Hz, 1H), 3.70 (s, 3H), 2.8−2.7 (m, 1H), 2.71 (dd, J = 5.1, 17.9 Hz,

1H), 2.5−2.35 (m, 1H), 2.14 (dd, J = 12.3, 17.9 Hz, 1H), 1.8−1.67 (m, 2H), 1.40 (d, J = 6 Hz, 3H), 1.44−1.32 (m, 1H), 1.3−1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.5, 155.8, 79.3, 52.8, 45.1, 43.5, 42.8, 36.4, 34.9, 31.1, 19.8.

Dimethyl (*E*)-Glutaconate (32). To a stirred solution of 5.0 g (38 mmol) of technical (~90%) *trans*-glutaconic acid (**31**), 13 mL of trimethyl orthoformate, and 9.3 mL of MeOH was added 0.2 mL of concentrated sulfuric acid. The resulting yellow solution was heated at reflux for 16 h, allowed to cool to rt, and diluted with EtOAc. The mixture was washed with H_2O, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated and the residue distilled (bp 160−165 °C, 10 mm Hg) to afford 5.8 g (~100%) of the known glutaconate **32**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05−6.9 (m, 1H), 5.97−5.85 (m, 1H), 3.72, 3.70, and 3.69, and 3.67 (s, 6H); 3.26−3.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.1, 139.7, 124.2, 52.1, 51.5, 37.1; IR (film) 3549, 3446, 3005, 2943, 2841, 1739, 1662, 1436, 1271, 1210, 1159, 1087, 1030, 990, 933, 846, 733 cm^{-1}; MS (CI) m/z 159, 127.

Dimethyl 3-[(*Z*)-1-Propenyl]glutarate (33). Under a nitrogen atmosphere, a solution of the (*Z*)-1-propenylmagnesium bromide (100 mL, 1 M in THF) was added dropwise to a stirring suspension of 1.8 g of CuI (9.5 mmol) in 100 mL of THF. The resulting mixture was stirred at rt until a dark color persisted (~5 min). The mixture was then cooled to −78 °C, and 12 mL (95 mmol) of (TMS)Cl (freshly distilled from CaH_2) and a solution of diester **32** (5.0 g, 32 mmol) and ~10 mL of THF were introduced sequentially. The reaction was stirred at −78 °C for 3 h and then allowed to warm to rt over 6 h. The reaction then was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The phases were separated, the aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (1:20 EtOAc−hexanes) to afford 5.2 g (84%) of **33** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (dq, J = 10.9, 6.9 Hz, 1H), 5.13 (dd, J = 10.8, 10.4 Hz, 1H), 3.61 (s, 6H), 3.35 (m, 1H), 2.41 and 2.26 (ABX, J_{AB} = 15.1 Hz, J_{AX} = 6.2 Hz, J_{BX} = 8.0 Hz, 4H), 1.62 (dd, J = 6.9, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 131.1, 126.1, 51.5, 39.4, 30.6, 12.9; IR (film) 1740 cm^{-1}; HRMS (CI, isobutane) m/z 201.1137 (201.1126 calcd for $C_{10}H_{17}O_4$, MH). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.96; H, 8.07.

Methyl (*R*)-3-[(*Z*)-1-Propenyl]glutarate (34). To a stirred suspension of 0.50 g (2.5 mmol) of diester **33** in 50 mL of 1.0 M phosphate buffer (pH 7.0) was added 0.10 mL (3.2 M in $(NH_4)_2SO_4$) of pig liver esterase (Sigma EC 3.1.1.1, 11 mg of protein/mL, 230 units/mg of protein). The resulting mixture was stirred at rt for 5 h filtered, and concentrated HCl was introduced to obtain pH 2. The mixture then was diluted with EtOAc, the phases were separated, and the aqueous phase was extracted with EtOAc, and the combined organic phases were dried ($MgSO_4$) and concentrated to give 0.46 g (~100%) of the monoacid **34**. This sample exhibited an ee of 71% by capillary GLC analysis on a Cyclodex B column (130 °C, isothermal).

One recystallization from 1:10 $CHCl_3$−hexanes of this sample of **34** with (*R*)-methylbenzylamine afforded the salt which was dissolved in ethyl acetate and washed with 1 N HCl to generate (after drying and concentration) 60% acid **34**: >98% ee (GLC analysis on a Cyclodex B column, 130 °C); $[\alpha]^{25}_D$ +7.6°, $[\alpha]^{25}_{Hg^{577}}$ +6.6°, $[\alpha]^{25}_{Hg^{546}}$ +7.7°, $[\alpha]^{25}_{Hg^{435}}$ +21.0°, $[\alpha]^{25}_{Hg^{405}}$ +24.8° (*c* 1.1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dq, J = 10.7, 6.9 Hz, 1H), 5.19 (dt, J = 10.4, 1.7 Hz, 1H), 3.66 (s, 3H), 3.39 (tt, J = 9.5, 7.1 Hz, 1H), 2.57−2.31 (m, 4H), 1.67 (dd, J = 6.9, 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 172.2, 130.8, 126.4, 51.6, 39.3 (2C), 30.4, 12.9; IR (film) 3300 (br), 3016, 2955, 2921, 1735, 1718, 1438, 1261, 1156 cm^{-1}; HRMS (CI, isobutane) m/z 187.0974 (187.0970 calcd for $C_9H_{15}O_4$, MH).

Methyl (*R*)-3-[(*N*-Benzylcarbamoyl)methyl]-(*Z*)-4-hexenoate (35). To a solution of the (*R*)-monoester **34** (1.0 g, 5.4 mmol, dried by azeotroping with toluene, 71% ee) in CH_2Cl_2 (15 mL) containing 1 drop of DMF was added dropwise oxalyl chloride (0.95 mL, 11 mmol). After 20 min at rt, the solution was concentrated and the unpurified acid chloride was dissolved in THF (20 mL). Benzylamine (1.3 mL, 12 mmol) then was added dropwise over 1 min, and the mixture was stirred for 20 min. After addition of H_2O (20 mL) and extraction with CH_2Cl_2 (3 × 40 mL), the combined organic phases were washed with 5% K_2CO_3 and 0.5 M HCl, dried ($MgSO_4$), and concentrated to give 1.5 g of a viscous oil that was further purified on silica (50 g, gradient elution, 1:5 → 1:3 → 1:1 EtOAc−hexanes) to yield 1.4 g (93%) of **35** (96% pure by GLC analysis) as a colorless oil: the enantiopurity of **35** was determined by HPLC analysis on Chiralcel OB-H (9:1 hexane−2-propanol, flow 1.0 mL/min) to be 63% ee; $[\alpha]^{25}_D$ −14.2° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.35−7.2 (m, 5H), 6.36 (br s, 1H), 5.51 (dq, J = 6.9, 10.8 Hz, 1H), 5.18 (dt, J = 10.8, 1.5 Hz, 1H), 4.39 (2dd, J = 3.1, 10.2 Hz, 2H), 4.34 and 3.62 (s, 3H), 3.38 (tt, J = 6.7, 9.2 Hz, 1H), 2.45 (dd, J = 5.9, 14.9 Hz, 1H), 2.33 (dd, J = 5.9, 14.0 Hz, 1H), 2.27 (dd, J = 7.9, 14.9 Hz, 1H), 2.15 (dd, J = 8.2, 14.0 Hz, 1H), 1.62 (dd, J = 1.5, 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 171.0, 138.1, 131.3, 128.4, 127.5, 127.2, 126.1, 51.36, 43.30, 41.49, 39.29, 31.06, 12.83; IR (film) 3300 (br), 3084, 3076, 2972−2919, 1739, 1652, 1646, 1542, 1436, 1154 cm^{-1}; HRMS (EI) m/z 275.1532 (275.1521 calcd for $C_{16}H_{21}NO_3$, M). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.59; H, 7.74.

(*R*)-3-[(*N*-Benzylcarbamoyl)methyl]-(*Z*)-4-hexenoic Acid (36). A solution of ester **35** (1.2 g, 4.2 mmol), THF (25 mL), and 0.2 M LiOH (30 mL) was maintained for 5 h at rt. After acidification with concentrated HCl to pH 2, the aqueous phase was extracted with CH_2Cl_2. Drying ($MgSO_4$) of the extracts and concentration gave 1.1 g of the unpurified acid **36**. Upon dissolution in CH_2Cl_2−methanol (100:1, 100 mL) at 50 °C and addition of hexanes, 630 mg of *rac*-**36** crystallized as colorless needles (mp 119−119.5 °C; $[\alpha]^{25}_D$ +0.0° (*c* 1.0, methanol). Another 362 mg of **36** (~50% ee, by HPLC analysis on Chiralel OB-H after conversion to the methyl ester with CH_2N_2) was isolated from the mother liquor, giving a combined yield of 990 mg (90%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (m, 5H), 6.44 (t, J = 5.5 Hz, 1H), 5.50 (dq, J = 6.8, 10.4 Hz, 1H), 5.20 (dt, J = 10.4, 1.5 Hz, 1H), 4.39 (2dd, J = 5.7, 14.8 Hz, 2H), 4.34, 3.31−3.41 (m, 1H), 2.42 (dd, J = 6.2, 14.5 Hz, 2H), 2.31 (dd, J = 6.9, 15.0 Hz, 1H), 2.21 (dd, J = 8.4, 13.9 Hz, 1H), 1.59 (dd, J = 1.5, 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.3, 171.1, 137.8, 131.1, 128.5, 127.7, 127.4, 126.4, 43.59, 41.24, 39.42, 31.09, 12.96; IR (KBr) 3303, 3015, 2933, 2911, 1734, 1600, 1423, 1210, 1188, 934, 741, 716, 698 cm^{-1}; HRMS (CI, isobutane) m/z 262.1439 (262.1443 calcd for $C_{15}H_{20}NO_3$, MH).

(1*R,4a*S**,8a*S**)-7-Benzyl-1-methylhexahydropyrano[3,4-*c*]pyridine-3,6-dione (37).** Racemic acid **36** (110 mg, 0.42 mmol), paraformaldehyde (320 mg, 11 mmol CH_2O), nitromethane (5 mL), and TFA (2.5 mL) were stirred at rt for 17 h. The mixture then was poured into 1 M K_2CO_3 (40 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (40 mL). The combined organic phases were washed with 1 M K_2CO_3 and brine, dried ($MgSO_4$), and concentrated to give an oil. Purification of this sample on silica gel (10 g, gradient elution, 1:1 EtOAc−hexanes → EtOAc) gave 98 mg (85%) of racemic **37**: capillary GC−MS analysis revealed an isomeric purity of 97:3; ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 4.85 (d, J = 14.7 Hz, 1H), 4.66 (dq, J = 5.5, 6.6 Hz, 1H), 4.40 (d, J = 14.7 Hz, 1H), 3.23 (dd, J = 5.1, 12.1 Hz, 1H), 3.02 (t, J = 11.7 Hz, 1H), 2.86 (dd, J = 6.6, 18.3 Hz, 1H), 2.81 (dd, J = 5.7, 17.4 Hz, 1H), 2.4−2.32 (m, 1H), 2.30−2.15 (m, 1H), 2.18 (dd, J = 10.3, 18.3 Hz, 2H), 1.27 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 167.9, 136.3, 128.8, 128.0, 127.7, 75.76, 50.15, 47.43, 38.50, 36.85, 35.32, 26.43, 16.89; IR (film) 2983, 2939, 2926, 1736, 1685, 1644, 1455, 1382, 1209, 913, 731, 702 cm^{-1}; HRMS (CI, isobutane) m/z 274.1421 (274.1443 calcd for $C_{16}H_{20}NO_3$, MH).

3-[2-[*N*-[(Benzyloxy)carbonyl]amino]ethyl]indoline (62). The general procedure of Maryanoff was employed.[38] A 1 M solution of BH_3·THF in THF (120 mL, 120 mmol) was added dropwise to a stirred, cooled (0 °C) mixture of indole **61** and 120 mL of TFA. The resulting mixture was stirred at 0 °C for 30 min, and then 80 mL of H_2O was introduced dropwise. The mixture was allowed to warm to rt with stirring over 1 h and then was concentrated under reduced pressure. The resulting residue was treated with 2 M aqueous NaOH to pH 10 extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (1:2 EtOAc−hexanes) to afford 17 g (97%) of indoline **62** as a nearly colorless viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5H), 7.05 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.70 (t, J = 6.3 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 5.07 (s, 2H), 5.06 (m, 1H), 3.86 (bs, 1H), 3.62 (t, J = 8.4 Hz, 1H), 3.27−3.14 (m,

4H), 1.98−1.89 (m, 1H), 1.72−1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 150.9, 136.5, 132.0, 128.4 (2C), 127.9, 127.5, 123.8, 118.7, 109.6, 66.5, 53.0, 39.4, 38.9, 34.3; IR (film) 3346, 3041, 2932, 2855, 2245, 1708, 1605, 1528, 1251, 1136, 1022, 907, 746 cm^{-1}; HRMS (CI, isobutane) *m/z* 296.1529 (296.1525 calcd for $C_{18}H_{20}N_2O_2$, M).

3-[2-[*N*-[(Benzyloxy)carbonyl]amino]ethyl]-*N*-[(trifluoromethyl)-sulfonyl]indoline (63). Freshly distilled triflic anhydride (11 mL, 65 mmol) was added to a cooled (−78 °C) solution of 17 g (57 mmol) of indoline **62**, 12 mL (86 mmol) of Et_3N, and 100 mL of CH_2Cl_2. The resulting solution was maintained at −78 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$ and allowed to warm to rt. The mixture was diluted with EtOAc, and the phases were separated. The organic phase was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:3 EtOAc−hexanes) to afford 22 g (88%) of indoline **63**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 5H), 7.20−7.15 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 5.15 (m, 1H), 5.07 (s, 2H), 4.26 (t, *J* = 9.6 Hz, 1H), 3.83 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.38 (m, 1H), 3.25−2.95 (m, 2H), 1.96−1.90 (m, 1H), 1.71−1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 139.1, 136.2, 134.2, 128.4, 128.3, 128.3, 128.0, 127.9, 124.9, 124.7, 114.1, 66.6, 56.7, 46.1, 38.4, 37.5, 34.8; IR (film) 3422, 3335, 3062, 3030, 2942, 2354, 2245, 1784, 1703, 1599, 1534 cm^{-1}; HRMS (CI, isobutane) *m/z* 429.1085 (429.1096 calcd for $C_{19}H_{20}F_3N_2O_4S$, MH).

3-(2-Aminoethyl)-*N*-[(trifluoromethyl)sulfonyl]indoline (64). 1,4-Cyclohexadiene (7.7 mL, 81 mmol) was added to a stirred, cooled (0 °C) suspension of 3.5 g (8.2 mmol) of carbamate **63** and 3.5 g of 10% Pd/C in 80 mL of EtOH. The resulting mixture was allowed to warm to rt and was stirred for 16 h. The mixture then was filtered through Celite and the Celite was washed with $CHCl_3$. The filtrate was concentrated, affording 2.1 g (88%) of primary amine **64**, which required no additional purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 1H), 7.17−7.12 (m, 2H), 7.04 (t, *J* = 7.1 Hz, 1H), 4.23 (t, *J* = 9.7 Hz, 1H), 3.80 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.48−3.42 (m, 1H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.92−1.83 (m, 1H), 1.68−1.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 134.8, 128.1, 124.9, 124.6, 114.1, 56.9, 39.5, 38.1, 37.8 (*C*F_3 not observed); IR (film) 3363, 3280, 2928, 2856, 1708, 1594, 1475, 1459, 1392, 1226, 1190, 1143, 1102, 1050, 988, 926, 755 cm^{-1}; HRMS (CI, isobutane) *m/z* 295.0728 (295.0728 calcd for $C_{11}H_{14}F_3N_2O_2S$, MH).

Methyl (*R*)-3-[[[2-[2,3-Dihydro-1-[(trifluoromethyl)sulfonyl]-1*H*-indol-3-yl]ethyl]carbamoyl]methyl]-hex-4-enoate (65). DMF (1 drop) was added to a cooled (0 °C) solution of 0.33 g (1.8 mmol) of monoester **34** and 5 mL of CH_2Cl_2, followed by the dropwise addition of 0.31 mL (3.5 mmol) of oxalyl chloride. The resulting solution was allowed to warm to rt over 30 min and then was concentrated. The crude acid chloride was dissolved in dry THF (10 mL) and added to a cooled (0 °C) solution of 0.78 g (2.7 mmol) of indoline **64**, 0.49 mL (3.5 mmol) of Et_3N, and dry THF (30 mL). The resulting mixture was stirred for 1 h while warming to rt. The reaction then was quenched with H_2O and diluted with EtOAc. The phases were separated, and the organic phase was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography on silica gel (2:1 EtOAc−hexanes) to give 0.73 g (89%) of amide **65**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 1H), 7.18 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.69 (m, 1H), 5.48 (dq, *J* = 10.7, 6.9 Hz, 1H), 5.16 (t, *J* = 11.0 Hz, 1H), 4.25 (t, *J* = 9.0 Hz, 1H), 3.85 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.60 (s, 3H), 3.55 (m, 1H), 3.39−3.23 (m, 3H), 2.90 (t, *J* = 6.7 Hz, 1H), 2.44−2.04 (m, 4H), 1.92 (m, 1H), 1.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.3, 139.1 134.1, 131.2 128.3, 126.1, 124.9/124.7, 123.3(q), 114.1, 56.6, 51.4, 41.5, 39.1, 37.6, 36.8, 34.6/34.5, 31.0, 12.8; IR (film) 3305, 3076, 3008, 2939, 1731, 1646, 1543, 1474, 1434, 1400, 1228, 1148, 1102, 1051, 753 cm^{-1}; HRMS (CI, isobutane) *m/z* 463.1504 (463.1514 calcd for $C_{20}H_{25}F_3N_2O_5S$, MH).

(1*S*,4a*R*,8a*R*)-1-Methyl-7-[2-[2,3-dihydro-1-[(trifluoromethyl)sulfonyl]-1*H*-indol-3-yl]ethyl]hexahydropyrano[3,4-*c*]pyridine-3,6-dione (67). LiOH monohydrate (6 mg, 0.14 mmol) was added to a solution of 35 mg (0.076 mmol) of ester **65** in 2 mL of 50% aqueous THF. The resulting mixture was stirred at rt for 30 min during which time a yellow solution formed. This solution was concentrated, and the residual lithium carboxylate was used without purification.

Paraformaldehyde (11 mg, 0.37 mmol) was added to a solution of this sample of lithium salt **66** and 3 mL of $CHCl_3$. After 5 min, 1 mL of TFA was introduced, and the resulting dark solution was allowed to stand at rt for 14 h. The solution was then diluted with H_2O and extracted with $CHCl_3$, the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (elution with 3% MeOH−$CHCl_3$) to afford 30 mg (86%) of the diastereomeric lactams **67**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.20 (m, 2H), 7.07 (m, 1H), 4.70 (m, 1H), 4.25 (dt, *J* = 9.5, 4.2 Hz, 1H), 3.88 (m, 1H), 3.45−3.05 (m, 6H), 2.84−2.63 (m, 2H), 2.30−1.70 (m, 5H), 1.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 167.2, 138.8, 133.9, 128.1, 124.7, 124.4, 119.7(q), 113.8, 76.4/75.3, 56.3/56.2, 51.5, 47.9, 44.5/44.3, 38.1/37.5, 36.6/36.5, 34.9, 31.3/31.2, 26.1/26.1, 16.5; IR (film) 3436, 2928, 2234, 1728, 1635, 1485, 1392, 1226, 1055, 988, 915, 729 cm^{-1}; HRMS (CI, isobutane) *m/z* 461.1367 (461.1358 calcd for $C_{20}H_{24}F_3N_2O_5S$, MH).

(1*S*,4a*R*,8a*R*)-1-Methyl-7-[2-[2,3-dihydro-1-[(trifluoromethyl)sulfonyl]-1*H*-indol-3-yl]ethyl]hexahydropyrano[3,4-*c*]pyridine-3,6-dione (68). A. Preparation from Indoline 67. A solution of 35 mg (0.076 mmol) of indoline **67**, 52 mg (0.23 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and 2 mL of benzene was heated at 140 °C for 2 h in a sealed tube, during which time the reaction turned black. The cooled reaction mixture then was filtered through basic alumina with 10% MeOH−$CHCl_3$. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (3% MeOH−$CHCl_3$) to afford 20 mg (57%) of indole **68**.

B. Preparation from Indoline 73. LiOH monohydrate (32 mg, 0.76 mmol) was added to a solution of 0.21 g (0.38 mmol) of ester **73** and 4 mL of 50% aqueous THF. The resulting mixture was heated to 50 °C for 5 h during which time a yellow solution formed. This solution was concentrated under reduced pressure, and the crude lithium salt **74** was used without purification.

A small amount of a sample of comparable material was acidified and the resulting acid purified by chromatography on silica gel (elution with 4:1 EtOAc−hexanes) to give a pure specimen of the corresponding acid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 1H), 7.20−7.16 (m, 2H), 7.11 (m, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.42 (s, 1H), 6.40 (m, 1H), 5.42 (m, 1H), 5.21 (m, 1H), 4.38 (s, 2H), 4.19 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.72 (m, 2H), 3.33 (m, 4H), 2.60−2.27 (m, 4H), 1.94 (m, 1H), 1.59 (bs, 3H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 172.7, 160.8, 158.2, 139.1, 134.5, 131.8, 128.5, 128.2, 125.5, 124.9, 120.1(q), 116.1, 114.1, 104.0, 98.6, 56.7, 55.3; 55.1, 47.0, 43.6, 40.3, 37.9, 32.2, 31.1, 20.9, 12.9; IR (film) 3398, 3007, 2935, 1712, 1609, 1589, 1507, 1455, 1394, 1286, 1224, 1193, 1147, 1034, 931, 834, 751 cm^{-1}; HRMS (FAB) *m/z* 599.2026 (599.2039 calcd for $C_{28}H_{34}F_3N_2O_7S$, MH).

Paraformaldehyde (56 mg, 1.9 mmol), the sample of the crude lithium carboxylate described above, and 10 mL of 1:1 TFA−$CHCl_3$ were stirred at rt for 14 h and then concentrated. The resulting crude residue was filtered through silica gel (1:10 MeOH−$CHCl_3$) to give a mixture of the diastereomeric lactams **67**, which were used directly without further purification.

A solution of this sample of crude indoline **67**, 0.43 g (1.9 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and 5 mL of benzene was heated to 140 °C for 5 h in a sealed tube, during which time the reaction turned black. The reaction mixture then was filtered through basic alumina (1:10 MeOH−$CHCl_3$), the filtrate was concentrated, and the crude residue was purified by chromatography on silica gel (3% MeOH−$CHCl_3$) to afford 64 mg (40% from ester **73**) of the indole **68**: $[\alpha]^{24}_D$ −15.7° (*c* 0.5, $CHCl_3$), $[\alpha]^{24}_{Hg577}$ −19.1°, $[\alpha]^{24}_{Hg546}$ −21.8°, $[\alpha]^{24}_{Hg435}$ −23.4°, $[\alpha]^{24}_{Hg405}$ −35.9°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.62 (m, 1H), 7.32 (m, 2H), 7.15 (s, 1H), 4.53 (dq, *J* = 6.6, 4.8 Hz, 1H), 3.60 (m, 2H), 3.12 (dd, *J* = 11.8, 4.8 Hz, 1H), 2.94 (m, 3H), 2.74 (dd, *J* = 17.9, 5.8 Hz, 1H), 2.63 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.21−1.95 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 167.3, 135.4, 130.6, 126.1, 124.7, 122.7, 122.2, 119.8, 113.7, 75.4, 49.1, 47.5, 38.6, 36.9, 35.2, 26.4, 22.5, 16.6 (*C*F_3 not observed); IR (film) 3441, 3111, 2991, 2936, 1731, 1637, 1494, 1450, 1412, 1379, 1274, 1230, 1203, 1148, 1104, 983, 752 cm^{-1}; HRMS (CI, isobutane) *m/z* 459.1202 (459.1201 calcd for $C_{20}H_{22}F_3N_2O_5S$, MH).

***N*-(2,4-Dimethoxybenzoyl)tryptamine (69).** Oxalyl chloride (4.3 mL, 49 mmol) was added dropwise to a cooled (0 °C) solution of 6.0 g (33 mmol) of 2,4-dimethoxybenzoic acid and 40 mL of CH_2Cl_2 containing 50 μL of DMF. The resulting solution was allowed to warm to rt (~30 min), and the solution then was concentrated. The resulting crude benzoyl chloride was dissolved in 20 mL of THF and added to a solution of 5.8 g (36 mmol) of tryptamine (**52**), 9.2 mL (66 mmol) of Et_3N, and 20 mL of THF. The reaction was stirred at rt for 20 min and then quenched with H_2O and diluted with EtOAc. The phases were separated, and the organic phase was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to afford 11 g (98%) of amide **69**, a nearly colorless viscous oil that was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 8.23 (d, J = 8.7 Hz, 1H), 8.01 (br s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.3, 7.7 Hz, 1H), 7.09 (dd, J = 7.4, 7.3 Hz, 1H), 7.04 (s, 1H), 6.51 (dd, J = 8.7, 1.1 Hz, 1H), 6.33 (s, 1H), 3.85 (dt, J = 11.4, 5.8 Hz, 2H), 3.73 (s, 3H), 3.45 (s, 3H), 3.07 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 163.0, 158.6, 136.3, 133.2, 127.1, 122.4, 121.1, 118.7, 118.4, 114.0, 112.2, 111.3, 104.9, 98.1, 55.1, 55.1, 40.0, 24.9; IR (film) 3394, 3261, 2933, 2235, 1641, 1600, 1533, 1492, 1451, 1266, 1205, 1169, 1112, 1025, 907, 835, 738 cm^{-1}; HRMS (CI, isobutane) m/z 325.1554 (325.1552 calcd for $C_{19}H_{21}N_2O_3$, MH).

3-[2-[(2,4-Dimethoxybenzoyl)amino]ethyl]indoline (70). Following a general procedure,[37] a 1 M solution of BH_3·THF in THF (60 mL, 60 mmol) was added dropwise to a stirred, cooled (0 °C) mixture of indole **69** and 60 mL of TFA. The resulting mixture was stirred at 0 °C for 30 min, and then 40 mL of H_2O was introduced dropwise. The resulting mixture was allowed to warm to rt with stirring over 1 h and then was concentrated. The crude residual then was treated with 2 M aqueous NaOH to pH 10 and extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash column chromatography on silica gel (2:1 EtOAc−hexanes) to afford 7.1 g (71%) of indoline **70** and 2.0 g (20%) of the starting indole **69**. Characterization data for **70**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 1H), 7.76 (br s, 1H), 7.07 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.66 (dd, J = 7.8 Hz, 7.0 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.53 (dd, J = 8.7, 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.68 (t, J = 7.9 Hz, 1H), 3.51 (t, J = 7.4 Hz, 1H), 3.49 (t, J = 7.0 Hz, 1H), 3.36−3.30 (m, 1H), 3.24 (dd, J = 7.9, 7.0 Hz, 1H), 2.12−2.01 (m, 1H), 1.86−1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 163.2, 158.7, 151.2, 133.8, 132.3, 127.5, 123.8, 118.5, 114.5, 109.5, 105.1, 98.5, 55.8, 55.4, 53.3, 39.9, 37.8, 34.1; IR (film) 3401, 3318, 2931, 2837, 2225, 1642, 1601, 1537, 1490, 1460, 1313, 1266, 1208, 1166, 1114, 1025, 920, 831, 749, cm^{-1}; HRMS (CI, isobutane) m/z 327.1720 (327.1709 calcd for $C_{19}H_{23}N_2O_3$, M).

3-[2-[(2,4-Dimethoxybenzoyl)amino]ethyl]-*N*-[(trifluoromethyl)-sulfonyl]indoline (71). Freshly distilled triflic anhydride (2.5 mL, 15 mmol) was added to a cooled (−78 °C) solution of 4.4 g (13 mmol) of indoline **70**, 3.8 mL (27 mmol) of Et_3N, and 50 mL of CH_2Cl_2. The resulting solution was maintained at −78 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$ and allowed to warm to rt. This mixture was diluted with EtOAc, and the phases were separated. The organic phase was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (1:3 EtOAc−hexanes) to afford 5.4 g (87%) of indoline **71**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.7 Hz, 1H), 7.81 (t, J = 5.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.12 (dd, J = 7.8, 7.6 Hz, 1H), 7.01 (dd, J = 7.9, 7.6 Hz, 1H), 6.49 (dd, J = 8.7, 2.3 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 4.27 (t, J = 9.8 Hz, 1H), 3.88 (m, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.53−3.40 (m, 3H), 2.08−2.01 (m, 1H), 1.81−1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 163.3, 158.6, 139.1, 134.5, 133.5, 128.1, 124.9, 124.7, 120.0 (q), 114.0, 113.9, 105.1, 98.3, 56.8, 55.7, 55.3, 37.9, 37.0, 34.6; IR (film) 3405, 2933, 2235, 1789, 1646, 1605, 1528, 1482, 1400, 1271, 1194, 1112, 1051, 1030, 918, 835, 753, 733 cm^{-1}; HRMS (CI, isobutane) m/z 459.1183 (459.1201 calcd for $C_{20}H_{22}F_3N_2O_5S$, MH).

3-[2-[(2,4-Dimethoxybenzyl)amino]ethyl]-*N*-[(trifluoromethyl)sulfonyl]indoline (72). A 1 M solution of BH_3·THF and THF (4.9 mL, 4.9 mmol) was added to a solution of 1.5 g (3.3 mmol) of amide **71** and 5 mL of THF. The resulting solution was heated at reflux for 1 h and then allowed to cool to rt. The reaction was quenched with 10% HCl in MeOH and after 2 h was concentrated. The residue was treated with 2 M NaOH and extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated to give 1.3 g (87%) of amine **72**, which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 1H), 7.26−7.21 (m, 2H), 7.14−7.08 (m, 2H), 6.48−6.43 (m, 2H), 4.28 (t, J = 9.7 Hz, 1H), 3.88−3.82 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 2H), 3.53 (m, 1H), 2.69 (t, J = 7.1 Hz, 2H), 2.05−1.96 (m, 1H), 1.79−1.67 (m, 1H), 1.60 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 158.5, 139.2, 135.0, 130.3, 128.1, 124.9, 124.7, 120.5, 120.1(q), 114.1, 103.6, 98.4, 77.4, 57.0, 55.1, 48.7, 46.1, 38.2, 34.7; IR (film) 3405, 3333, 3005, 2933, 2830, 1610, 1584, 1502, 1456, 1394, 1287, 1205, 1148, 1102, 1041, 912, 830, 748 cm^{-1}; HRMS (CI, isobutane) m/z 445.1417 (445.1409 calcd for $C_{20}H_{24}F_3N_2O_4S$, MH).

Methyl (*R*)-3-[[[2-[2,3-Dihydro-1-[(trifluoromethyl)sulfonyl]-1*H*-indol-3-yl]ethyl]-*N*-(2,4-dimethoxybenzyl)carbamoyl]methyl]-hex-4(*Z*)-enoate (73). DMF (1 drop) was added to a cooled (0 °C) solution of 70 mg (0.38 mmol) of monoester **34** (>98% ee) and 5 mL of CH_2Cl_2 followed by the dropwise addition of 50 μL (0.57 mmol) of oxalyl chloride. The resulting solution was allowed to warm to rt over 30 min and then was concentrated. The crude acid chloride was dissolved in dry THF (10 mL) and added to a cooled (0 °C) solution of 0.25 g (0.56 mmol) of indoline **72** and 0.10 mL (0.72 mmol) of Et_3N and dry THF (5 mL). The resulting mixture was stirred for 1 h while warming to rt. The reaction then was quenched with H_2O and diluted with EtOAc. The phases were separated, and the organic phase was washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (1:1 EtOAc−hexanes) to give 0.21 g (91%) of amide **73** as a mixture of stereoisomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 10.6 Hz, 1H), 7.11 (m, 2H), 7.00 (dd, J = 7.7, 6.9 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 6.39 (m, 1H), 5.42 (dq, J = 10.7, 6.8 Hz, 1H), 5.14 (dt, J = 10.5, 1.5 Hz, 1H), 4.36 (s, 2H), 4.18 (t, J = 9.7 Hz, 1H), 3.75 (m, 1H), 3.73 (s, 6H), 3.54 (s, 3H), 3.51−3.10 (m, 4H), 2.50−2.17 (m, 4H), 1.95−1.84 (m, 1H), 1.59 (d, J = 6.9 Hz, 3H), 1.56−1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5/172.4, 171.7/170.8/, 160.6/160.2, 158.2/158.1, 139.1, 134.5, 131.8/131.5, 128.5/128.2, 128.1, 125.6/125.4, 125.0/124.9, 124.6/124.5, 120.0/119.9-(q), 116.5, 114.2/114.1, 104.4/103.9, 98.5/98.1, 56.7/56.3, 55.2/55.2; 55.1, 51.2, 46.5, 43.2/41.9, 39.5/39.1, 37.9/37.7, 32.3, 30.8, 30.7, 12.9; IR (film) 3005, 2943, 1733, 1641, 1610, 1584, 1507, 1456, 1394, 1225, 1189, 1148, 1030, 933, 753 cm^{-1}; HRMS (CI, isobutane) m/z 613.2204 (613.2195 calcd for $C_{29}H_{36}F_3N_2O_7S$, MH). Anal. Calcd for $C_{29}H_{35}F_3N_2O_7S$: C, 56.85; H, 5.76; N, 4.57. Found: C, 56.66; H, 5.71; N, 4.52.

(−)-Ajmalicine (1). Tetracycle **68** (64 mg, 0.14 mmol) was dissolved in 1 mL of *t*-BuOCH(NMe_2)$_2$ (Brederick's reagent), and the resulting solution was maintained at rt for 3 d and then concentrated. Excess Brederick's reagent was removed by Kugelrohr distillation at 90 °C (0.1 mmHg), and the crude vinylogous carbamate was dissolved in 10 mL of 10% HCl in MeOH. This solution was heated to 120 °C in a sealed tube for 24 h and then concentrated. The residue was dissolved in EtOAc and washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to afford a 6:1 mixture (^1H NMR analysis) of compounds **75** and **76**, which was used without further purification.

This mixture of **75** and **76**, 0.19 g (1.4 mmol) of K_2CO_3, and 5 mL of MeOH were heated at reflux for 4 h. After cooling to rt, the mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, and dried ($MgSO_4$). Concentration gave a mixture of **77** and **78**, which was used without further purification.

A solution of this sample of indoles **75** and **76** and 10 mL of benzene were treated at rt with 0.13 mL (1.4 mmol) of freshly distilled $POCl_3$, and the resulting solution was heated at reflux for 1 h. After cooling to rt, the reaction was concentrated, the crude iminium ion product was dissolved in 5 mL of MeOH, and 5 mg (0.13 mmol) of $NaBH_4$ was introduced. The resulting solution was maintained at rt for 20 min and then was concentrated. The resulting residue was purified by flash column chromatography on silica gel (2% MeOH−$CHCl_3$) to

afford 18 mg (37% from lactone **68**) of (−)-ajmalicine: $[\alpha]^{25}_D$ −60.1° (*c* 0.65, $CHCl_3$), $[\alpha]^{24}_{Hg577}$ −62.1°, $[\alpha]^{24}_{Hg546}$ −67.4°; (lit.[15e] $[\alpha]^{25}_D$ −60° ($CHCl_3$), lit.[44] $[\alpha]^{20}_D$ −62° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95; Found: C, 71.51; H, 6.89; N, 7.97.

The 500 MHz ^1H NMR, 125 MHz ^{13}C NMR, IR, and mass spectra of this sample were indistinguishable from those of an authentic specimen.[44]

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Supporting Information Available: Text describing the experimental details and characterization data for the preparation of **12**, **13**, **20**, **39**−**44**, **46**−**51**, **54**, and **56**−**58** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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