Heterocycle Formation through Aza-Annulation: Stereochemically Controlled Syntheses of (±)-5-Epitashiromine and (±)-Tashiromine

K. Paulvannan and John R. Stille*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322

Received November 18, 1993•

N-alkylenamines, stabilized through conjugation with an electron-withdrawing group, undergo aza-annulation with acryloyl chloride to provide a convergent route for the construction of six-membered nitrogen heterocycles. In addition to enhancing the *C*-alkylation process of annulation relative to the competing *N*-acylation process, the electron withdrawing substituent controlled the regioselectivity of alkene formation in both the intermediate enamine and in the unsaturated lactam product. A variety of functional groups, which include –COMe, –COPh, $-CO_2R$, –CONHPh, –CN, $-P(O)(OEt)_2$, and $-SO_2Ph$, were used to determine the effect of the electron-withdrawing substituents upon both the annulation reaction with acryloyl chloride and the subsequent hydrogenation process. When the enamide annulation product was stabilized through conjugation with ester or amide substituents, catalytic hydrogenation of the aza-annulation product resulted in the formation of vicinal stereocenters with high cis selectivity. The utility of this methodology was demonstrated by application of the condensation/aza-annulation/hydrogenation sequence as the key for construction and stereochemical control of the indolizidine ring system of (±)-tashiromine.

Introduction

Alkaloids that contain saturated six-membered nitrogen heterocycles, such as piperidine,[1] indolizidine,[2] and quinolizidine[2] natural products, have been popular synthetic targets due to the array of potent biological activities of these compounds, and the variety of structural challenges that are encountered in their construction. A general approach to the preparation of these ring systems, which has had numerous applications, has been the aza-annulation with imines and various acrylate derivatives.[3] Unfortunately, the initial use of acid chlorides for these annulation reactions often produced low yields due to the generation of side products,[4] and the use of acrylate esters or other acrylic acid anhydride derivatives was necessary for optimum annulation.[3] In a recent study of aza-annulation with imine substrates, a number of alternative acrylate derivatives were used for efficient preparation of δ-lactams.[3] However, restrictions to this methodology persist and include the lack of alkene regioselectivity, poor yields that result from the imines of aldehydes, and limited methods for reduction of the resultant double bond.

Cyclic enamines, which have carbonyl substituents at the nucleophilic enamine carbon, have been used to overcome these limitations in the construction of nitrogen heterocycles. Aza-annulation of a β-enamino ketone with acrylic acid has been used in the synthesis of annotinine,[5] and a related study has reported efficient annulation with acryloyl chloride under milder conditions.[6] Generation of the indolizidine ring system through the aza-annulation reaction of heterocyclic enamino ester substrates with acrylate derivatives, such as esters,[7] acid chlorides,[7] and acid anhydrides,[7a,8] has predominated, and the use of anhydride and ester acrylate annulation has led to elegant syntheses of biologically active molecules.[9] Examples of heterocycle formation by treatment of an acyclic enamino ester[6] and an enamino nitrile[10] substrate with acrylate esters have also been reported.

With the variety of different electron withdrawing groups (EWG) available, and the structural diversity of enamine substrates, many synthetic opportunities present themselves. Herein, we report studies of the aza-annulation of enamine substrates **1** with acryloyl chloride to form **2**, with an emphasis on (1) the use of acyclic enamines, (2) the stereochemically controlled incorporation of ring substituents by reduction to **3**, and (3) the application of this methodology for the stereoselective synthesis of indolizidine natural products (Scheme 1).

Results and Discussion

Methodological Development. The reaction of acyclic β-enamino ketone species with acryloyl chloride resulted

• Abstract published in *Advance ACS Abstracts,* March 1, 1994.

(1) For reviews of piperidine alkaloids, see: (a) Wang, C. J.; Wuonola, M. A. *Org. Prep. Proc. Int.* **1992**, *24*, 585. (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, 491. (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, 17. (d) Pinder, A. R. *Nat. Prod. Rep.* **1990**, 447. (e) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987, Vol. 31, Chapter 6. (f) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed.; Wiley: New York, 1985, Vol. 31, Chapter 1. (g) Jones, T. H.; Blum, M. S. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983, Vol. 1, Chapter 2.

(2) For reviews of indolizidine and quinolizidine alkaloids, see: (a) Michael J. P. *Nat. Prod. Rep.* **1993**, 52. (b) Michael, J. P. *Nat. Prod. Rep.* **1991**, 553. (c) Michael, J. P. *Nat. Prod. Rep.* **1990**, 485. (d) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986, Vol. 28, p. 183. (e) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985, Vol. 5, Chapter 1.

(3) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319 and references cited therein.

(4) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 1358.

(5) (a) Wiesner, K.; Jirkovsky, I.; Fishman, M.; Williams, C. A. J. *Tetrahedron Lett.* **1967**, 1523. (b) Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433.

(6) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112.

(7) (a) Nagasaka, T.; Inoue, H.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 1099. (b) Brunerie, P.; Célérier, J.-P.; Huché, M.; Lhommet, G. *Synthesis* **1985**, 735.

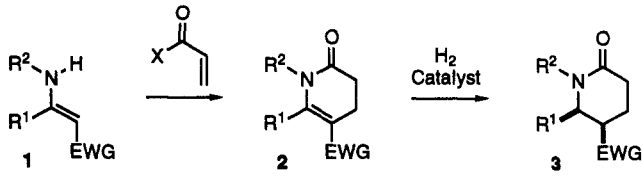
(8) Nagasaka, T.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848.

(9) (a) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611. (b) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621. (c) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430.

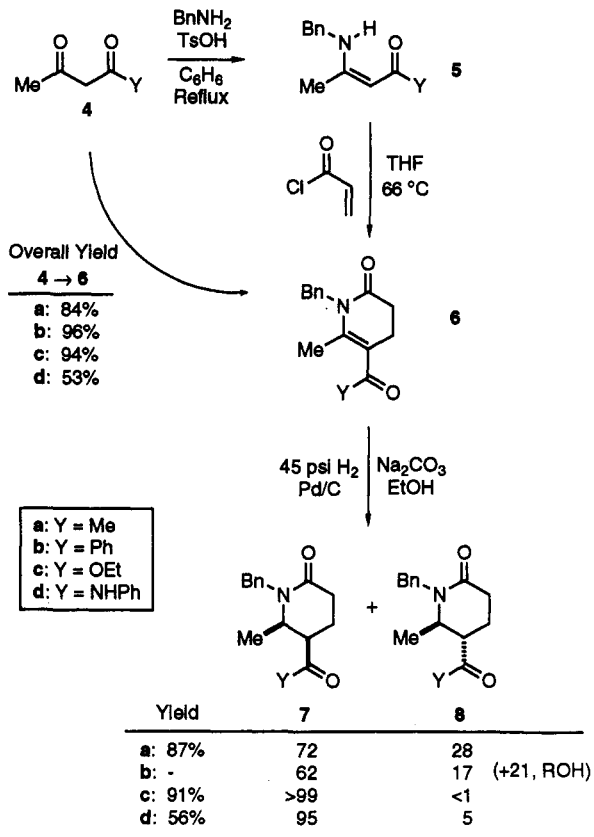
(10) Singh, B.; Lesher, G. Y.; Brundage, R. P. *Synthesis* **1991**, 894.

0022-3263/94/1959-1613$04.50/0

Scheme 1. General Route for Formation of δ-Lactams by Aza-Annulation/Hydrogenation



Scheme 2. Formation and Aza-Annulation of β-Enamino Ketone, Ester, and Amide Substrates

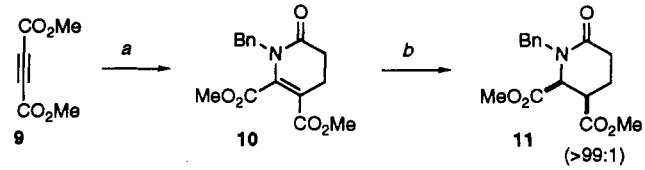


Yield	7	8	
a: 87%	72	28	
b: -	62	17	(+21, ROH)
c: 91%	>99	<1	
d: 56%	95	5	

in very efficient formation of six membered nitrogen heterocycles.[11] In general, condensation of **4** with $BnNH_2$ produced regio- and stereoselective formation of **5** as determined by ^1H NMR, and subsequent treatment of **5** with acryloyl chloride regioselectively generated **6** (Scheme 2). Even in the case of the unsymmetrical β-diketone **4b**, complete regioselectivity for enamine formation at the carbonyl of the methyl ketone was observed. Although benzene has been used for both the condensation and annulation reactions,[6] higher yields were obtained by the use of THF instead of benzene for the annulation step.[12]

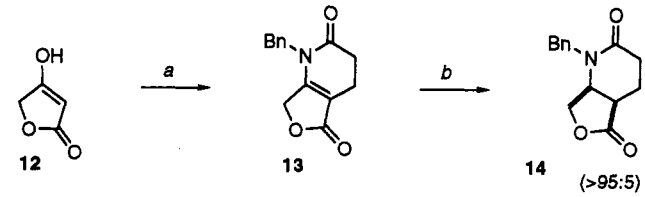
Hydrogenation of the tetrasubstituted vinylogous amide **6a** gave a mixture of diastereomers **7a** and **8a**, and the reaction conditions had a significant influence on the cis/trans product ratio. Although cis/trans ratios ranged from 83:17 to 24:76, depending on concentration and amount of catalyst, standard conditions generated a reproducible 72:28 ratio of ketones (Scheme 2).[13] Treatment of a 61:39 ratio of **7a**/**8a** with DBU under equilibrium conditions

Scheme 3. Formation and Hydrogenation of 10[a]



[a] Key: (a) (i) $BnNH_2$, benzene, (ii) acryloyl chloride, THF, reflux (84%); (b) 3 atm of H_2, Pd/C, MeOH (80%).

Scheme 4. Stereoselective Conversion of 12 to 14[a]



[a] Key: (a) (i) $BnNH_2$, TsOH, benzene, reflux, (ii) acryloyl chloride, THF, reflux (70%); (b) 3 atm of H_2, Pd/C, Na_2CO_3, EtOH (83%).

produced a 30:70 ratio of the two isomers with quantitative recovery of compound.[14] The reduction of **6b** was complicated by the partial reduction of the benzylic carbonyl and, as a result, gave a 62:17:21 ratio of **7b**/**8b**/benzylic alcohol.

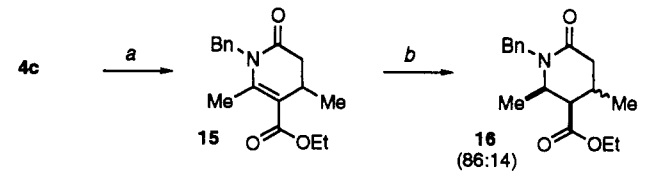
The condensation/aza-annulation/hydrogenation sequence was particularly attractive when acyclic enamino esters were used. The two step condensation/aza-annulation led to a high overall yield of **6c** from **4c**,[12] and the hydrogenation of **6c** led to diastereoselective formation of the δ-lactam product **7c** (>99:1). Alternatively, conjugate addition of $BnNH_2$ to **9** was used for preparation of the corresponding β-enamino ester, which produced **10** upon aza-annulation with acryloyl chloride (Scheme 3).[15] As observed for reduction of **6c**, the cis product (**11**) was stereoselectively formed upon hydrogenation of **10**. Enamine formation from tetronic acid (**12**) followed by reaction with acryloyl chloride gave the corresponding bicyclic product **13**, which was reduced selectively to **14** (Scheme 4).

The cis selectivity obtained through reduction of the vinylogous carbamates, which resulted in the formation of piperidine products with ester substituents, has a great deal of synthetic value. The greater hydrogenation selectivity obtained for the ester relative to ketone substrates was rationalized based on the increased propensity for epimerization at carbon centers α to ketone as compared to ester functionality. Compound **15**, which was prepared through the aza-annulation of **4c** with crotonyl chloride, was used to determine the effect of vinylogous carbamate asymmetry on the stereoselective cis hydrogenation (Scheme 5). Catalytic hydrogenation of **15** produced **16** with 86:14 facial selectivity relative to the existing stereogenic center.[16]

The formation of quaternary carbon centers was accomplished in high yield by the aza-annulation of tetrasubstituted enamine substrates.[17] The reaction of **17** with

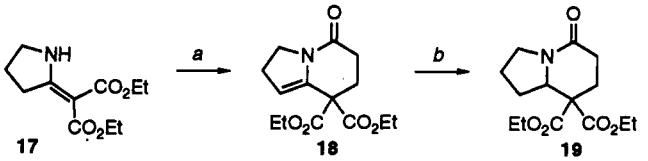
(11) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197.
(12) This modified procedure demonstrated a significant increase in yield over the previously reported syntheses of **6c** (THF, 94% yield; benzene, 42% yield).[6]
(13) The addition of Na_2CO_3 produced optimum results for cis selectivity. (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438. (b) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988.
(14) Additional support for the stereochemical assignments of **7a** (2.79 ppm, J = 4.2 Hz) and **8a** (2.44 ppm, J = 6.5 Hz) was provided by relative values of vicinal coupling constants.
(15) Ramaiah, D.; Ashok, K.; Barik, R.; Venugopal, D.; Rath, N. P.; Bhattacharyya, K.; Das, P. K.; George, M. V. *J. Org. Chem.* **1992**, *57*, 6032
(16) The major stereoisomer (α or β) of the methyl substituent relative to the two cis substituents in **16** was not confirmed.

Scheme 5. Effect of Asymmetry on Hydrogenation of 15[a]



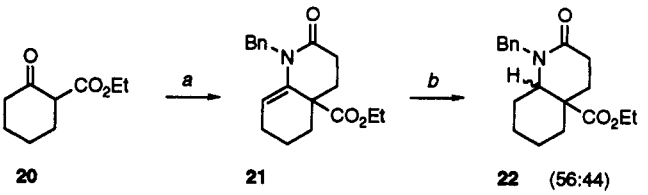
[a] Key: (a) (i) $BnNH_2$, TsOH, benzene, reflux, (ii) crotonyl chloride, THF, reflux (75%); (b) 3 atm of H_2, Pd/C, Na_2CO_3, EtOH (53%).

Scheme 6. Annulation of β-Enamino Diester 17 for Quaternary Carbon Formation[a]



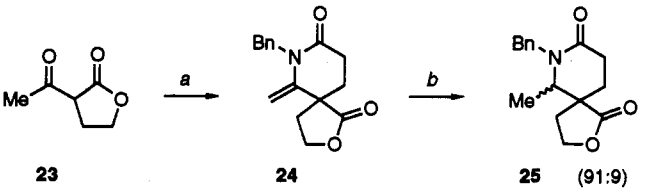
[a] Key: (a) acryloyl chloride, THF, reflux (75%); (b) 3 atm of H_2, Pd/C, EtOH (85%).

Scheme 7. Formation of the Decahydroquinolone Ring System[a]



[a] Key: (a) (i) $BnNH_2$, TsOH, benzene, reflux, (ii) acryloyl chloride, THF, reflux (89%); (b) 3 atm of H_2, Pd/C, Na_2CO_3, EtOH (85%).

Scheme 8. Aza-Annulation for the Formation of Spirocyclic 25[a]

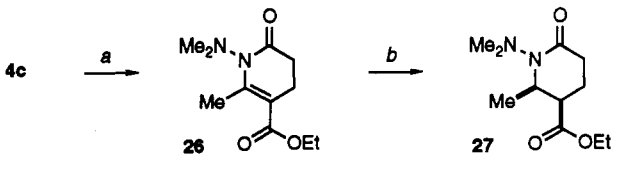


[a] Key: (a) (i) $BnNH_2$, TsOH, benzene, reflux, (ii) acryloyl chloride, THF, reflux (84%); (b) 3 atm of H_2, Pd/C, Na_2CO_3, EtOH (83%).

acryloyl chloride gave **18**, with the alkene exocyclic relative to the ring generated through annulation (Scheme 6). Hydrogenation of the trisubstituted alkene produced the indolizidine **19**. Annulation with **20** resulted in formation of the octahydroquinolone system with an angular carboxyl group, **21**, and subsequent hydrogenation produced **22** with poor stereoselectivity (Scheme 7). Performing the condensation/aza-annulation sequence with **23** gave the spirocyclic product **24**, which was reduced selectively to generate a 91:9 mixture of diastereomers (Scheme 8).

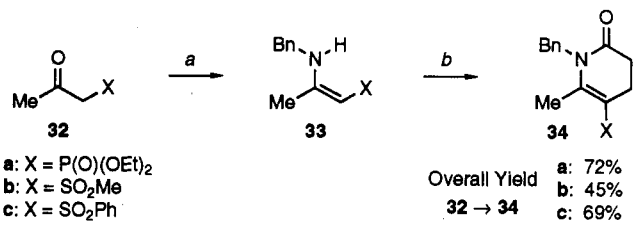
This aza-annulation methodology was also very versatile with respect to variability at the amine substituent. Treatment of **4c** with dimethyl hydrazine resulted in formation of the corresponding enamine, which was converted to **26** upon treatment with acryloyl chloride (Scheme 9). The yield obtained was comparable to that for conversion of **4c** to **6c**. Reduction of **26** selectively gave **27** with a diastereomeric ratio of >99:1.

Scheme 9. Formation and Hydrogenation of Hydrazine Derivative 26[a]



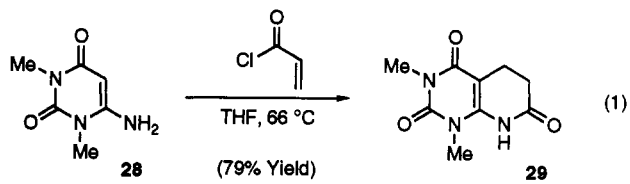
[a] Key: (a) (i) Me_2NNH_2, TsOH, benzene, reflux, (ii) acryloyl chloride, THF, reflux (75%); (b) 3 atm of H_2, Pd/C, EtOH (87%, >99:1).

Scheme 10. Formation and Aza-Annulation of β-Enamino Phosphonate and Sulfonate Substrates[a]



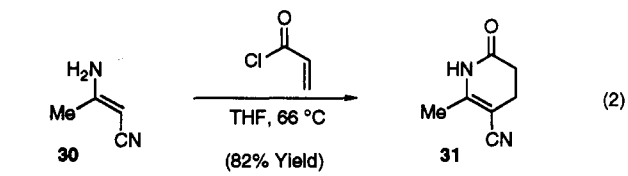
[a] Key: (a) $BnNH_2$, TsOH, benene, reflux; (b) acryloyl chloride, THF, reflux.

Other carboxylate derivatives were also effective in aza-annulation reactions with acryloyl chloride. The β-enamino amide **4d** was converted to vinylogous urea **6d**, and subsequent hydrogenation produced 95:5 selectivity for the cis product isomer **7d** (Scheme 2). In a related example, the treatment of the amino uracil derivative **28** with acryloyl chloride resulted in efficient aza-annulation which gave the nucleobase analog **29** (eq 1). Despite the presence



(1)

of the less hindered primary enamine,[3] aza-annulation of **30** with acryloyl chloride was observed to produce **31** without evidence for *N*-acylation (eq 2). Compound **31** could not be reduced under the standard hydrogenation conditions.



(2)

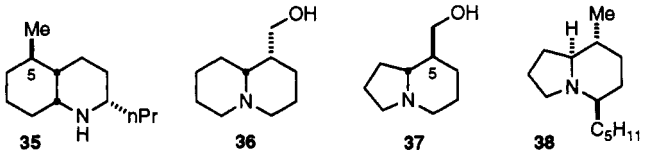
Phosphorous- and sulfur-based electron-withdrawing substituents were also effective in selective aza-annulation reactions (Scheme 10). The two-step condensation/annulation procedure was utilized for the formation of **34a** from **32a** in 72% yield, and subsequent hydrogenation generated a 78:22 ratio of diastereomeric products in 67% yield. In the analogous reaction with β-keto sulfones, the sulfone substituent had a significant effect on the outcome of the reaction. While the reaction with **32b** was poor, annulation of **32c** with acryloyl chloride resulted in

(17) The asymmetric formation of a quaternary center through aza-annulation with imine substrates has been reported. (a) d'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1988**, *29*, 2667. (b) Audia, J. E.; Lawhorn, D. E.; Deeter, J. B. *Tetrahedron Lett.* **1993**, *34*, 7001.

productive formation of **34c**. Unfortunately, reduction of **34c** could not be affected under the standard hydrogenation conditions.

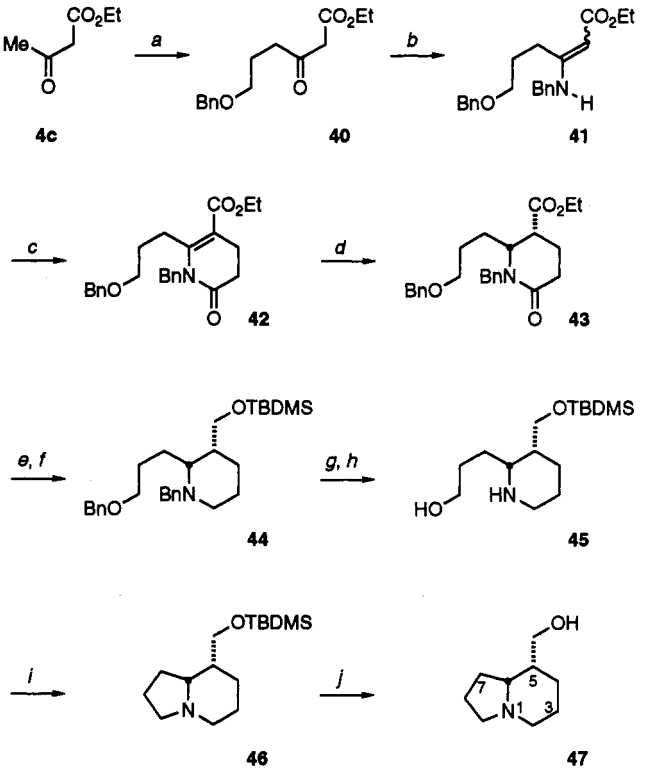
This versatile aza-annulation methodology has significant potential for widespread application in organic synthesis. For example, compounds of the general formula **2** and **3** represent an interesting class of rotationally constrained β-amino acid analogs which have been used in the rapidly growing area of peptidomimetics.[18] Previously, ring systems have been used in the design and synthesis of molecules that resemble the peptide backbone but incorporate a greater degree of conformational control.[19] In related studies, cyclic systems were used to constrain the conformations of 1,2- and 1,3-heteroatom relationships in molecules that imitate naturally occurring β-pleated sheet conformations[20] and β-turns.[21] Substitution of β-amino acids for α-amino acids in biologically active peptides has also been used to provide increased potency and stability of the enzyme.[22] As demonstrated by the synthesis of **29**, similar opportunities are also available for nucleobase analogs.

Applications to Alkaloid Synthesis. In addition to potential use in the synthesis of non-natural substances, this aza-annulation methodology employed electron-withdrawing groups to provide an efficient route to six-membered heterocyclic rings as intermediates for the construction of naturally occurring alkaloids.[9] The effectiveness of the condensation/annulation/hydrogenation sequence has been utilized for formation of the decahydroquinoline ring system of **35** as the C-5 epimer.[23] This methodology was also effective for formation of the quinolizidine ring system of lupinine (**36**),[24] which has demonstrated marked local anesthetic action as the *p*-aminobenzoate derivative.[25] Herein, we report two routes for the total synthesis of the indolizidine alkaloid tashiromine (**37**). In addition, an intermediate in the synthesis of tashiromine contains the key structural features of indolizidine 209-B (**38**).[2]



With the methodology in place for (1) construction of six-membered nitrogen heterocycles, (2) control over regioselective placement of ring substituents, and (3) stereoselective reduction of the vinylogous carbamate, this series of steps was used in the stereocontrolled total synthesis of (±)-epitashiromine (**47**, Scheme 11). The indolizidine alkaloid tashiromine (**37**) was isolated from *Maackia tashiroi*,[26] and the synthesis of this natural product has been reported.[27] Two features, the size of the second ring and the relationship of the stereogenic centers, differentiate tashiromine from lupinine. However, application of the aza-annulation methodology can accommodate these differences.

Scheme 11. The Total Synthesis of (±)-5-Epitashiromine (47)[a]

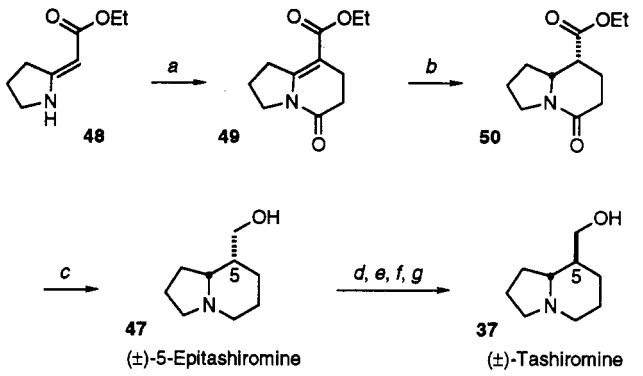


[a] Reaction conditions: (a) (i) 1 equiv of NaH, (ii) 1 equiv of BuLi, (iii) ICH_2CH_2OBn (**39**) (75%); (b) $BnNH_2$, TsOH, benzene; (c) acryloyl chloride, THF, reflux (82% from **40**); (d) 3 atm of H_2, Pd/C, Na_2CO_3 (90%); (e) $LiAlH_4$; (f) TBDMSCl, imidazole (68%); (g) H_2, Pd/C; (h) Li, NH_3 (66%); (i) Ph_3P, CBr_4, NEt_3 (55%); (j) TBAF (60%).

(±)-Epitashiromine (**47**) was prepared through the condensation/aza-annulation/hydrogenation sequence by extension of the methodology developed for **4c** (Scheme 11). Modification of **4c** by alkylation of the corresponding mixed dianion[28] with **39** was accomplished in moderate yield to provide the required β-keto ester substrate **40**. The intermediate β-enamino ester **41** was prepared by acid-catalyzed condensation of **40** with $BnNH_2$ in benzene, accompanied by the azeotropic removal of H_2O. Removal of the benzene provided crude **41**, which was then dissolved in THF and treated with acryloyl chloride to generate the first ring of the epitashiromine system as **42** in 82% overall yield from **40**. Stereoselective hydrogenation of **42** in the presence of Na_2CO_3 established the relative stereochem-

(18) (a) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 543. (b) Chorev, M.; Goodman, M. *Acc. Chem. Res.* **1993**, *26*, 266.
(19) (a) Melnick, M. J.; Bisaha, S. N.; Gammill, R. B. *Tetrahedron Lett.* **1990**, *31*, 961. (b) Freidinger, R. M.; Schwenk Perlow, D.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104.
(20) (a) Smith, A. B., III; Holcomb, R. C.; Guzman, M. C.; Keenan, T. P.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1993**, *34*, 63. (b) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672.
(21) (a) Genin, M. J.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 2334. (b) Genin, M. J.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 860 and references cited therein.
(22) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, pp 331–3 and references cited therein.
(23) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.
(24) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215.
(25) Glasby, J. S. In *Encyclopedia of The Alkaloids*; Plenum Press; New York, 1975; Vol. 2, p 866.
(26) (a) Ohmiya, S.; Kubo, H.; Otomasu, H.; Saito, K.; Murakoshi, I. *Heterocycles* **1990**, *30*, 537. (b) Ohmiya, S.; Kubo, H.; Nakaaze, Y.; Saito, K.; Murakoshi, I.; Otomasu, H. *Chem. Pharm. Bull.* **1991**, *39*, 1123.
(27) Nagao, Y.; Dai, W-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148.
(28) Lee, W. Y.; Jang, S. Y.; Kim, M.; Park, O. S. *Synth. Commun.* **1992**, *22*, 1283.

Scheme 12. The Total Synthesis of (±)-Tashiromine (37)[a]



[a] Reaction conditions: (a) acryloyl chloride, THF, reflux (87%); (b) 3 atm of H_2, Pd/C, Na2CO3 (95%, >95:5 cis/trans); (c) $LiAlH_4$ (91%); (d) Swern oxidation; (e) piperidine, TsOH; (f) $(CO_2H)_2 \cdot 2H_2O$, H_2O; (g) $LiAlH_4$ (58% from 47).

istry of the two stereogenic centers of the 5-epitashiromine precursor (**43**, >95:5).

The final stages of this synthesis involved the reduction of the amide and ester carbonyl functionality, followed by protection as the TBDMS ether **44**. Removal of the *N*-benzyl protecting group was performed by hydrogenation, and subsequent treatment with Li/NH_3 was necessary to produce complete removal of the *O*-benzyl to generate **45**. Ring formation from the corresponding amino alcohol with $PPh_3/CBr_4/NEt_3$ generated the indolizidine ring system **46**,[29] and desilylation of this intermediate completed the synthesis of **47** in 8% overall yield from **4c**.[30]

A more direct route to the synthesis of **47** involved aza-annulation of **48** with acryloyl chloride, which circumvented the steps necessary for five-membered ring formation (Scheme 12).[31] The annulation of **48** with acryloyl chloride efficiently generated the indolizidine ring system of **49** in the same manner as previously reported.[32] Hydrogenation of **49** occurred stereoselectively to give **50**, which was transformed to **47** upon $LiAlH_4$ reduction. Epimerization of C-5 was performed by oxidation of **47** to the corresponding aldehyde, epimerization of the α stereogenic center, and subsequent reduction to give the naturally occurring **37** in 44% overall yield from **48**.

Summary. Aza-annulation methodology represents an efficient approach to the synthesis of δ-lactams through stepwise *C*-alkylation (conjugate addition) and *N*-acylation of the enamine functionality with acryloyl chloride derivatives. Through the use of electron-withdrawing groups as enamine substituents, the ketimine–enamine equilibrium was shifted in favor of the β-enamino carbonyl tautomer. The resulting increase in electron density at the carbon produced a greater propensity for *C*-alkylation over *N*-acylation of the enamine and produced higher reaction yields associated with the generation of fewer side products. In contrast to ketimines which are not stabilized by electron withdrawing groups,[3,4] the use of acryloyl chloride has produced efficient aza-annulation, and the regioselective formation of alkene products was directed by the electron-withdrawing substituent. Hydrogenation of the annulation product resulted in selective introduction of vicinal stereogenic centers when stabilized by ester and amide functionality. The utility of this methodology was demonstrated through the selective construction of the indolizidine ring system of (±)-5-epitashiromine and (±)-tashiromine, in which catalytic hydrogenation of the vinylogous carbamate produced the necessary stereochemical control for the less thermodynamically favorable isomer.

Experimental Section

General Methods. The reactions were typically carried out performing standard inert atmosphere techniques to exclude moisture and oxygen.[33] Azeotropic removal of H_2O was assisted by the use of 4-Å molecular sieves.[34]

General Procedure for Enamine Formation through Condensation. A mixture of the primary amine (12 mmol), ketone (10 mmol), and TsOH (0.01 g, 0.05 mmol) in 66 mL of benzene was heated at reflux for 12–24 h with azeotropic removal of H_2O.[34] After enamine formation was complete, as determined by ^1H NMR, the reaction mixture was cooled to rt and then concentrated to give the corresponding crude enamine.

Preparation of Enamino Ester from 9. To a cooled solution (0–5 °C) of **9** (1.42 g, 10.0 mmol) in 50 mL of benzene was slowly added $BnNH_2$ (1.1 g, 10 mmol). The reaction mixture was stirred at rt for 12 h, and removal of solvent gave the crude enamino ester, which was used in the annulation reaction without further purification.

General Procedure for Aza-Annulation. The crude enamine (≈10 mmol) was taken up in 66 mL of THF, the appropriate α,β-unsaturated acid chloride (13 mmol) was added slowly to the rt solution, and the reaction mixture was heated at reflux until the disappearance of starting materials was complete (6–24 h), as determined by ^1H NMR. The mixture was quenched with 25 mL of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with 4 × 40 mL of CH_2Cl_2, and the organic fractions were combined and dried (Na_2SO_4). Following concentration of the solution, the residue was purified by flash column chromatography to give the corresponding lactam product.

6a: ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 6 H), 2.65 (s, 4H), 5.02 (s, 2 H), 7.12–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.8, 21.8, 29.4, 30.9, 44.3, 117.0, 125.7, 126.8, 128.3, 137.0, 145.9, 170.3, 198.6; IR (neat) 3030, 1690, 1669, 1591, 1383, 1186 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_2$ *m/z* 243.1259, obsd *m/z* 243.1260.

6b: mp 70–72 °C (recrystallized from CH_2Cl_2:EtOAc = 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, J = 1.4 Hz, 3 H), 2.62 (m, 2 H), 2.72 (m, 2 H), 5.04 (s, 2 H), 7.16–7.73 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0, 23.1, 31.2, 44.2, 117.4, 125.8, 126.8, 128.2, 128.3, 128.4, 132.3, 137.2, 138.1, 142.8, 170.3, 196.7; IR (KBr) 3029, 2967, 1682, 1655, 1605, 1576, 1451, 1385, 1364 cm^{-1}; HRMS calcd for $C_{20}H_{19}NO_2$ *m/z* 305.1415, obsd *m/z* 305.1402.

6c: mp 75–77 °C (recrystallized from Et_2O:petroleum ether = 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3 H), 2.35 (t, J = 1.4 Hz, 3 H), 2.57–2.71 (m, 4 H), 4.18 (q, J = 7.1 Hz, 2 H), 5.03 (s, 2 H), 7.10–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 16.0, 20.8, 30.9, 44.4, 59.9, 109.0, 125.7, 126.7, 128.3, 137.1, 148.0, 167.0, 171.0; IR (KBr) 2984, 2959, 2845, 1684, 1617, 1377, 1269, 1184, 1120 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ *m/z* 273.1364, obsd *m/z* 273.1363.

6d: ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, J = 1.5 Hz, 3 H), 2.62 (m, 2 H), 2.72 (m, 2 H), 5.04 (s, 2 H), 7.19–7.71 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.0, 22.0, 30.9, 44.4, 113.3, 119.8,

(29) Shishido, Y. Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.

(30) The final product was consistent with published ^1H and ^{13}C NMR spectral data.[26]

(31) The synthesis of **48** was accomplished through methods described in: Celerier, J. P.; Deloisy-Marchalant, E.; Lhommet, G.; Maitte, P. *Org. Synth.* **1988**, *67*, 170.

(32) The aza-annulation of **48** to **49** with the use of similar reaction conditions (acryloyl chloride, pyridine, toluene, reflux, 72%) has been reported.[7b]

(33) For more detailed general experimental procedures from these laboratories, see: Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461.

(34) Dehydration of condensation reactions was performed with the use of a modified Dean-Stark apparatus in which the cooled distillate was passed through 4-Å molecular sieves prior to return of the solvent to the reaction mixture. Barta, N. S.; Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Synth. Commun.* **1994**, *24*, 583.

124.1, 125.7, 126.9, 128.4, 128.6, 137.1, 137.4, 140.3, 167.0, 170.1; IR (KBr) 3029, 2969, 1680, 1655, 1605, 1385, 1364, 1281 cm^{-1}; HRMS calcd for $C_{20}H_{20}N_2O$ *m/z* 304.1575, obsd *m/z* 304.1530.

10: mp 86–88 °C (recrystallized from Et_2O:petroleum ether = 40:60); ^1H NMR (300 MHz, $CDCl_3$) δ 2.50–2.62 (m, 4 H), 3.52 (s, 3 H), 3.60 (s, 3H), 4.67 (s, 2 H), 7.05–7.21 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 29.9, 46.4, 51.7, 52.3, 108.3, 126.7, 127.1, 128.0, 136.1, 142.6, 163.5, 165.1, 169.3; IR (KBr) 3038, 2955, 1736, 1692, 1628, 1458, 1441, 1381, 1300 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_5$ *m/z* 303.1106, obsd *m/z* 303.1120.

13: mp 115–117 °C (recrystallized from Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (m, 2 H), 2.85 (td, *J* = 8.0, 1.1 Hz, 2 H), 4.65 (t, *J* = 2.0 Hz, 2 H), 4.81 (s, 2H), 7.16–7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.5, 30.2, 45.6, 64.9, 102.4, 126.5, 127.9, 128.8, 135.0, 159.7, 169.1, 170.8; IR (KBr) 3038, 2982, 2959, 1746, 1695, 1664, 1435, 1275, 1196 cm^{-1}; HRMS calcd for $C_{14}H_{13}NO_3$ *m/z* 243.0895, obsd *m/z* 243.0896.

15: mp 84–85 °C (recrystallized from Et_2O:petroleum ether = 40:60); ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 2.34 (s, 3 H), 2.48 (dd, *J* = 15.7, 2.2 Hz, 1 H), 2.71 (dd, *J* = 15.7, 6.6 Hz, 1 H), 3. 01 (quintd, J = 1.8, 6.9 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.78 (d, *J* = 16.2 Hz, 1 H), 5.22 (d, *J* = 16. 2 Hz, 1 H), 7.13–7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 16.2, 17.6, 26.6, 37.8, 44.6, 59.8, 113.5, 126.1, 126.8, 128.3, 137.3, 146.6, 167.1, 170.0; IR (KBr) 3034, 2980, 2959, 1678, 1615, 1383, 1124 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_3$ *m/z* 287.1520, obsd *m/z* 287.1521.

18: ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 6 H), 2.34–2.40 (m, 4 H), 2.62 (m, 2 H), 3.91 (dd, *J* = 9.2, 8.6 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 4 H), 5.25 (t, *J* = 2.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 26.2, 26.4, 28.2, 44.2, 54.4, 61.8, 109.6, 135.6, 164.9, 167.6; IR (neat) 2982, 2869, 1736, 1667, 1647, 1439, 1414, 1372 cm^{-1}; HRMS calcd for $C_{14}H_{19}NO_5$ *m/z* 281.1262, obsd *m/z* 281.1187.

21: mp 72–74 °C (recrystallized from Et_2O:petroleum ether = 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.15 Hz, 3 H), 1.37 (m, 1 H), 1.49 (ddd, *J* = 13.8, 13.0, 2.5 Hz, 1 H), 1.66 (m, 1 H), 1.78 (td, *J* = 13.3, 5.7 Hz, 1 H), 2.03 (dddd, *J* = 17.9, 9.3, 6.3, 3.0 Hz, 1 H), 2.16 (m, 1 H), 2.25–2.38 (m, 2 H), 2.49 (ddd, *J* = 6.1, 12.8, 18.4 Hz, 1 H), 2.70 (ddd, *J* = 18.4, 5.8, 1.5 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.63 (d, *J* = 15.9 Hz, 1 H), 5.18 (dd, *J* = 5.1, 3.0 Hz, 1 H), 5.33 (d, *J* =15.9 Hz, 1 H), 7.20-7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.1, 23.8, 29.6, 30.3, 34.4, 46.0, 47.3, 60.8, 107.6, 125.9, 126.2, 127.9, 136.5, 137.2, 167.8, 173.6; IR (KBr) 3063, 2980, 1719, 1669, 1644, 1451, 1404, 1373 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_3$ *m/z* 313.1677, obsd *m/z* 313.1692.

24: ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (ddd, *J* = 13.4, 6.3, 3.1 Hz, 1 H), 2.22 (ddd, *J* = 12.8, 9.8, 8.2 Hz, 1 H), 2.34 (ddd, *J* = 12.8, 6.5, 2.5 Hz, 1 H), 2.43 (ddd, *J* = 12.0, 13.5, 6.0 Hz, 1 H), 2.63 (ddd, 18.1, 12.0, 6.2 Hz, 1 H), 2.93 (ddd, *J* = 18.1, 6.0, 3.3 Hz, 1 H), 4.16 (dt, *J* = 9.8, 6.6 Hz, 1 H), 4.24 (d, 3.1 Hz, 1 H), 4.38 (ddd, *J* = 9.2, 8.2, 2.6 Hz, 1 H), 4.54 (d, *J* = 3.1 Hz, 1 H), 4.93 (d, *J* = 15.7 Hz, 1 H), 5.03 (d, *J* = 15.7 Hz, 1 H), 7.15–7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.3, 28.5, 33.8, 46.3, 47.3, 64.9, 94.2, 126.1, 126.7, 128.2, 136.1, 142.4, 167.7, 176.7; IR (neat) 3032, 2942, 1775, 1673, 1620, 1456, 1186, 1028 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_3$ *m/z* 271.1208, obsd *m/z* 271.1215.

26: ot 95–105 °C, <1 Torr; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3 H), 2.41 (t, *J* = 1.5 Hz, 3 H), 2.42–2.48 (m, 2 H), 2.51–2.58 (m, 2 H), 2.85 (s, 6 H), 4.19 (q, *J* = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 15.0, 20.6, 32.0, 43.0, 56.6, 106.4, 151.3, 167.0, 169.8; IR (neat) 2980, 2896, 1696, 1620, 1541, 1379, 1273 cm^{-1}; HRMS calcd for $C_{11}H_{18}N_2O_3$ *m/z* 226.1317, obsd *m/z* 226.1322.

29: mp 222–225 °C (recrystallized from EtOAc:CH_2Cl_2 = 65:35); ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (m, 2 H), 2.80 (m, 2 H), 3.37 (s, 3 H), 3.54 (s, 3 H), 9.29 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8, 27.9, 29.4, 29.9, 88.7, 144.0, 150.7, 161.1, 172.6; IR (KBr) 3289, 3048, 2957, 1715, 1667, 1634, 1507 cm^{-1}; HRMS calcd for $C_9H_{11}N_3O_3$ *m/z* 209.0800, obsd *m/z* 209.0803.

31: mp 211–213 °C (recrystallized from EtOAc:CH_2Cl_2 = 30:70); ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 2.57 (s, 4 H), 7.96 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.6, 21.9, 29.4, 84.6, 118.5, 148.4, 170.9; IR (KBr) 3212, 3139, 2205, 1690, 1653, 1373, 1327 cm^{-1}; HRMS calcd for $C_7H_8N_2O$ *m/z* 136.0636 obsd *m/z* 136.0645.

34a: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (dt, *J* = 7.1, 0.6 Hz, 6 H), 2.30 (m, 3 H), 2.51 (m, 2 H), 2.60 (m, 2 H), 4.03 (m, 4 H), 5.00 (s, 2 H), 7.09–7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, includes C–P coupling) δ 15.8, 15.9, 16.9, 17.0, 21.3, 21.4, 31.0, 31.1, 44.2, 61.0, 61.1, 102.3, 104.9, 125.6, 126.7, 128.3, 137.0, 149.2, 149.5, 170.4; IR (neat) 3065, 3033, 2982, 2938, 2905, 1688, 1624, 1389, 1366, 1252, 1233, 1024 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_4P$ *m/z* 337.1443, obsd *m/z* 337.1443.

34c: mp 110–112 °C (recrystallized from Et_2O:petroleum ether = 70:30); ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (t, *J* = 1.6 Hz, 3 H), 2.60 (m, 2 H), 2.74 (m, 2 H), 4.98 (s, 2H), 7.04–7.83 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.6, 21.3, 30.8, 44.6, 117.6, 125.5, 126.1, 127.0, 128.4, 128.8, 132.6, 136.5, 141.8, 147.6, 169.4; IR (KBr) 3061, 3032, 2957, 1688, 1622, 1449, 1360, 1302, 1173 cm^{-1}; HRMS calcd for $C_{19}H_{19}NO_3S$ *m/z* 341.1086, obsd *m/z* 341.1060.

42: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.81 (m, 2 H), 2.57 (m, 2 H), 2.66 (m, 2 H), 2.86 (m, 2 H), 3.55 (t, *J* = 5.9 Hz, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.49 (s, 2 H), 5.06 (s, 2 H), 7.07 (brd, *J* = 8.1 Hz, 2 H), 7.18–7.38 (m, 8 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 20.8, 25.6, 28.8, 31.1, 43.7, 59.9, 69.1, 72.6, 109.3, 125.8, 126.6, 127.2, 127.3, 127.9, 128.2, 137.4, 138.0, 151.9, 166.8, 171.2; IR (neat) 3088, 3063, 3032, 2978, 2855, 1688, 1617, 1497, 1455, 1372, 1271 cm^{-1}; HRMS calcd for $C_{25}H_{29}NO_4$ *m/z* 407.2096, obsd *m/z* 407.2079.

49: mp 45–47 °C (recrystallized from Et_2O:petroleum ether = 65:35); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 1.97 (quint, *J* = 7.6 Hz, 2H), 2.51 (m, 2 H), 2.65 (m, 2H), 3.14 (tt, *J* = 15.4, 1.8 Hz, 2 H), 3.72 (t, *J* = 7.2 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 20.7, 20.9, 30.4, 31.2, 45.4, 59.5, 100.4, 152.5, 166.5, 168.9; IR (KBr) 2980, 1689, 1634, 1385, 1294, 1265, 1200, 1129 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_3$ *m/z* 209.1051, obsd *m/z* 209.1068.

General Procedure for the Hydrogenation of the Annulation Products. A solution of the lactam (2.00 mmol) and 10% Pd/C (0.2 g) in 27 mL of absolute EtOH or MeOH (for 11) was placed under H_2 (3 atm) for 12–48 h. In some cases, Na_2CO_3 (0.74 g, 7.0 mmol) was also added.[13] The catalyst and Na_2CO_3 were removed by filtration, and the mixture was concentrated. The crude residue was taken up in CH_2Cl_2, filtered, and concentrated again to give the corresponding lactam. Solids were crystallized from CH_2Cl_2.

7a/8a: ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.09 (d, *J* = 6.5 H, 1.2 H, minor), 1.24 (d, *J* = 6.5 Hz, 1.8 Hz, major), 1.93 (s, 1.8 H, major), 1.96–2.16 (m, 2.0 H, both), 2.08 (s, 1.2 H, minor), 2.44 (dt, *J* = 17.9, 6.5 Hz, 1 H, minor), 2.52–2.65 (m, 2 H), 2.79 (dt, *J* = 12.6, 4.2 Hz, 1 H, major), 2.79 (dt, *J* = 12.6, 4.1 Hz, 0.4 H, minor), 3.78–3.88 (m, 1 H, both), 3.94 (d, *J* = 15.1 Hz, 0.4 H, minor), 4.03 (d, 15.1 Hz, 0.6 H, major), 5.28 (d, *J* = 15.1 Hz, 0.6 H, major), 5.36 (d, *J* = 15.1 Hz, 0.4 H, minor), 7.20–7.39 (m, 5 H, both); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 17.2, 19.5, 19.8, 27.5, 28.1, 29.3, 29.9, 46.9, 47.7, 51.0, 52.2, 126.9, 127.0, 127.3, 127.7, 128.1, 128.2, 136.8, 136.9, 168.7, 168.9, 206.3, 207.1; IR (neat) 2975, 1711, 1638, 1474, 1453, 1161 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ *m/z* 245.1415, obsd *m/z* 245.1422.

7c: mp 51–53 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.5 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 2.02–2.20 (m, 2 H), 2.50 (ddd, *J* = 18.3, 10.5, 8.5 Hz, 1 H), 2.63 (ddd, *J* = 18.3, 6.6, 3.0 Hz, 1 H), 2.81 (dt, *J* = 12.0, 4.8 Hz, 1 H), 3.82 (m, 1 H), 3.99 (d, *J* = 15.1 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5. 28 (d, *J* = 15.1 Hz, 1 H), 7.23–7.37 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 14.6, 17.7, 30.0, 43.4, 47.8, 51.7, 60.4, 126.9, 127.3, 128.2, 136.9, 168.6, 171.0; IR (KBr) 3032, 2978, 1732, 1643, 1497, 1474, 1453 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_3$ *m/z* 275.1521, obsd *m/z* 275.1508.

7d: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.5 Hz, 3 H), 2.00 (m, 1 H), 2.31 (m, 1 H), 2.52 (ddd, *J* = 18.2, 10.9, 7.7 Hz, 1 H), 2.68 (ddd, *J* = 18.2, 7.7, 1.6 Hz, 1 H), 2.80 (ddd, *J* = 12.7, 4.5, 3.7 Hz, 1 H), 3.82 (quint, *J* = 6.1 Hz, 1 H), 4.01 (d, *J* = 15.1 Hz, 1 H), 5.29 (d, *J* = 15.1 Hz, 1 H), 7.08–7.49 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 18.1, 29.9, 45.4, 48.1, 52.9, 119.6, 124.2, 127.3, 127.4, 128.3, 128.6, 136.9, 137.1, 168.8, 168.9; IR (KBr)

3298, 3132, 3065, 2980, 1661, 1645, 1599, 1541, 1497, 1443 1240 cm^{-1}; HRMS calcd for $C_{20}H_{22}N_2O_2$ *m/z* 322.1681, obsd *m/z* 322.1684.

11: ^1H NMR (300 MHz, $CDCl_3$) δ 1.98–2.22 (ddd, J = 8.1, 10.7, 15.5 Hz, 2 H), 2.49 (m, 1 H), 2.67 (ddd, J = 18.2, 6.9, 2.2 Hz, 1 H), 2.90 (dt, J = 12.9, 4.7 Hz, 1 H), 3.62 (s, 3 H), 3.65 (s, 3 H), 3.91 (d, J = 15.0 Hz, 1 H), 4.32 (dd, J = 4.1, 1.3 Hz, 1 H), 5.28 (d, J = 15.0 Hz, 1 H), 7.19–7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.5, 29.9, 42.0, 49.2, 51.8, 52.2, 59.1, 127.3, 127.9, 128.2, 135.7, 169.0, 169.5, 170.3; IR (neat) 3011, 2955, 1748, 1655, 1414, 1311, 1209 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_5$ *m/z* 305.1262, obsd *m/z* 305.1210.

14: ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (m, 1 H), 2.31 (m, 1 H), 2.41 (m, 1 H), 2.47–2.59 (m, 1 H), 2.97 (m, 1 H), 4.18–4.26 (m, 4 H), 5.13 (d, J = 15.1 Hz, 1 H), 7.19–7.39 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 29.1, 37.4, 47.4, 55.0, 70.8, 127.3, 127.4, 128.5, 135.8, 169.1, 176.0; IR (KBr) 3032, 2959, 2946, 2922, 1788, 1644, 1470, 1451, 1362, 1163 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_3$ *m/z* 245.1051, obsd *m/z* 245.1050.

16: ^1H NMR (300 MHz, $CDCl_3$, major) δ 1.05 (d, J = 6.9 Hz, 3 H), 1.20 (d, J = 6.7 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 2.27 (m, 1 H), 2.49–2.68 (m, 2 H), 2.77 (t, J = 4.7 Hz, 1 H), 3.67 (m, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.40 (d, J = 15.7 Hz, 1 H), 5.10 (d, J = 15.7 Hz, 1 H), 7.20–7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 17.6, 18.5, 28.4, 36.2, 45.6, 50.1, 52.5, 60.0, 126.4, 126.7, 128.0, 137.4, 170.1, 170.4; IR (neat) 3063, 3028, 2978, 2934, 1728, 1644, 1497, 1449, 1412, 1292 cm^{-1}; HRMS calcd for $C_{17}H_{23}NO_3$ *m/z* 289.1677, obsd *m/z* 289.1677.

19: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.65–1.98 (m, 2 H), 2.02–2.29 (m, 3 H), 2.42–2.60 (m, 3 H), 3.45–3.55 (m, 2 H), 3.85 (dd, J = 9.7, 6.8 Hz, 1 H), 4.14–4.26 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.4, 21.5, 28.1, 28.2, 28.4, 44.9, 54.9, 60.9, 61.2, 167.3, 167.6, 169.0; IR (neat) 2980, 2883, 1734, 1649, 1460, 1414, 1370, 1252 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO_5$ *m/z* 283.1419, obsd *m/z* 283.1425.

22: ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.25 (t, J = 7.1 Hz, 3 H, major) 1.27 (t, J = 7.1 Hz, 3 H minor), 1.33–1.59 (m, 1 H, both), 1.60–1.84 (m, 2 H, both), 1.85–2.1 (m, 2 H, both), 2.1–2.37 (m, 2 H, both), 2.38–2.56 (m, 1 H, both), 2.58–2.75 (m, 1 H, both), 3.26 (dd, J = 12.1 Hz, 0.56 H, major), 4.12–4.26 (m, 2 H, both), 4.47 (d, J = 15.9 Hz, 0.56 H, major), 4.63 (d, J = 15.9 Hz, 0.44 H, minor), 5.08–5.20 (m, 1 H minor), 5.32 (d, J = 15.9 Hz, 0.56 H, major), 7.18–7.35 (m, 5 H, both); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.2, 21.8, 23.8, 24.5, 25.7, 29.7, 30.4, 32.3, 34.5, 35.9, 45.0, 46.0, 47.4, 47.5, 60.2, 60.9, 62.1, 107.8, 125.9, 126.2, 126.4, 128.0, 136.6, 137.2, 137.8, 168.0, 169.8, 172.7, 173.8; HRMS calcd for $C_{19}H_{25}NO_3$ *m/z* 315.1834, obsd *m/z* 315.1841.

25: ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.25 (d, J = 6.6 Hz, 3 H), 1.49 (m, 1 H), 1.67 (ddd, J = 13.0, 6.8, 2.8 Hz, 1 H), 1.87 (ddd, J = 12.9, 9.6, 8.7 Hz, 1H), 2.25–2.42 (m, 2H), 2.54 (m, 1H), 3.19 (qd, J = 6.6, 1.6 Hz, 1 H), 3.44–3.60 (m, 2H), 3.99 (td, J = 9.2, 2.8 Hz, 1 H), 5.48 (d, J = 14.3 Hz, 1 H), 7.12–7.26 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.2, 23.7, 27.5, 32.4, 45.6, 47.2, 52.4, 64.1, 127.6, 128.3, 128.6, 136.3, 167.6, 176.9; IR (KBr) 2973, 2946, 1763, 1644, 1495, 1472, 1455, 1219 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ *m/z* 273.1364, obsd *m/z* 273.1374.

27: mp 40–42 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J = 6.4 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.85–1.95 (m, 2 H), 2.28 (ddd, J = 18.1, 10.2, 9.1 Hz, 1 H), 2.43 (ddd, J = 18.1, 5.1, 4.9 Hz, 1 H), 2.78 (m, 1 H), 2.84 (s, 6 H), 3.89 (quint, J = 6.1 Hz, 1 H), 4.08–4.25 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 14.7, 17.1, 31.5, 43.2 (br), 44.2, 56.3, 60.4, 168.2, 170.8; IR (KBr) 2977, 2951, 1734, 1649, 1404, 1233, 1169 cm^{-1}; HRMS calcd for $C_{11}H_{20}N_2O_3$ *m/z* 228.1473, obsd *m/z* 228.1480.

43: ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.55–1.74 (m, 4 H), 2.00–2.24 (m, 2 H), 2.53 (dd, J = 18.4, 8.8 Hz, 1 H), 2.64 (ddd, J = 18.4, 8.3, 3.3 Hz, 1 H), 2.76 (dt, J = 12.4, 4.6 Hz, 1 H), 3.38–3.43 (m, 2 H), 3.75 (brq, J = 4.5 Hz, 1 H), 3.91 (d, J = 15.1 Hz, 1 H), 4.04–4.15 (m, 2 H), 4.48 (s, 2 H), 5.40 (d, J = 15.1 Hz, 1 H), 7.20–7.39 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 18.3, 27.3, 28.1, 29.4, 43.6, 49.2, 56.3, 60.5, 69.4, 72.5, 126.9, 127.2, 127.4, 127.9, 128.2, 136.8, 137.9, 169.1, 171.1; IR (neat) 3031, 2955, 1732, 1644, 1468, 1453, 1237 cm^{-1}; HRMS calcd for $C_{25}H_{31}NO_4$ *m/z* 409.2252, obsd *m/z* 409.2239.

Reduction of 34a: ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.14–1.34 (m, 9 H), 1.90–2.72 (m, 5 H), 3.68 (m, 1 H), 3.85–4.15 (m, 5 H), 5.14 (d, J = 14.8 Hz, 0.24 H, minor isomer), 5.31 (d, J = 14.8 Hz, 0.76 H, major isomer), 7.19-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, mixture of isomers) δ 15.7, 16.2, 16.3, 16.9, 17.0, 18.7, 18.8, 21.7, 21.8, 30.4, 30.5, 30.6, 30.9, 36.3, 37.2, 38.3, 39.1, 47.8, 47.9, 50.6, 50.9, 51.0, 61.7, 61.8, 61.9, 62.0, 127.2, 127.3, 127.8, 128.3, 128.4, 128.5, 137.2, 168.6, 169.8; HRMS calcd for $C_{17}H_{26}NO_4P$ *m/z* 339.1600, obsd *m/z* 339.1589.

50: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3 H), 1.63–1.85 (m, 2 H), 1.87–2.05 (m, 3 H), 2.16 (m, 1 H), 2.37 (ddd, J = 17.9, 7.6, 2.6 Hz, 1 H), 2.52 (ddd, J = 17.9, 10.8, 7.4 Hz, 1 H), 2.96 (q, J = 4.2 Hz, 1 H), 3.47–3.54 (m, 2 H), 3.66 (quint, J = 5.3 Hz, 1 H), 4.12 (qd, J = 7.1, 1.4 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 21.6, 23.4, 27.8, 29.2, 40.0, 44.6, 58.5, 59.9, 168.1, 171.1; IR (neat) 2977, 2880, 1730, 1640, 1460, 1414, 1327, 1302, 1177 cm^{-1}; HRMS calcd for $C_{11}H_{17}NO_3$ *m/z* 211.1208, obsd *m/z* 211.1147.

Alkylation of Ethyl Acetoacetate (4c). To a cooled (~−20 °C) suspension of NaH (1.65 g, 68.7 mmol) in 70 mL of THF was added dropwise a solution of **4c** (8.95 g, 68.8 mmol) in 15 mL of THF. The reaction mixture was stirred at this temperature until all of the NaH was consumed (~15 min), and then a solution of BuLi (2.5 *M* in hexane, 27.5 mL, 68.8 mmol) was slowly added to give an orange solution. After the mixture was stirred at 0 °C for 15 min, a solution of **39** (15.0 g, 57.3 mmol) in 15 mL of THF was added dropwise. The solution was stirred at 0 °C for 1.5 h, warmed to rt to stir for an additional 12 h, and then quenched with 50 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with 4 × 50 mL of Et_2O, and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to produce a crude residue, which was purified by SiO_2 chromatography (eluent: hexane:Et_2O = 80:20) to give **40** (11.34 g, 42.9 mmol) in 75% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3 H), 1.92 (quint, J = 6.1 Hz, 2 H), 2.67 (t, J = 7.1 Hz, 2 H), 3.44 (s, 2 H), 3.50 (t, J = 6.1 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.48 (s, 2 H), 7.27–7.39 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 23.2, 39.3, 48.9, 60.9, 68.6, 72.4, 127.1, 127.2, 127.9, 137.9, 166.8, 202.2; IR (neat) 3065, 3032, 2982, 2936, 2865, 1743, 1715, 1647, 1455, 1368, 1314 cm^{-1}; HRMS calcd for $C_{15}H_{21}O_4$ *m/z* 264.1361, obsd *m/z* 264.1370.

Preparation of 44. To a solution of **43** (5.09 gm, 12.4 mmol) in 50 mL of THF at 0 °C was slowly added $LiAlH_4$ (1.0 M in THF, 49.8 mL, 49.8 mmol). The reaction mixture was heated at reflux for 12 h, cooled to 0 °C, and then quenched by the sequential addition of 1.9 mL of H_2O, 1.9 mL of 15% w/v aqueous NaOH, and 5.7 mL of H_2O. After being stirred for 1 h at rt, the aluminum salts were removed by filtration, and the combined filtrate and washings were dried (Na_2SO_4), filtered, and concentrated to give the crude alcohol, which was used without further purification.

A mixture of the crude alcohol (12.4 mmol), imidazole (2.12 g, 31.1 mmol), and TBDMSCl (2.25 g, 14.9 mmol) in 20 mL of DMF was stirred at rt for 12 h. The reaction mixture was then quenched with 25 mL of saturated aqueous $NaHCO_3$ and extracted with 4 × 30 mL of Et_2O. The combined organic fractions were washed with 50 mL of H_2O, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (eluent: Et_2O: petroleum ether:NH_4OH = 20:80:1.3) to give **44** (3.96 g, 8.48 mmol) in 68% yield: ^1H NMR (300 MHz, $CDCl_3$) δ −0.1 (s, 3 H), 0.1 (s, 3 H), 0.84 (s, 9 H), 1.10–1.42 (m, 2 H), 1.46–1.80 (m, 6 H), 2.07 (m, 1 H), 2.36–2.50 (m, 1 H), 2.56–2.78 (m, 2 H), 3.41 (m, 4 H), 3.72 (s, 2 H), 4.46 (s, 2 H), 7.22–7.34 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.8, −5.7, 17.8, 20.2, 21.4, 22.8, 25.5, 27.4, 38.3, 45.3, 57.7, 58.1, 64.7, 70.3, 72.3, 126.2, 127.0, 127.2, 127.6, 127.9, 128.3, 138.4, 140.2; IR (neat) 3087, 3063, 3029, 2928, 2857, 1495, 1472, 1362, 1256, 1101 cm^{-1}; HRMS calcd for $C_{29}H_{45}NO_2Si$ *m/z* 467.3219, obsd *m/z* 467.3207.

Preparation of 45. A solution of **44** (3.15 g, 6.75 mmol) in 65 mL of MeOH was hydrogenated at 3 atm over 10% Pd/C (1.4 g) for 24 h. The catalyst was removed by filtration, and the combined filtrate and washings were concentrated to give the crude deprotected amine, which was used for Li/NH_3 reduction without further purification.

A solution of the crude amine in 15 mL of THF was added to liquid NH_3 (150-200 mL) at −78 °C, and small pieces of lithium rod were added slowly to generate a dark blue color. The reaction mixture was warmed to −33 °C, stirred for 2 h, and then cooled again to −78 °C. After the reaction was quenched by the addition

of solid NH_4Cl, the reaction vessel was allowed to warm to rt, and the NH_3 was evaporated. The remaining white solid was dissolved in CH_2Cl_2 and then filtered to remove the insoluble inorganic salts. Purification of the crude amino alcohol was accomplished by flash column chromatography (eluent: 15:85 MeOH–CH_2Cl_2) to give **45** (1.29 g, 4.49 mmol) in 66% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 1.51–1.62 (m, 2 H), 1.68–2.0 (m, 5 H), 2.26–2.38 (m, 1 H), 3.06–3.22 (m, 2 H), 3.53–3.83 (m, 6 H), 8.73 (brs, 1 H), 9.60 (brs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ –6.0, –5.9, 17.6, 19.8, 21.7, 23.2, 25.4, 28.4, 37.5, 40.6, 55.3, 61.1, 61.9; IR (KBr) 3449, 3248, 2955, 2856, 2804, 1584, 1471, 1258, 1092 cm^{-1}; HRMS calcd for $C_{15}H_{33}NO_2Si$ *m/z* 287.2280, obsd *m/z* 287.2297.

Preparation of 46. To a solution of **45** 0.18 g, 0.61 mmol) and CBr_4 (0.26 g, 0.77 mmol) in 2.5 mL of CH_2Cl_2 was added PPh_3 (0.24 g, 0.92 mmol) at 0 °C. The reaction mixture was stirred for 1 h, and then NEt_3 (1.04 g, 9.82 mmol) was added at 0 °C. After being stirred for 30 min, the mixture was warmed to rt to stir for an additional 30 min. The solvent was then removed to give a crude solid, which was extracted with 5 × 25 mL of petroleum ether. Following concentration of the petroleum ether extracts, the residue was purified by flash column chromatography (eluent: Et_2O:petroleum ether:NH_4OH = 80:20:1.3) to give **46** (0.090 g, 0.34 mmol) in 55% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.16–2.26 (m, 12 H), 2.93–3.03 (m, 2 H), 3.64 (dd *J* = 10.0, 8.2 Hz, 1 H), 3.78 (dd, *J* = 10.0, 5.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ –5.8, 17.8, 20.2, 21.1, 24.8, 25.2, 25.5, 37.9, 52.9, 54.5, 60.8, 65.2. HRMS calcd for $C_{15}H_{31}NOSi$ *m/z* 269.2175, obsd *m/z* 269.2179.

Deprotection of 46. To a solution of **46** (0.30 g, 1.11 mmol) in 4 mL of THF was added 2.2 mL of a 1 M solution of (*n*-Bu)$_4$NF (TBAF, 2.2 mmol) in THF. The mixture was stirred at rt for 24 h and then washed with 5 mL of 10% aqueous NaOH. The aqueous layer was extracted with 4 × 15 mL of EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash column chromatography (eluent: 90:10:1.5 Et_2O–MeOH–NH_4OH) to give **47** (0.11 g, 0.67 mmol) in 60% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.63 (m, 2 H), 1.64–1.91 (m, 6 H), 1.92–2.13 (m, 3 H), 2.21–2.32 (m, 1 H), 2.94–3.03 (m, 1 H), 3.05–3.13 (m, 1 H), 3.71 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.14 (ddd, *J* = 10.8, 4.2, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 22.9, 25.6, 29.6, 35.7, 53.4, 54.4, 64.5, 66.5; IR (neat) 3370, 2934, 2787, 2730, 1447, 1379, 1327 cm^{-1}; HRMS calcd for $C_9H_{17}NO$ *m/z* 155.1310, obsd *m/z* 155.1351.

Preparation of (±)-5-Epitashiromine (47) from Lactam 50. To a solution of lactam **50** (1.11 g, 5.23 mmol) in 26 mL of THF at 0 °C was slowly added a 1 M solution of $LiAlH_4$ (13.10 mL, 13.10 mmol). The solution was heated at reflux for 6 h, cooled to 0 °C, and then quenched by the sequential addition of 0.5 mL of H_2O, 0.5 mL of 15% w/v aqueous NaOH, and 1.5 mL of H_2O. After the solution was stirred for 1 h at rt, the aluminum salts were removed by filtration, and the combined filtrate and washings were dried (Na_2SO_4), filtered, and concentrated to give (±)-5-epitashiromine (**47**) in 91% yield.

Conversion of (±)-5-Epitashiromine (47) to Tashiromine (37). To a cooled solution (–65 to –70 °C) of oxalyl chloride (0.91 g, 7.2 mmol) in 13 mL of CH_2Cl_2 was slowly added a solution of DMSO (1.82 g, 14.4 mmol) in 3 mL of CH_2Cl_2. After the mixture was stirred at this temperature for 10 min, a solution of the alcohol (**47**) in 12 mL of CH_2Cl_2 was added slowly, and the mixture was stirred for 45 min at –60 to –50 °C. Following the addition of NEt_3 (2.90 g, 28.7 mmol), the reaction mixture was stirred at –60 to –50 °C for 20 min, warmed to rt, and then stirred at this temperature for an additional 1 h. The mixture was then quenched by the addition of 30 mL of H_2O, stirred for 1 h, and then extracted with 4 × 25 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde.

A mixture of the crude aldehyde (4.78 mmol), piperidine (0.45 g, 5.26 mmol) and TsOH (0.005 g, 0.024 mmol) in 32 mL of benzene was heated at reflux for 10 h with azeotropic removal of H_2O.[34] The solution was then cooled to rt, concentrated, and dissolved in 8 mL of CH_2Cl_2. A solution of $(CO_2H)_2{\cdot}2H_2O$ (0.63 g) in 5 mL of H_2O was added, and the mixture was stirred at rt for 4 h and then heated at reflux for 1 h. After the mixture was cooled to rt, 10 mL of H_2O, 15 mL of CH_2Cl_2, and 10 mL of 15% aqueous NaOH were added. The mixture was stirred for 30 min and was then extracted with 4 × 20 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde.

To a solution of the crude aldehyde (4.78 mmol) in 19 mL of THF at 0 °C was slowly added a solution of $LiAlH_4$ (1 M in THF, 7.20 mL, 7.20 mmol), and the mixture was stirred at rt for 6 h. The solution was cooled to 0 °C and was then quenched by the sequential addition of 0.27 mL of H_2O, 0.27 mL of 15% w/v aqueous NaOH, and 0.82 mL of H_2O. After the mixture was stirred for 1 h at rt, the aluminum salts were removed by filtration. The combined filtrate and washings were dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was purified by flash column chromatography (eluent: 85:15:2 Et_2O–MeOH–NH_4OH) to give (±)-tashiromine (**37**) in 58% overall yield from (±)-5-epitashiromine (**47**).

37: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (qd, *J* = 12.7, 4.7 Hz, 1 H), 1.36–1.97 (m, 10 H), 2.03 (q, *J* = 9.0 Hz, 1 H), 2.98–3.10 (m, 2 H), 3.44 (dd, *J* = 10.8, 6.3 Hz, 1 H), 3.67 (dd, *J* = 10.8, 4.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2, 24.6, 27.2, 28.5, 44.1, 52.2, 53.7, 64.6, 66.0; IR (neat) 3374, 2932, 2793, 1462, 1445, 1385, 1331, 1279 cm^{-1}; HRMS calcd for $C_9H_{17}NO$ *m/z* 155.1310, obsd *m/z* 155.1334.

Acknowledgment. This project was supported in part by BRSG Grant No. 2-S07 RR07049-15 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health. Support from the National Institutes of Health (GM44163) is gratefully acknowledged. Spectral product characterization was performed on NMR instrumentation purchased in part with funds from NIH Grant 1-S10-RR04750 and from NSF Grant CHE-88-00770. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility which is supported, in part, by a grant (DDR-00480) from the Biotechnology Resources Branch, Division of Research Resources, National Institutes of Health.

Supplementary Material Available: ^1H NMR spectra of all compounds in the Experimental Section (35 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.