Construction of Hydroxylated Alkaloids (±)-Mannonolactam, (±)-Deoxymannojirimycin, and (±)-Prosopinine through Aza-Annulation

Gregory R. Cook, Lars G. Beholz, and John R. Stille*,†

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

Received February 1, 1994®

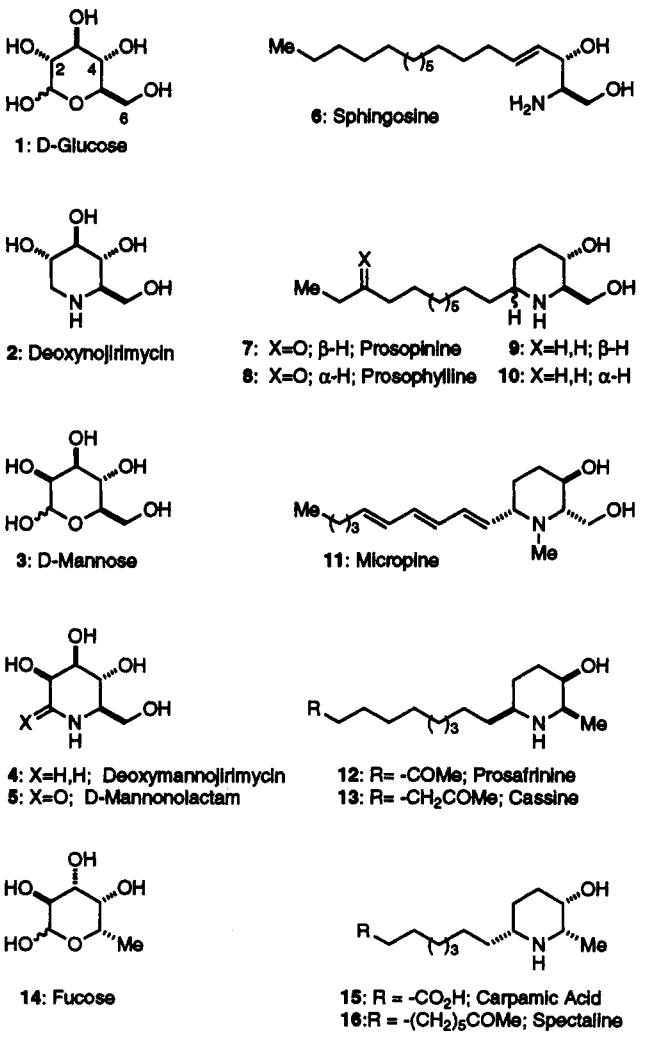
The aza-annulation of β-enamino carbonyl substrates with acrylate derivatives provides an efficient and convenient route for the regioselective construction of δ-lactams. This two-step ring-forming sequence involved initial generation of the benzyl enamine through either a condensation or conjugate addition reaction with $BnNH_2$, followed by aza-annulation with acryloyl chloride or acrylic anhydride. Controlled by the rigid framework of the intermediate lactam, introduction of ring substituents was accomplished with high relative stereoselectivity. The carbonyl functionality, which was necessary to direct the regioselectivity of the aza-annulation reaction, was then transformed into a protected hydroxyl substituent through Baeyer–Villiger oxidation. The resultant δ-lactam product was used as a valuable intermediate in the synthesis of three natural products. Subsequent modification of this δ-lactam gave the naturally occurring α-mannosidase inhibitors (±)-mannonolactam and (±)-deoxymannojirimycin, while synthesis of the alkaloid (±)-prosopinine was accomplished through homologation of the lactam carbonyl.

Introduction

Hydroxylated piperidine alkaloids are found frequently in living systems,[1] and the wide range of potent physiological effects stems from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[2] With the pivotal role that carbohydrates play in biological processes such as cell recognition and differentiation, these alkaloids have become important synthetic targets.[3] Important structure–activity relationships for these molecules center around the stereochemical configuration of hydroxyl functionality which are β to the nitrogen. Due to the prominance of D-glucose (**1**) and D-mannose (**3**) in biological processes, many alkaloids mimic the C-4 and C-6 structural features of these carbohydrates (Chart 1).

Polyhydroxylated piperidine alkaloids exhibit selective inhibition of a number of biologically important pathways, including the binding and processing of glycoproteins.[4] For example, compound **4** has been shown to inhibit α-L-fucosidase, α-D-mannosidase, and α-D-glucosidase activity,[5] while the analogous lactam **5** inhibited both α-D-mannosidase and α-D-glucosidase.[5e] The piperidine

Chart 1



† Present address: Chemical Process Research and Development, Lilly Research Laboratories, Indianapolis, IN 46285-4813.

® Abstract published in *Advance ACS Abstracts,* May 15, 1994.

(1) For reviews that include piperidine alkaloids, see: (a) Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Proc. Int.* **1992**, *24*, 585. (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491. (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17. (d) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 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. 3, Chapter 1.

(2) For more specific information on hydroxylated piperidines, see the following articles and the references cited within: (a) van den Broek, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (d) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. Plagiarizing Plants: Aminosugars as a Class of Glycosidase Inhibitors In *Bioactive Compounds from Plants*; Wiley: Chichester (Ciba Foundation Symposium 154), 1990; pp 112–125. (e) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

(3) (a) Sharon, N.; Lis, H. *Sci. Am.* **1993**, *268*, 82. (b) Sharon, N.; Lis, H. *Science* **1989**, *246*, 227. (c) Karlsson, K.-A. *Trends Pharm. Sci.* **1991**, *12*, 265.

(4) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497.

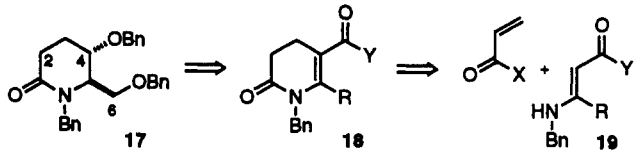
0022-3263/94/1959-3575$04.50/0

alkaloid **2** has exhibited selective inhibition of α-glucosidases I and II without effective inhibition of α-mannosidase,[2,7] and this glucose analog has potential for use in the therapy of diabetes mellitus, hyperlipoproteinemia, cancer, and arthritis.[8] Interestingly, when compared to **2**, synthetic derivatives such as *N*-butyl-**2** and *N*-decyl-**2** show pronounced antiviral activity through inhibition of syncytia formation in HIV-1.[2a,9]

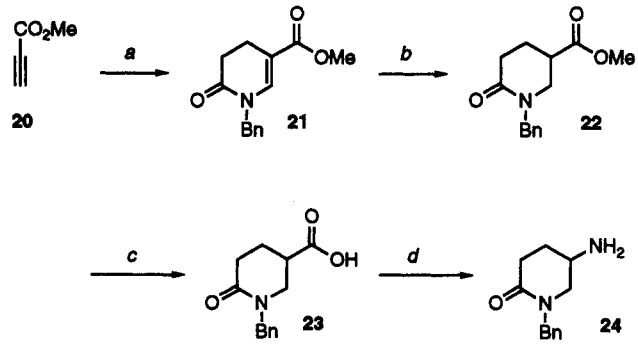
Naturally occurring heterocyclic amines with long aliphatic appendages, such as the *Prosopis* (**7** and **8**) and *Cassia* alkaloids (**12**, **13**, **15**, and **16**), have also been reported.[1] These compounds are found throughout the world and have received increasing attention as medicinal agents due to the variety of pharmacological properties they exhibit.[10] The *Prosopis* alkaloids **7** and **8** are particularly intriguing because they contain a blend of physiologically important structural features.[11] At one end of the molecule is the polar head group with a configuration of hydroxyl substituents similar to that found in **2** and **4**, while a lipophilic tail portion resembles that of the membrane lipid sphingosine (**6**). Similar mixtures of alkyl chain "tail" and carbohydrate "head" structural features are found in penaresidines A and B, which display potent ATPase-activating properties, and BAY R 1005, which shows promise for immunization of patients with defective T-lymphocytes such as patients with AIDS.[12] In each of these molecules, the alkyl chain serves to (1) facilitate transfer across membranes, (2) anchor the active compound in the membrane with the polar portion protruding, or (3) interact with the hydrophobic portion of the enzymes to which these compounds bind.

Our approach to the construction of several hydroxylated piperidines utilized the aza-annulation reaction for efficient construction of nitrogen heterocycle **18** from β-enamino carbonyl derivative **19** (Scheme 1).[13] The heterocycle was then used as a framework to control the relative stereochemistry of the C-4 and C-5 ring substituents in the generation of **17**.[14] From this versatile intermediate, the naturally occurring alkaloids (±)-mannonolactam (**5**), (±)-deoxymannojirimycin (**4**), and (±)-prosopinine (**7**) were prepared.

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



Scheme 2. Heterocycle Formation through Conjugate Addition/Aza-Annulation[a]



[a] Reagents and conditions: (a) (i) $BnNH_2$, C_6H_6, rt, (ii) acryloyl chloride, THF, 66 °C (53%); (b) 3 atm of H_2, PdC, EtOH (98%); (c) (i) NaOH, H2O, (ii) HCl, H_2O (90%); (d) (i) DPPA, NEt_3, *t*-BuOH, (ii) HCl, (iii) NaOH, H_2O (24%).

Results and Discussion

Method Development. The use of ketone and ester functionality as electron-withdrawing substituents was found to significantly enhance the efficiency and selectivity of the aza-annulation reaction (Scheme 1; Y = Me, OEt).[13] However, several key transformations were required to adapt this methodology to the synthesis of hydroxylated alkaloids. Of initial importance was the need for additional methods of enamine preparation that were compatible with the subsequent aza-annulation reaction. In conjunction with these studies, aza-annulation was explored as a route to **19** in which R ≠ Me, followed by subsequent stereoselective introduction of the C-5 substituent. In addition, methods for conversion of the C-4 carbonyl substituent to a hydroxyl group and homologation of the resulting lactam carbonyl were required.

One approach to the desired δ-lactam products involved the combination of three fragments, an acetylenic ester, a primary amine, and an acrylate derivative, to produce the desired heterocycles (Scheme 2). Conjugate addition of $BnNH_2$ to **20** generated the intermediate β-enamino ester, which gave the corresponding six-membered nitrogen heterocycle **21** upon aza-annulation with acryloyl chloride. A variety of reagents, which included $Me_2CuCNLi_2$, $Me_2CuCNLi_2/BF_3{\cdot}OEt_2$, $Me_2CuBrLi_2$, and $MeCu{\cdot}BF_3$, were employed for possible introduction of a methyl

(5) (a) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755. (b) Elbein, A. D.; Legler, G.; Tlutsy, A.; McDowell, W.; Schwarz, R. *Arch. Biochem. Biophys.* **1984**, *235*, 579. (c) Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61. (d) Niwa, T.; Tsuruoka, T.; Goi, H.; Kodama, Y.; Itoh, J.; Inouye, S.; Yamada, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J. Antibiot.* **1984**, *37*, 1579. (e) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

(6) (a) Ishida, N.; Kumagai, K.; Niida, T.; Hamamoto, K.; Shomura, T. *J. Antibiotics* **1967**, *A20*, 62. (b) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.

(7) (a) Niwa, T.; Inouye, S.; Tsuruoka, T.; Koaze, Y.; Niida, T. *Agric. Biol. Chem.* **1970**, *34*, 966. (b) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (c) Fuhrmann, U.; Bause, E.; Ploegh, H. *Biochim. Biophys. Acta* **1985**, *825*, 95. (d) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219. (e) Fellows, L. E. *Chem. Br.* **1987**, *23*, 842.

(8) Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926 and references cited therein.

(9) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229.

(10) These compounds are found in Africa (**8**), Pakistan (juliflorinine), Philippines (**11**), and South America (**13**); they exhibit a variety of pharmacological properties (prosopinine (**7**) and prosopine: anesthetic, analgesic, and antibiotic activities;[11] carpaine, the macrolactone dimer of **15**: antituberculotic and antitumor activity, effects on the brain and cardiovascular system, hemolytic effects, and hypotensive effects).[1]

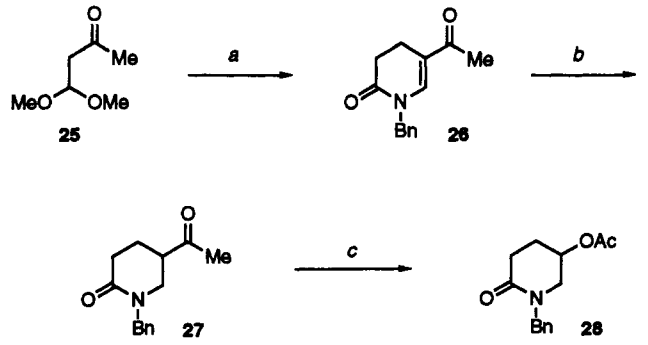
(11) (a) Fr. Pat. FR 1524395; *Chem. Abstr.* **1969**, *71*, 91733w. (b) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787; *Chem. Abstr.* **1969**, *71*, 29012g. (c) Bourrinet, P.; Quevauviller, A. *C. R. Soc. Biol.* **1968**, *162*, 1138; *Chem. Abstr.* **1969**, 70, 95233K.

(12) (a) Penaresidine A and B: Kobayashi, J.; Cheng, J.-F.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (b) BAY R 1005: Lockhoff, O. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1611.

(13) (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (d) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (e) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197.

(14) For continuity, the carbohydrate numbering system was used in this manuscript when referring to the pyridones.

Scheme 3. Formation and Oxidation of 27[a]



[a] Reagents and conditions: (a) (i) H_2O, TsOH, C_6H_6, (ii) $BnNH_2$, C_6H_6, 80 °C, (iii) acryloyl chloride, THF, 66 °C (23%); (b) 1 atm of H_2, Pd/C, EtOH (87%); (c) CF_3CO_2H, *m*-CPBA (89%).

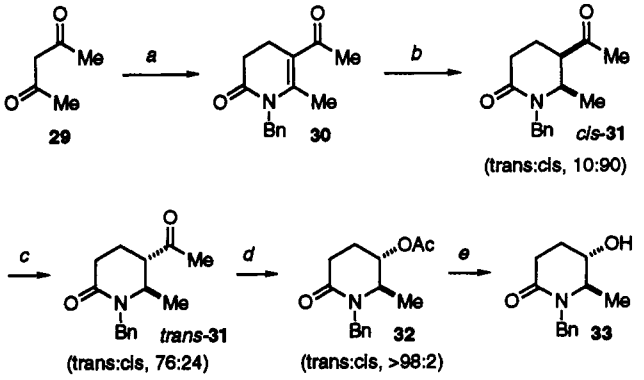
substituent β to the ester, but conjugate addition to the vinylogous carbamate **21** was not observed.[15]

In order to explore modification of the carboxyl substituent at C-4, **21** was reduced through catalytic hydrogenation to give **22**, and selective hydrolysis of the ester produced the corresponding β-amino acid derivative **23**. Attempts at oxidative decarboxylation with the use of established methods were not successful for selective introduction of the C-4 hydroxyl due to the formation of complex product mixtures.[16] However, a similar oxidative procedure for introduction of an amino group resulted in partial success. Treatment of **23** with DPPA/NEt_3 in *t*-BuOH, followed by hydrolysis of the intermediate *tert*-butylcarbamate, provided amine **24** in low yield.[17] Optimization of this transformation was not pursued.

Related studies were performed with the corresponding methyl ketone derivative **26** (Scheme 3). Hydrolysis of **25** produced the corresponding aldehyde, which was condensed with $BnNH_2$ and treated with acryloyl chloride to give **26**. The low yield obtained for this three-step process resulted from self-condensation of the intermediate aldehyde. As found for **21**, conjugate addition of nucleophiles to vinylogous imide **26** did not proceed under established conditions.[14] Baeyer–Villiger oxidation of **27** to **28** generated very promising results for the introduction of an oxygen substituent at C-4.[18] However, the inability to introduce substituents at the position β to the ester or ketone group required that the C-5 substituent be in place prior to aza-annulation.

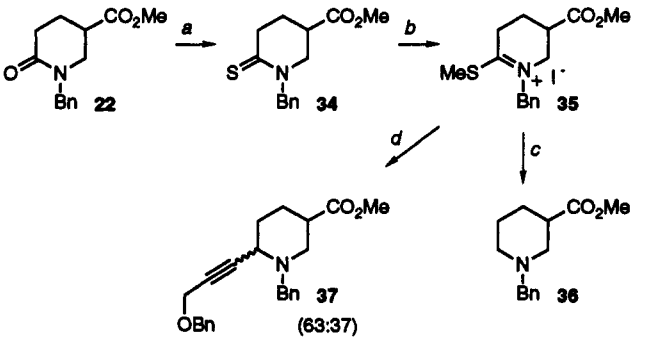
As previously reported,[13d] **29** was condensed with $BnNH_2$ and treated with acryloyl chloride to produce the corresponding aza-annulation product **30**, and catalytic hydrogenation generated **31** as a 10:90 mixture of trans and cis isomers (Scheme 4).[19] In order to access alkaloids **12** and **16**, a variety of conditions were used to affect the desired Baeyer–Villiger oxidation of *cis*-**31**.[18] However, **32** was the only acetate derivative generated under these conditions. Epimerization of **31**, by treatment with DBU, generated an equilibrium ratio of trans/cis isomeric products (76:24), and oxidation of this predominantly trans substrate mixture resulted in the formation of **32** in 45% yield. When compared to the successful oxidation of **27**, steric constraints imposed by the cis methyl substituent prevented efficient Baeyer–Villiger oxidation of *cis*-**31**, while *trans*-**31** was transformed to the corresponding ester. Hydrolysis of the acetate resulted in deprotection of the hydroxyl group to generate **33**.

Scheme 4. Formation and Oxidation of 31[a]



[a] Reagents and conditions: (a) (i) $BnNH_2$, C_6H_6, 80 °C, (ii) acryloyl chloride, THF, 66 °C (94%); (b) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (81%); (c) DBU; (d) CF_3CO_2H, *m*-CPBA (45%); (e) NaOH, H_2O (74%).

Scheme 5. Homologation of the Lactam Carbonyl[a]



[a] Reagents and conditions: (a) Lawesson's reagent (99%); (b) MeI; (c) (i) PrMgBr, (ii) $NaBH_4$, (72% from **34**); (d) (i) $BnOCH_2C{\equiv}CLi$, (ii) $NaBH_4$ (45%) from **34**).

The final stage of method development focused on homologation of the lactam carbonyl, which was necessary in order to append lipophilic tail segments to the alkaloid portion of these molecules. Initial studies of lactam carbonyl homologation were performed with **22** (Scheme 5). Lawesson's reagent provided an extremely efficient method for the transformation of **22** to thiolactam **34**, and subsequent *S*-methylation generated the corresponding imidate salt **35**.[20] Treatment of **35** with a carbon nucleophile, to generate the intermediate iminium species,

(15) (a) ($Me_2CuCNLi_2$) Dodd, D. S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1991**, *32*, 3643. (b) ($Me_2CuBrLi_2$) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425. (c) Lipshutz, B. H. *Synthesis* **1987**, 325. (d) ($MeCu{\cdot}BF_3$) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (e) ($Me_2CuCNLi_2$) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

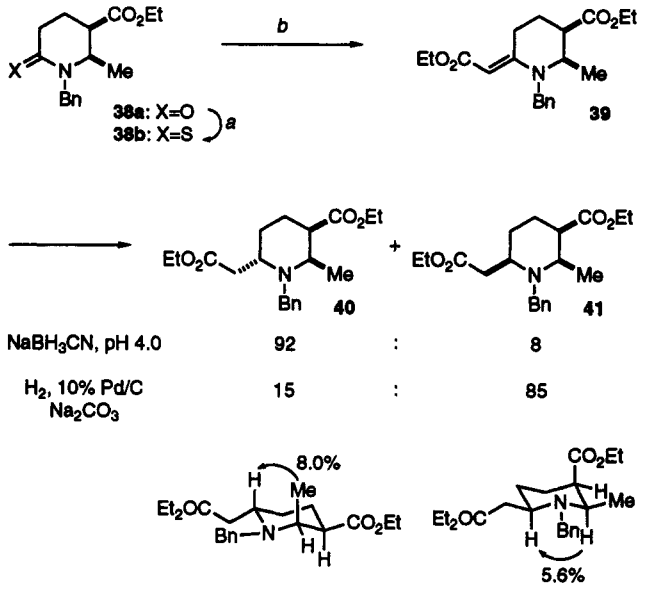
(16) (a) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621. (b) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440. (c) Barton, D. H. R.; Coates, I. H.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. I* **1973**, 599. (d) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.

(17) (a) Mostowicz, D.; Belzecki, C.; Chmielewski, M. *Synthesis* **1991**, 273. (b) Sato, M.; Katagiri, N.; Takayama, K.; Hirose, M.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 665. (c) Eaton, P. E.; Ravi Shankar, B. K.; Price, G. D; Pluth, J. J.; Gilbert, E. E.; Alster, J. Sandus, O. *J. Org. Chem.* **1984**, *49*, 185. (d) Haefliger, W.; Klöppner, E. *Helv. Chim. Acta.* **1982**, *65*, 1837. (e) Chantegrel, B.; Gelin, S. *Synthesis* **1981**, 315.

(18) (a) Canan Koch, S. S.; Chamberlin, R. *Synth. Commun.* **1989**, *19*, 829. (b) Wilson, S. R.; Di Grandi, M. J. *J. Org. Chem.* **1991**, *56*, 4766. (c) Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489. (d) Baxter, A. J. G.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. I* **1977**, 2343. (e) Narasaki, K.; Sakkakura, T.; Uchimaru, T.; Guédin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

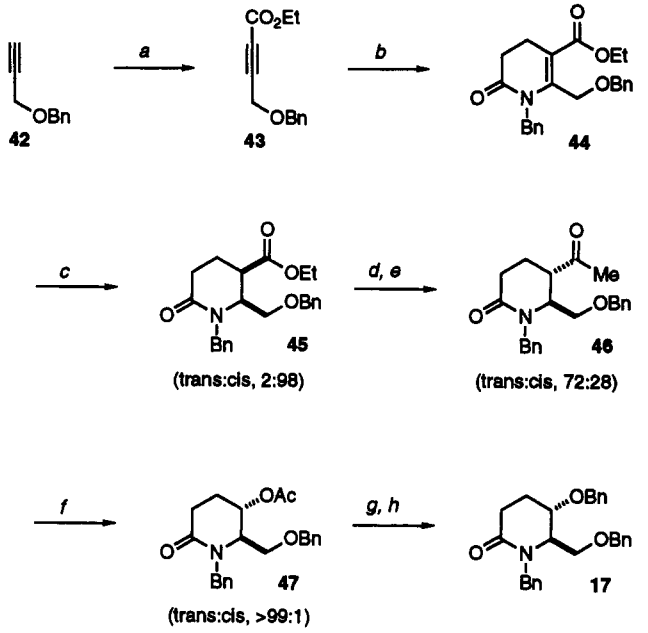
(19) The addition of Na_2CO_3 produced optimum results for cis selectivity, and prevented the removal of the benzyl protection of hydroxyl groups, when present. (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438. (b) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988.

Scheme 6. Homologation of 38[a]



[a] Reagents and conditions: (a) Lawesson's reagent (99%); (b) (i) EtO_2CCH_2Br, (ii) NEt_3, PPh_3 (79%).

Scheme 7. Synthesis of Intermediate 17[a]



[a] Reagents and conditions: (a) (i) BuLi, (ii) $ClCO_2Et$, (88%); (b) (i) $BnNH_2$, THF, 66 °C, (ii) acrylic anhydride, THF, 66 °C (62%); (c) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (80%); (d) NEt_3, MeMgBr; (e) DBU (68%, 2 steps from **45**); (f) CF_3CO_2H, *m*-CPBA (55%); (g) KOH, H_2O (85%); (h) KOH, BnBr (84%).

followed by $NaBH_4$ reduction, was used as a strategy for homologation of this system. With the use of PrMgBr, the reaction conditions resulted in formation of **36** as the only reaction product. In contrast, the addition of an acetylide followed by treatment with $NaBH_4$ gave **37** as a 63:37 ratio of diastereomers in 45% yield, with the balance of the substrate converted to **36**.[21] Unfortunately, extension of this methodology to the homologation of the methyl-substituted derivative **38a** was not effective.

An alternative route for carbonyl homologation of **38a** was explored through the Eschenmoser contraction/sulfide extrusion procedure.[22] Thiolactam formation of **38b** and alkylation with ethyl bromoacetate generated the corresponding thioimidate salt, and subsequent contraction/sulfide extrusion produced the corresponding vinylogous carbamate **39** (Scheme 6). Homologation of **38a** through this sequence provided an efficient and attractive route to **39** as a single isomer. On the basis of steric constraints, this isomer was designated as the corresponding *E* alkene isomer. Reduction with $NaBH_3CN$ transformed **39** to a mixture of diastereomers **40** and **41**, in a ratio of 92:8, while catalytic hydrogenation provided the complementary 15:85 ratio of these products.[23] Stereochemical assignments of **40** (8.0% enhancement) and **41** (5.6% enhancement) were established through NMR NOE techniques on each isomer by irradiation of the H and Me substituents α to the nitrogen (Scheme 6).

Applications to Alkaloid Synthesis. With the model studies complete for both construction and elaboration of **17**, two separate approaches to **17** were explored in which different substrates for enamine formation were used. The first approach to **17** involved the conjugate addition of $BnNH_2$ for generation of the β-enamino ester species required for aza-annulation (Scheme 7).[24] The reaction of $BnNH_2$ with **43**, prepared by deprotonation and ethoxycarboxylation of **42**, led to the corresponding β-enamino ester intermediate.[25] Treatment with acrylic anhydride resulted in aza-annulation to generate **44** in 62% yield for the two-step process, while the use of acryloyl chloride produced less favorable results for this transformation (35% yield). Catalytic hydrogenation of **44** in the presence of Na_2CO_3 stereoselectively generated **45** without deprotection of the hydroxyl group,[19] and treatment with NEt_3 followed by MeMgBr gave the corresponding methyl ketone (**46**) as a 2:98 ratio of trans/cis products.[26] Base-catalyzed epimerization changed the trans/cis ratio to 72:28, and Baeyer–Villiger oxidation under optimized conditions gave **47** as a single diastereomer. Deprotection of the secondary hydroxyl group, followed by benzylation, provided the desired intermediate **17**.

An alternative route to **17** involved condensation of $BnNH_2$ with tetronic acid (**48**) to form the required β-enamino ester intermediate (Scheme 8). Subsequent aza-annulation with acrylic anhydride (71%) or acryloyl chloride (70%) resulted in formation of the corresponding δ-lactam **49**. Catalytic hydrogenation generated the cis-fused bicyclic system **50**, and conversion of the lactone to methyl ketone **51** (2:>98, trans/cis) was performed under the same conditions used for the transformation of **45** to **46**. Benzylation of the hydroxyl group under basic conditions resulted in formation of an equilibrium mixture

(20) Jain, S.; Sujatha, K.; Rama Krishna, K. V.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *48*, 4985.

(21) (a) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. I* **1989**, 1211. (b) Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529.

(22) (a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665.

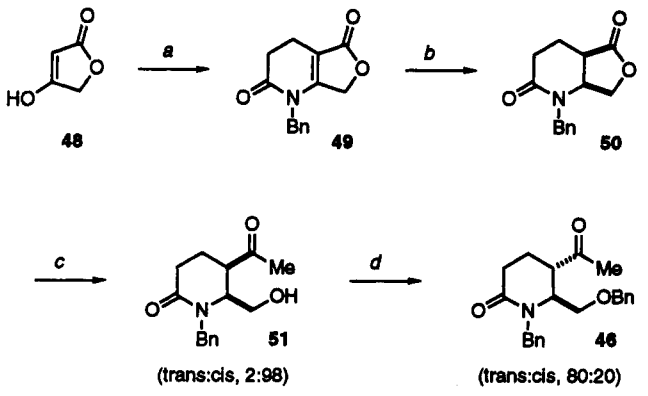
(23) Hydrogenation of **39** at 1 atm H_2 only proceeded to ~50% conversion after 48 h. The crude products consisted of a mixture of **39**, **40**, and **41** (15:85, respectively), and a small amount of the *N*-debenzylated analog. Reduction at higher pressures (3 atm) resulted in nearly complete removal of the *N*-benzyl group and gave the deprotected analogs of **40** and **41** in the same 15:85 ratio, respectively.

(24) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669.

(25) Analogous acylation of **42** with acetyl chloride, followed by conjugate addition of $BnNH_2$ in an attempt to access **46** by a more direct route, generated a mixture of both possible β-enamino ketone regioisomers.

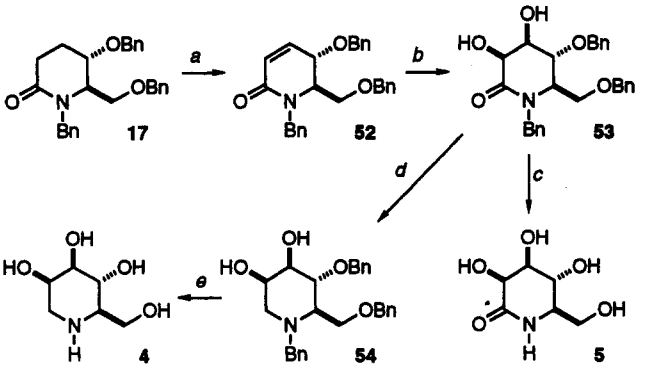
(26) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877.

Scheme 8. Conversion of 48 to 46[a]



[a] Reagents and conditions: (a) (i) $BnNH_2$, C_6H_6, 80 °C, (ii) acrylic anhydride, THF, 66 °C (71%); (b) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (83%); (c) NEt_3, MeMgBr (27%); (d) KOH, BnBr (71%).

Scheme 9. Synthesis of Deoxymannojirimycin (4) and Mannolactam (5)[a]



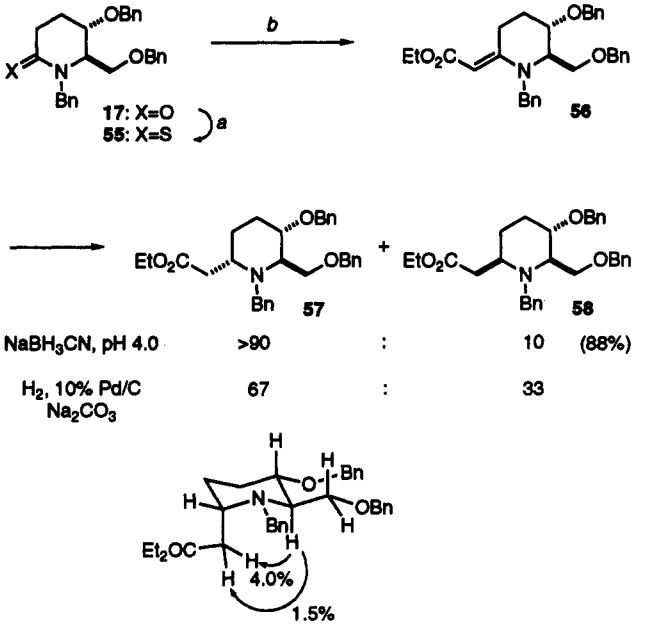
[a] Reagents and conditions: (a) (i) LDA, (ii) PhSeCl, (iii) $NaIO_4$ (78%); (b) OsO_4, NMO (64%); (c) Li/NH_3 (44%); (d) (i) $LiAlH_4$, (ii) NaOH, H_2O (>98%); (e) 1 atm of H_2, Pd/C, MeOH (52%).

of **46** (80:20, trans/cis). Although methods for a more efficient transformation of **50** to **51** were not fully pursued, this synthetic scheme provided an alternative route to **46**, and ultimately to **17**.

(±)-Mannonolactam (5) and (±)-Deoxymannojirimycin (4). The conversion of **17** to the tetrahydroxylated derivatives **4** and **5** was accomplished by introduction of the cis hydroxyl substituents through OsO_4 dihydroxylation (Scheme 9). Treatment of the anion of **17** with PhSeCl, followed by periodate oxidation and elimination of selenic acid, produced the α,β-unsaturated species **52**.[27] Dihydroxylation gave **53**, which was used for the syntheses of both **4** and **5**.[28] Removal of the benzyl protecting groups from **53** generated **5** in 44% yield after recrystallization.[29] Stepwise reduction of the lactam carbonyl followed by deprotection with catalytic hydrogenation gave **4** in 52% yield, and white crystalline material was obtained in 33% yield after recrystallization.[30] Overall, the syntheses of **4** and **5** were both achieved in 3% overall yield from **42**.

(±)-Prosopinine. Two representative *Prosopis* alkaloids, **7** and **8**, isolated from the leaves of the African

Scheme 10. Homologation of 17[a]



[a] Reagents and conditions: (a) Lawesson's reagent (94%); (b) (i) EtO_2CCH_2Br, (ii) NEt_3, PPh_3 (81%).

mimosa *Prosopis africana* Taub,[31] differ only in the stereochemistry of the carbon at which the alkyl chain and the heterocycle are connected. Although the synthesis of **7** has not been reported, synthetic efforts have resulted in the construction of desoxoprosopinine (**9**),[32] prosophylline (**8**),[33] and desoxoprosophylline (**10**).[32a,b,e] Due to the diastereomeric relationship of prosopinine (**7**) and prosophylline (**8**), our approach to the synthesis of these molecules was designed around the control of stereochemistry during homologation of the lactam. As observed during formation of **40** and **41**, stereochemical control was a function of the reagent used for reduction of the iminium ion generated from **39** (Scheme 6).

Homologation of the lactam carbonyl of **17** was performed in the same manner described for **38** (Scheme 6).[24] Formation of the thiolactam, followed by the Eschenmoser contraction/sulfide extrusion procedure, gave **56** in good overall yield (Scheme 10).[22] Hydride reduction of **56** selectively produced **57** in a >90:10 ratio of the two possible diastereomers, with the stereochemistry of the major product similar to that of **7**. In contrast to the results observed for **38**, catalytic hydrogenation of **56** also produced **57** as the major diastereomer. In this case, lower product selectivity was obtained (67:33, **57**/**58**), and selective formation of **58**, the intermediate related in structure to **8**, was not accomplished.

The final stages of the prosopinine synthesis required extension of the chain through Wittig methodology (Scheme 11). Further reduction of **57** generated **59**, which

(27) (a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (b) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

(28) (a) Nishiyama, S.; Yamamura, S.; Hasegawa, K.; Sakoda, M. Harada, K. *Tetrahedron Lett.* **1991**, *32*, 6753. (b) Guillerm, G.; Varkados, M.; Auvin, S.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 535.

(29) The physical data for **4** were consistent with those reported: Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.

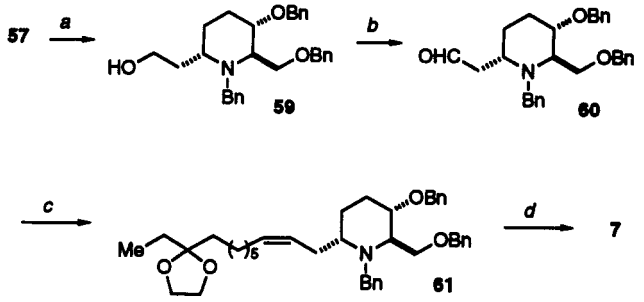
(30) The physical data for **5** were consistent with those reported:[29] Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327.

(31) (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. (c) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443.

(32) (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (c) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (d) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (e) Tadano, K.; Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Ogawa *Synlett* **1993**, 565.

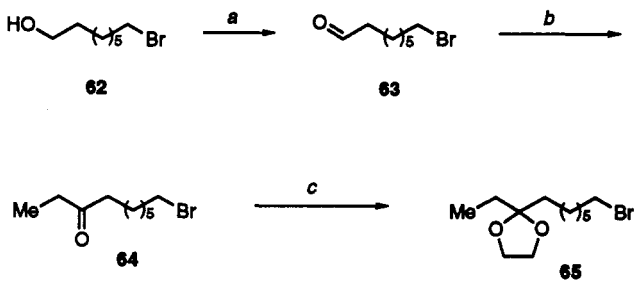
(33) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973.

Scheme 11. Conversion of 57 to 7[a]



[a] Reagents and conditions: (a) (i) $LiAlH_4$, (ii) NaOH (87%); (b) DMSO, $(COCl)_2$, NEt_3; (c) **65**, PPh_3, *n*-BuLi (55% from **59**); (d) (i) HCl, H_2O, (ii) 3 atm of H_2, Pd/C, HCl (90%).

Scheme 12. Preparation of 65[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2 (74%); (b) (i) EtMgBr, (ii) H_3O^+, (iii) PCC, CH_2Cl_2 (76% from **63**); (c) $HOCH_2CH_2OH$, H_2SO_4 (72%).

was then partially oxidized to the corresponding aldehyde **60**. Chain extension of **60** with the ylide formed from **65** (Scheme 12) gave **61** as a 15:85 mixture of trans/cis alkene isomers on the alkyl appendage. Deprotection of the carbonyl, followed by reduction of the alkene and debenzylation during hydrogenation, gave **7** in 3% overall yield from **42**.[34]

Summary. The aza-annulation of β-enamino ketone and ester substrates with either acryloyl chloride or acrylic anhydride has provided an efficient and convenient route for the regioselective construction of δ-lactams. This annulation procedure was performed in tandem with two different methods for enamine generation, through conjugate addition of $BnNH_2$ to an α,β-acetylenic ester or by condensation of $BnNH_2$ with a β-keto ester or ketone to form the desired δ-lactam. Once established, the δ-lactam framework was used to control the stereochemical preference of substituents on the ring, and the carbonyl functionality was transformed into a protected hydroxyl substituent. From δ-lactam **17**, the naturally occurring α-mannosidase inhibitors (±)-mannonolactam and (±)-deoxymannojirimycin were prepared. In addition, homologation of the lactam carbonyl of **17** also provided a route to the alkaloid (±)-prosopinine.

Experimental Section

General Methods. All reactions were carried out by performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were carried out under an atmosphere of either nitrogen or argon.[35] Azeotropic removal of H_2O was assisted by the use of 3- or 4-Å molecular sieves.[36] In each case, diastereomeric product ratios were determined by ^1H NMR.

Formation of 21. $BnNH_2$ (10.72 g, 100 mmol) was added to a solution of **20** (8.41 g, 100 mmol) in Et_2O (100 mL) at 0 °C. After the solution was warmed to rt, the mixture was stirred for 12 h. The mixture was then concentrated and dissolved in THF (600 mL), and acryloyl chloride (9.92 g, 110 mmol) was added at rt. After being heated for 16 h at reflux, the solution was washed with saturated aqueous $NaHCO_3$ (200 mL), and the aqueous layer was extracted with 3 × 200 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and purified by chromatography (70:30 petroleum ether/Et_2O) to give **21** (13.12 g, 53 mmol) in 53% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 4 H), 3.68 (s, 3 H), 4.71 (s, 2 H), 7.19–7.35 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.8, 30.7, 49.8, 51.5, 108.8, 127.6, 127.8, 128.8, 136.4, 139.4, 166.6, 169.6; IR (neat) 3080, 3065, 3032, 2951, 2905, 2849, 1690, 1649, 1439, 1377, 1294, 1254, 1184, 1121, 729, 700 cm^{-1}.

Formation of 26. Substrate **25** (1.32 g, 10 mmol) was dissolved in benzene (20 mL), and TsOH (15 mg) and H_2O (20 mL) were added. After the mixture was stirred at rt for 12 h, the solution was extracted with 2 × 20 mL of benzene, and the combined organic layers were dried ($MgSO_4$). The solution was filtered, $BnNH_2$ (1.071 g, 10 mmol) was added, and the mixture was heated at reflux for 48 h. Concentration gave the crude enamine, which was dissolved in THF (60 mL). Acryloyl chloride (1.11 g, 10 mmol) was added, and the solution was heated at reflux. After 20 h, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with 4 × 40 mL of Et_2O. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography (40:60 petroleum ether/Et_2O) to give **26** (0.517 g, 2.3 mmol) in 23% yield: mp 72–75 °C (from petroleum ether/Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3 H), 2.55–2.66 (m, 4 H), 4.76 (s, 2 H), 7.15 (s, 1 H), 7.20–7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 24.7, 30.6, 49.9, 119.4, 127.5, 128.0, 128.9, 136.2, 140.3, 169.8, 194.8; IR (neat) 3087, 3065, 3032, 3005, 2967, 2928, 2904, 2849, 1694, 1636, 1373, 1292, 1184, 702 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_2$ *m*/*z* 229.1103, found *m*/*z* 229.1109.

General Method for the Hydrogenation of Enamides. A mixture of enamide (1 equiv), Na_2CO_3 (3.0 equiv),[19] and 10% Pd on carbon (0.1 g/mmol enamide) in EtOH (0.05–0.2 M) was stirred under an atmosphere of H_2 (1–3 atm) for 16–48 h. The solids were removed by filtration, the mixture was concentrated, and the crude product was purified by chromatography.

22: 5.23 g, 21.66 mmol, 98% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (ddt, *J* = 6.0, 13.5, 9.6 Hz, 1 H), 2.12 (m, 1 H), 2.45 (ddd, *J* = 6.3, 9.6, 17.8 Hz, 1 H), 2.59 (ddd, *J* = 5.2, 6.3, 17.8 Hz, 1 H), 2.76 (dddd, *J* = 3.9, 5.8, 9.9, 12.4 Hz, 1 H), 3.36 (ddd, *J* = 1.1, 5.8, 12.4 Hz, 1 H), 3.42 (dd, *J* = 8.5, 12.4 Hz, 1 H), 3.63 (s, 3 H), 4.50 (d, *J* = 14.7 Hz, 1 H), 4.67 (d, *J* = 14.7 Hz, 1 H), 7.20–7.36 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8, 30.6, 38.9, 47.9, 50.0, 52.0, 127.4, 128.0, 128.5, 136.6, 168.8, 172.4; IR (neat) 3086, 3063, 3030, 2953, 2875, 1736, 1642, 1495, 1454, 1437, 1381, 1356, 1332, 1264, 1204, 1171, 1013, 727, 700 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_3$ *m*/*z* 247.1209, found *m*/*z* 247.1206.

27: 0.15 g, 0.65 mmol, 62% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79–1.94 (m, 2 H), 2.14 (s, 3 H), 2.49 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 2.59 (ddd, *J* = 17.8, 6.4, 4.4 Hz, 1 H), 2.79 (tdd, *J* = 9.9, 5.2, 3.8 Hz, 1 H), 3.29 (ddd, *J* = 12.6, 5.3, 1.4 Hz, 1 H), 3.41 (dd, *J* = 12.3, 9.3 Hz, 1 H), 4.47 (d, *J* = 14.7 Hz, 1 H), 4.73 (d, *J* = 14.7 Hz, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.79, 28.01, 30.96, 46.58, 47.17, 50.07, 127.40, 128.05, 128.52, 136.70, 168.63, 207.21; IR (oil/NaCl) 3032, 2932, 2876, 1713, 1642, 1495, 1455, 1262, 1167, cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ *m*/*z* 231.1259, found *m*/*z* 232.1251.

31: 8.19 g, 33.4 mmol, 81% yield, 90:10 (cis/trans); ^1H NMR (300 MHz, $CDCl_3$, cis isomer) δ 1.07 (d, *J* = 6.6 Hz, 3 H), 2.06 (s, 3 H), 1.92–2.17 (m, 4 H), 2.48 (ddd, *J* = 18.3, 10.4, 8.0 Hz,

(34) The physical and spectral data for **7** were consistent with those reported for **7** and **9**.[10,31–33]

(35) 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.

(36) Dehydration of condensation reactions was performed with the use of a modified Dean–Stark apparatus in which the cooled distillate was passed through either 3- or 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.

1 H), 2.61 (ddd, J = 18.3, 7.4, 2.0 Hz, 1 H), 2.79 (dt, J = 12.6, 4.2 Hz, 1 H), 3.84 (m, 1 H), 3.96 (d, J = 15.2 Hz, 1 H), 5.31 (d, J = 15.2 Hz, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 14.52, 17.33, 28.08, 29.96, 47.74, 51.03, 51.14, 127.04, 127.36, 128.28, 136.97, 168.67, 206.25; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ m/z 245.1416, found m/z 245.1415.

45: 0.63 g, 1.65 mmol, 80% yield, 98:2 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.13 (t, J = 7.2 Hz, 3 H), 2.03 (m, 1 H), 2.21 (ddt, J = 9.9, 7.8, 12.9 Hz, 1 H), 2.49 (ddd, J = 18.3, 10.0, 8.3 Hz, 1 H), 2.59 (ddd, J = 18.3, 7.8, 1.8 Hz, 1 H), 2.79 (dt, J = 15.0, 9.0 Hz, 1 H), 3.53 (d, J = 5.4 Hz, 2 H), 3.88–4.08 (m, 3 H), 4.15 (d, J = 15.2 Hz, 1 H), 4.37 (s, 2 H), 5.23 (d, J = 15.2 Hz, 1 H), 7.17–7.37 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 13.82, 19.18, 30.07, 42.40, 49.16, 56.17, 60.65, 68.62, 73.15, 127.19, 127.44, 127.59, 127.67, 128.19, 128.42, 137.22, 137.31, 169.56, 171.06; IR (oil/NaCl) 2959, 2870, 1734, 1645, 1173 cm^{-1}; HRMS calcd for $C_{23}H_{27}NO_4$ m/z 381.1940, found m/z 381.1988.

50: 0.36 g, 1.48 mmol, 79% yield, >98:2 (cis/trans); mp 98–101 °C (from petroleum ether/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 2.01 (m, 1 H), 2.30 (m, 1 H), 2.41 (m, 1 H), 2.52 (m, 1 H), 2.98 (m, 1 H), 4.18–4.30 (m, 4 H), 5.13 (d, J = 15.0 Hz, 1 H), 7.14–7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 19.88, 29.68, 37.85, 47.94, 55.20, 71.23, 127.93 (2), 128.97, 136.15, 169.49, 176.09; IR (solid/KBr) 3032, 2959, 2946, 2922, 1788, 1644, 1470, 1451, 1362, 1163 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_3$ m/z 245.0896, found m/z 245.1054.

Hydrolysis of 22. A solution of **22** (3.00 g, 12.0 mmol) and NaOH (0.96 g, 24.0 mmol) in a mixture of THF (50 mL) and H_2O (200 mL) was stirred for 20 h at rt, and the mixture was adjusted to pH <3.0 by addition of concd HCl. The mixture was extracted with 3 × 75 mL of $CHCl_3$, and the combined organic layers were dried ($MgSO_4$) and concentrated to give **23** (2.52 g, 10.8 mmol) in 90% yield: mp 156–157 °C (from $CHCl_3$/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (m, 1 H), 2.13 (m, 1 H), 2.50 (ddd, J = 6.3, 9.3, 17.9 Hz, 1 H), 2.63 (dt, J = 17.9, 5.5 Hz, 1 H), 2.76 (m, 1 H), 3.38 (dd, J = 5.8, 12.5 Hz, 1 H), 3.43 (dd, J = 8.5, 12.5 Hz, 1 H), 4.43 (d, J = 14.6 Hz, 1 H), 4.74 (d, J = 14.6 Hz, 1 H), 7.16–7.35 (m, 5 H), 11.24 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.6, 30.4, 38.8, 48.0, 50.5, 127.6, 128.1, 128.7, 136.2, 170.0, 175.7; IR (neat) 3070, 3029, 2930, 2872, 2780, 2670, 2492, 1940, 1713, 1591, 1455, 1421, 1375, 1302, 1223, 980, 752, 698 cm^{-1}; HRMS calcd for $C_{13}H_{15}NO_3$ m/z 233.1052, found m/z 233.1039.

General Procedure for DBU Epimerization. To a 90:10 solution of *cis*-**31**/*trans*-**31** (0.20 g, 1.12 mmol) in THF (2.2 mL) was added DBU (0.09 g, 0.56 mmol), and the mixture was stirred at rt. After 16 h, the reaction was quenched by addition of 3 mL of H_2O. The organic layers were separated, concentrated, and purified by chromatography (Et_2O) to give **31**.

***trans*-31**: 0.20 g, 0.82 mmol, >99% yield, 28:72 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (trans isomer) δ 1.22 (d, J = 6.6 Hz, 1 H), 1.89 (s, 3 H), 1.91–2.12 (m, 3 H), 2.35–2.63 (m, 3 H), 3.82 (m, 1 H), 4.01 (d, J = 15.2 Hz, 1 H), 5.23 (d, J = 15.2 Hz, 1 H), 7.22–7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (trans isomer) δ 19.53, 19.86, 27.47, 29.39, 46.98, 51.14, 52.26, 126.93, 127.78, 128.10, 136.97, 168.87, 207.05; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ m/z 245.1416, found m/z 245.1415.

***trans*-46** (from **51**): 0.20 g, 0.57 mmol, >99% yield, 17:83 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (trans isomer) δ 1.89 (s, 3 H), 1.95 (m, 1 H), 2.04 (m, 1 H), 2.44 (dt, J = 17.7, 6.5 Hz, 1 H), 2.58 (ddd, J = 17.7, 7.5, 6.5 Hz, 1 H), 2.95 (dt, J = 6.3, 4.8 Hz, 1 H), 3.42–3.52 (m, 2 H), 3.94 (m, 1 H), 4.10 (d, J = 15.0 Hz, 1 H), 4.37 (d, J = 1.5 Hz, 2 H), 5.14 (d, J = 15.0 Hz, 1 H), 7.16–7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (trans isomer) δ 19.93, 27.27, 29.58, 47.78, 47.98, 55.17, 69.36, 72.81, 127.01, 127.30, 127.45, 127.53, 127.82, 128.12, 136.91, 137.15, 169.86, 207.06; IR (oil/NaCl) 3088, 2924, 1713, 1644, 1161, 1101 cm^{-1}; HRMS calcd for $C_{22}H_{25}NO_3$ m/z 351.1835, found m/z 351.1818.

General Procedure for Baeyer–Villiger Oxidation. To a solution of **27** (0.10 g, 0.43 mmol) in CH_2Cl_2 (1 mL) were added *m*-CPBA (0.39 g, 2.25 mmol) and CF_3COOH (0.05 g, 0.43 mmol) at rt, and the reaction was heated at reflux. After 14 h, the reaction was cooled and concentrated, and the resulting slurry was purified by chromatography (Et_2O) to give **28**.

28: 0.069 g, 0.28 mmol, 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.02–2.08 (m, 2 H), 2.52 (ddd, J = 17.9, 6.0, 5.3 Hz, 1 H), 2.67 (ddd, J = 17.9, 9.6, 7.1 Hz, 1 H), 3.26 (ddd, J = 13.2, 3.9, 1.3 Hz, 1 H), 3.43 (dd, J = 13.2, 3.9 Hz, 1 H), 4.49 (d, J = 14.7 Hz, 1 H), 4.71 (d, J = 14.7 Hz, 1 H), 5.12 (dq, J = 3.8, 3.6 Hz, 1 H), 7.21–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97, 25.49, 27.86, 49.80, 50.46, 66.17, 127.49, 127.99, 128.60, 136.56, 168.73, 170.18; IR (oil/NaCl) 3063, 2959, 2873, 1738, 1646, 1491, 1365, 1421, 1238, 1182, 1075 cm^{-1}.

32: 4.49 g, 17.2 mmol, 41% yield; mp 66–67 °C (from petroleum ether/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 6.9 Hz, 3 H), 1.89 (s, 3 H), 1.97 (m, 1 H), 2.16 (dddd, J = 14.7, 11.4, 7.5, 2.7 Hz, 1 H), 2.51 (ddd, J = 18.3, 7.5, 2.1 Hz, 1 H), 2.66 (ddd, J = 18.3, 11.4, 7.5 Hz, 1 H), 3.46 (qt, J = 6.7, 2.0 Hz, 1 H), 3.80 (d, J = 15.3 Hz, 1 H), 4.88 (dt, J = 3.9, 2.1 Hz, 1 H), 5.46 (d, J = 15.3 Hz, 1 H), 7.20–7.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.80, 20.75, 21.03, 26.81, 47.18, 54.38, 70.07, 127.19, 127.72, 128.32, 136.95, 168.57, 169.89; IR (NaCl) 2975, 2942, 1736, 1634, 1482, 1246, 1179 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_3$ m/z 261.1365, found m/z 261.1363.

47: 0.59 g, 1.63 mmol, 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3 H), 1.94 (m, 1 H), 2.17 (dddd, J = 13.8, 10.8, 7.8, 3.0 Hz, 1 H), 2.51 (ddd, J = 18.3, 7.6, 2.7 Hz, 1 H), 2.63 (ddd, J = 18.3, 10.8, 7.6 Hz, 1 H), 3.45–3.60 (m, 3 H), 3.92 (d, J = 15.3 Hz, 1 H), 4.43 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 5.16 (m, 1 H), 5.39 (d, J = 15.3 Hz, 1 H), 7.18–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.86, 22.30, 27.00, 48.12, 58.52, 67.97, 68.74, 73.31, 127.37, 127.63, 127.92, 128.01, 128.44, 128.50, 136.91, 137.31, 169.72, 169.96; IR (oil/NaCl) 3063, 2934, 2869, 1738, 1647, 1240, 1181 cm^{-1}; HRMS calcd for $C_{22}H_{25}NO_4$ m/z 367.1784, found m/z 367.1768.

Formation of 33. To a solution of **32** (0.10 g, 0.383 mmol) in H_2O (0.6 mL) was added crushed NaOH (0.04 g, 1.12 mmol), and the reaction was heated at approximately 50 °C for 12 h. After this time, the product was extracted from the reaction mixture with 6 × 1 mL of $CHCl_3$. The organic layers were combined and dried, and the solvent was removed under reduced pressure. The product was recrystallized from Et_2O/petroleum ether to give **33** (0.062 g, 0.283 mmol) in 74% yield: mp 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6.6 Hz, 3 H), 1.88 (m, 1 H), 1.95–2.12 (m, 2 H), 2.42 (ddd, J = 18.0, 7.1, 2.8 Hz, 1 H), 2.71 (ddd, J = 18.0, 10.8, 7.4 Hz, 1 H), 3.34 (m, 1 H), 3.83 (dt, J = 4.8, 2.8 Hz, 1 H), 3.95 (d, J = 15.2 Hz, 1 H), 5.35 (d, J = 15.2 Hz, 1 H), 7.20–7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.37, 24.05, 26.92, 47.42, 57.96, 68.45, 127.23, 127.78, 128.56, 137.33, 169.42; IR (oil/NaCl) 3289, 3023, 2890, 1609, 1453, 1175, cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_2$ m/z 219.1259, found m/z 219.1245.

Preparation of Thioamides. Lawesson's reagent (0.5 equiv) was added to a solution of the lactam (1.0 equiv) in THF (0.4 M), and the mixture was stirred for 4–12 h. After evaporation of the solvent, the nonvolatile mixture was diluted with EtOAc (3 times the volume of THF), and the solution was washed sequentially with 3 portions of saturated aqueous $NaHCO_3$ ($^1/_3$ the volume of EtOAc) followed by 2 portions of saturated aqueous NaCl ($^1/_5$ the volume of EtOAc). The aqueous layers were combined and extracted with 2 portions of EtOAc ($^1/_2$ the volume of EtOAc). All organic layers were combined and then dried (Na_2SO_4). Purification by chromatography (Et_2O) afforded the pure thiolactam.

34: 5.36 g, 20.4 mmol, 99% yield; mp 63–65 °C (from Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (ddt, J = 5.8, 13.7, 9.1 Hz, 1 H), 2.00 (dq, J = 13.7, 5.8 Hz, 1 H), 2.78 (m, 1 H), 2.97 (ddd, J = 6.3, 8.8, 18.2 Hz, 1 H), 3.14 (dt, J = 18.2, 5.8 Hz, 1 H), 3.42–3.56 (m, 2 H), 3.56 (s, 3 H), 5.12 (d, J = 14.5 Hz, 1 H), 5.40 (d, J = 14.5 Hz, 1 H), 7.18–7.29 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0, 38.6, 40.3, 50.0, 52.0, 57.1, 127.6, 127.7, 128.5, 134.8, 172.0, 199.7; IR (neat) 3080, 3030, 2951, 2860, 1734, 1514, 1453, 1348, 1200, 1169, 1043, 704 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2S$ m/z 263.0980, found m/z 263.0962.

38b: 2.28 g, 7.82 mmol, 99% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6.6 Hz, 3 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.93–2.13 (m, 2 H), 2.77 (ddd, J = 4.7, 5.8, 11.5 Hz, 1 H), 3.14 (dt, J = 8.5, 19.5 Hz, 1 H), 3.29 (ddd, J = 3.3, 6.6, 19.5 Hz, 1 H), 3.98

(dq, J = 5.8, 6.6 Hz, 1 H), 4.09 (q, J = 7.1 Hz, 2 H), 4.45 (d, J = 14.8 Hz, 1 H), 6.23 (d, J = 14.8 Hz, 1 H), 7.23–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.7, 18.3, 40.0, 43.5, 54.9, 55.8, 61.0, 127.5, 127.7, 128.7, 135.3, 170.8, 199.8; IR (neat) 3087, 3061, 2980, 2938, 1732, 1497, 1452, 1348, 1171, 961, 708 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_2S$ m/z 291.1293, found m/z 291.1341.

55: 1.45 g, 3.36 mmol, 94% yield; mp 81–82 °C (from Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–2.05 (m, 2 H), 3.10 (ddd, J = 4.4, 6.1, 19.0 Hz, 1 H), 3.30 (ddd, J = 7.1, 9.6, 19.0 Hz, 1 H), 3.49 (dd, J = 6.6, 10.2 Hz, 1 H), 3.58 (dd, J = 4.4, 10.2 Hz, 1 H), 3.85 (m, 1 H), 3.91 (m, 1 H), 4.24 (d, J = 11.8 Hz, 1 H), 4.35 (d, J = 11.8 Hz, 1 H), 4.40–4.50 (m, 3 H), 6.45 (d, J = 15.1 Hz, 1 H), 7.14–7.40 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7, 37.3, 55.5, 61.1, 69.1, 70.0, 72.2, 73.3, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.5, 135.2, 137.1, 137.7, 201.8; IR (neat) 3100, 3090, 3031, 2940, 2867, 1497, 1453, 1345, 1173, 1073, 1028, 733, 696 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_2S$ m/z 431.1919, found m/z 431.1887.

General Method for Eschenmoser Sulfide Contraction. The thiolactam (1.0 equiv) and $BrCH_2CO_2Et$ (1.2 equiv) were stirred in Et_2O (1 M) for 24–36 h. After removal of solvent, the thionium salt was dissolved in CH_3CN (0.2 M), and PPh_3 (1.2 equiv) was added. The mixture was allowed to stir for 10 min, NEt_3 (1.5 equiv) was added, and the solution was heated to reflux. After 26 h, the solids were removed by filtration, and the resultant solution was concentrated. Chromatography (90:10 to 70:30 petroleum ether/Et_2O) provided the pure enaminoesters.

39: 0.426 g, 1.23 mmol, 79% yield; mp 69–71 °C (from petroleum ether/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.89–2.11 (m, 2 H), 2.86–3.00 (m, 2 H), 3.62 (ddd, J = 3.1, 6.7, 18.7 Hz, 1 H), 3.80 (quint, J = 6.3 Hz, 1 H), 3.99 (dq, J = 3.4, 7.0 Hz, 2 H), 4.02 (dq, J = 3.4, 7.0 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 4.26 (d, J = 16.5 Hz, 1 H), 4.55 (d, J = 16.5 Hz, 1 H), 4.63 (s, 1 H), 7.17 (d, J = 7.0 Hz, 2 H), 7.22–7.37 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.5, 14.6, 17.0, 25.4, 44.1, 54.0, 54.8, 58.2, 60.6, 85.7, 126.4, 127.1, 128.6, 136.1, 159.8, 168.6, 171.8; IR (neat) 3100, 3080, 3030, 2978, 2920, 2870, 1734, 1682, 1561, 1136, 1060, 1030, 966, 791, 727, 696 cm^{-1}; HRMS calcd for $C_{20}H_{27}NO_4$ m/z 345.1940, found m/z 345.1939.

56: 1.22 g, 2.51 mmol, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 2.95 (dt, J = 18.1, 6.2 Hz, 1 H), 3.41 (dd, J = 6.7, 9.7 Hz, 1 H), 3.50 (m, 1 H), 3.51 (dd, J = 4.5, 9.7 Hz, 1 H), 3.61 (ddd, J = 2.8, 4.4, 7.1 Hz, 1 H), 3.86 (ddd, J = 3.0, 4.4, 6.9 Hz, 1 H), 3.98 (dq, J = 3.8, 7.1 Hz, 1 H), 4.01 (dq, J = 3.8, 7.1 Hz, 1 H), 4.35 (d, J = 16.5 Hz, 1 H), 4.41 (s, 2 H), 4.43 (d, J = 14.6 Hz, 1 H), 4.52 (d, J = 14.6 Hz, 1 H), 4.53 (d, J = 16.5 Hz, 1 H), 4.60 (s, 1 H), 7.18–7.36 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 22.2, 22.3, 53.9, 58.2, 62.5, 70.1, 70.2, 73.2, 73.3, 84.8, 126.6, 127.0, 127.4, 127.5, 127.6, 127.8, 128.3, 128.4, 128.5, 136.3, 137.6, 138.2, 161.7, 168.9; IR (neat) 3100, 3080, 3031, 2980, 2934, 2867, 1680, 1561, 1497, 1455, 1362, 1142, 1094, 1073, 735, 696 cm^{-1}; HRMS calcd for $C_{31}H_{35}NO_4$ m/z 485.2567, found m/z 485.2559.

Formation of 43. To a solution of **42** (1.20 g, 8.19 mmol) in THF (16 mL) was added BuLi (3.28 mL, 2.5 M in hexane) at −78 °C. After the mixture was stirred for 10 min, $ClCO_2Et$ (0.89 g, 8.19 mmol) was added dropwise. The reaction was slowly warmed to 0 °C (until a deep red color began to form) and was then promptly quenched by addition of H_2O. The organic phase was separated, and the solvent was removed under reduced pressure to produce a crude oil, which was purified by chromatography (petroleum ether) to give **43** (1.61 g, 7.39 mmol) in 91% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.25 (s, 2 H), 4.59 (s, 2 H), 7.22–7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 56.53, 61.90, 71.81, 78.07, 82.94, 127.87, 127.90, 128.29, 136.59, 152.87; IR (oil/NaCl) 3032, 2984, 2872, 2236, 1713, 1248 cm^{-1}.

Aza-Annulation Procedure for Formation of 44. To a solution of **43** (1.61 g, 7.37 mmol) in THF (15 mL) was added $BnNH_2$ (0.70 g, 7.37 mmol) at rt, and the reaction was heated at reflux for 12 h. After the mixture was cooled to rt, acrylic anhydride (1.7 equiv) was added, and the reaction was heated at reflux for 14 h.[37] The solution was then cooled to rt and concentrated, and the crude product was purified by chromatography (10:90 Et_2O/petroleum ether) to give **44** (1.73 g, 4.56 mmol) in 62% yield: mp 84–87 °C (from Et_2O/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3 H), 2.49–2.58 (m, 2 H), 2.62–2.71 (m, 2 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.57 (s, 2 H), 4.60 (s, 2 H), 5.12 (s, 2 H), 6.97–7.03 (m, 2 H), 7.16–7.39 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 21.69, 30.82, 44.51, 60.76, 63.56, 72.65, 113.54, 126.06, 126.97, 127.93, 128.07, 128.42, 128.63, 137.61, 137.90, 146.08, 166.71, 170.92; IR (NaCl) 2984, 1682, 1636, 1269, 1130 cm^{-1}; HRMS calcd for $C_{23}H_{25}NO_4$ m/z 379.1784, found m/z 379.1777.

General Procedure for Conversion of Ester to Methyl Ketone Functionality. To a solution of MeMgBr (2.27 mL, 3.0 M in THF) in benzene (19 mL) was added NEt_3 (2.06 g, 20.4 mmol) at 0 °C. After 10 min, a solution of **45** (1.25 g, 3.41 mmol) in benzene (5 mL) was added with vigorous stirring, and the mixture was stirred for 3 h at 0 °C. The reaction was quenched by addition of 25 mL of 3 M aqueous HCl. The organic layer was separated and concentrated, and the resulting crude oil was purified by chromatography (Et_2O) to give **46**.

***cis*-46** (from **45**): 0.56 g, 1.60 mmol, 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.87 (m, 1 H), 2.02 (s, 3 H), 2.12 (m, 1 H), 2.32–2.64 (m, 2 H), 2.71 (dt, J = 13.2, 4.1 Hz, 1 H), 3.42 (dd, J = 9.9, 7.5 Hz, 1 H), 3.50 (dd, J = 9.9, 4.1 Hz, 1 H), 3.94 (m, 1 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.30 (d, J = 1.8 Hz, 2 H), 5.28 (d, J = 15.0 Hz, 1 H), 7.16–7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 18.07, 28.30, 29.82, 48.85, 49.63, 55.82, 67.89, 72.90, 127.12, 127.34, 127.49, 128.03, 128.11, 128.29, 136.91, 137.04, 169.23, 205.36; IR (oil/NaCl) 3088, 2924, 1713, 1644, 1161, 1101 cm^{-1}; HRMS calcd for $C_{22}H_{25}NO_3$ m/z 351.1835, found m/z 351.1818.

51: 0.17 g, 0.65 mmol, 25% yield, >98:2 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.90 (m, 1 H), 1.91 (s, 3 H), 2.10 (m, 1 H), 2.40 (dt, J = 17.7, 6.8 Hz, 1 H), 2.54 (dt, J = 17.7, 6.8 Hz, 1 H), 3.03 (dt, J = 6.6, 4.8 Hz, 1 H), 3.57 (dd, J = 11.6, 3.8 Hz, 2 H), 3.65 (dd, J = 11.4, 6.3 Hz, 1 H), 3.82 (m, 1 H), 3.92 (bs, 1 H), 4.08 (d, J = 15.0 Hz, 1 H), 5.19 (d, J = 15.0 Hz, 1 H), 7.21 (bd, J = 7.8 Hz, 2 H), 7.20–7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 20.11, 25.58, 29.86, 47.49, 48.03, 57.15, 61.87, 127.45, 127.91, 128.54, 136.91, 171.06, 207.88; IR (oil/NaCl) 3374, 3088, 2942, 1711, 1613, 1455, 1256, 1169 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_3$ m/z 261.1365, found m/z 261.1354.

Formation of 17. To a solution of **47** (0.30 g, 0.80 mmol) in H_2O (1.1 mL) was added crushed KOH (0.20 g, 0.52 mmol) at rt, and the reaction was heated at approximately 50 °C. After 12 h, the product was extracted from the reaction mixture with 6 × 2 mL of $CHCl_3$. The organic layers were combined and concentrated, and the resulting crude alcohol was purified by chromatography (Et_2O) to give an oil (0.22 g, 0.68 mmol) in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 1 H), 2.00 (dddd, J = 12.6, 9.9, 6.9, 3.0, 1 H), 2.37 (ddd, J = 18.3, 6.9, 4.8 Hz, 1 H), 2.64 (ddd, J = 16.8, 9.3, 6.9 Hz, 2 H), 3.39 (m, 1 H), 3.40 (s, 1 H), 3.51 (m, 1 H), 4.07 (d, J = 15.3 Hz, 1 H), 4.10 (bs, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 5.18 (d, J = 15.3 Hz, 1 H), 7.16–7.38 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.16, 27.37, 48.09, 62.13, 65.65, 69.42, 73.27, 127.15, 127.58, 127.71, 127.86, 128.45, 128.46, 137.23, 137.44, 170.28; IR (oil/NaCl) 3364 (br), 3063, 2928, 1617, 1453, 1181, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_3$ m/z 325.1678, found m/z 325.1666.

To a solution of the alcohol (0.50 g, 2.05 mmol) in Et_2O (4 mL) were added crushed KOH (0.23 g, 4.10 mmol) and molecular sieves (0.40 g) at rt. After 5–10 min of stirring, BnBr (0.39 g, 2.26 mmol) was added. The reaction was quenched after 3 h by addition of excess H_2O, and the mixture was extracted with 10 × 4 mL of Et_2O. The organic layers were combined and concentrated, and the resulting crude oil was purified by chromatography (Et_2O) to give **17** (0.57 g, 1.37 mmol) in 84% yield: mp 60–63 °C (from $CHCl_3/Et_2O$); ^{1}H NMR (300 MHz,

(37) Acrylic anhydride was prepared immediately prior to use by adding NaH (1.8 equiv) to acrylic acid (1.2 equiv) at −78 °C and allowing the mixture to warm to rt. Acryloyl chloride (1.0 equiv) was then added, and the mixture was stirred for 1 h. This mixture was transferred to the reaction vessel *via* cannula.

$CDCl_3$) δ 1.91–2.02 (m, 2 H), 2.40 (ddd, J = 18.0, 6.2, 3.9 Hz, 1 H), 2.69 (ddd, J = 18.0, 10.4, 8.5 Hz, 1 H), 3.39 (dd, J = 9.9, 7.2 Hz, 1 H), 3.52 (dd, J = 9.9, 3.9 Hz, 1 H), 3.65 (m, 1 H), 3.83 (dd, J = 6.2, 3.9 Hz, 1 H), 3.99 (d, J = 15.3 Hz, 1 H), 4.26 (d, J = 12.0 Hz, 1 H), 4.35 (d, J = 12.0 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.41 (d, J = 12.0 Hz, 1 H), 5.36 (d, J = 15.3 Hz, 1 H), 7.14–7.36 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.18, 27.22, 47.69, 58.37, 69.16, 69.77, 71.79, 73.03, 126.87, 127.07, 127.28, 127.37, 127.56, 127.65, 128.05, 128.21, 128.26, 137.06, 137.36, 137.85, 169.93; IR (NaCl) 3088. 3030, 2867, 1642, 1453, 1096 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_3$ m/z 415.2148, found m/z 415.2142.

Formation of 52. To a solution of **17** (1.00 g, 2.41 mmol) in THF (16 mL) was added BuLi (1.06 mL, 2.5 M in THF) at −78 °C. After 10 min, PhSeCl (0.51 g, 2.65 mmol) in THF (8 mL) was added and the reaction mixture allowed to warm to 0 °C for 3 min. The reaction was quenched by addition of 25 mL of H_2O, and the mixture was extracted with 4 × 10 mL of Et_2O. The combined organic layers were concentrated under reduced pressure. The residue was taken up in MeOH/THF/H_2O (16:8:1, 25 mL), and $NaIO_4$ (1.55 g, 7.23 mmol) was added. After this mixture was stirred for 14 h, the reaction was diluted with 25 mL of H_2O, and the mixture was extracted with 10 × 10 mL of Et_2O. The organic layers were combined and concentrated to give a crude solid, which was purified by recrystallization from Et_2O/petroleum ether to give **52** (0.78 g, 1.88 mmol) in 78% yield: mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, J = 9.2 Hz, 1 H), 3.48 (dd, J = 9.8, 5.0 Hz, 1 H), 3.84 (m, 1 H), 4.00 (d, J = 15.5 Hz, 1 H), 4.08 (dd, J = 5.9, 1.4 Hz, 1 H), 4.27 (d, J = 12.0 Hz, 1 H), 4.33 (d, J = 12.0 Hz, 1 H), 4.40 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 5.37 (d, J = 15.5 Hz, 1 H), 6.15 (d, J = 9.6 Hz, 1 H), 6.47 (ddd, J = 9.6, 5.9, 1.1 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.19–7.38 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.07, 57.40, 68.07, 68.60, 70.11, 73.24, 127.32, 127.52, 127.69, 127.75, 127.87, 128.04, 128.24, 128.29, 128.44, 128.51, 134.59, 136.91, 137.40, 137.52, 162.29; IR (NaCl) 3088, 2870, 1669, 1611, 1455, 1262, 1146, 1092 cm^{-1}; HRMS calcd for $C_{27}H_{27}NO_3$ m/z 413.1991, found m/z 413.1999.

Formation of 53. To a solution of **52** (0.10 g, 0.24 mmol) in *t*-BuOH (1.4 mL) were added NMO (excess) and OsO_4 (0.96 mL, 0.05 M in *t*-BuOH) at rt. After 3 h, the reaction was quenched by addition of excess solid Na_2SO_3. Solvent was removed under reduced pressure until the reaction color began to turn gray. The resulting mixture was purified by chromatography (solvent gradient: Et_2O to 50:50 Et_2O/MeOH) to give **53** (0.069 g, 0.154 mmol) in 64% yield: mp 95–98 °C (from Et_2O/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, J = 1.8 Hz, 1 H), 3.61–3.78 (m, 3 H), 3.84 (d, J = 1.2 Hz, 1 H), 3.97 (t, J = 3.1 Hz, 1 H), 4.32 (d, J = 15.6, 1 H), 4.37 (td, J = 3.6, 2.1 Hz, 1 H), 4.41 (s, 2 H), 4.42 (m, 1 H), 4.44 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 5.27 (d, J = 15.6 Hz, 1 H), 7.11–7.21 (m, 4 H), 7.21–7.39 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) 47.56, 58.98, 68.11, 68.85, 69.57, 71.48, 73.13, 75.21, 127.39, 127.55, 127.65, 127.74, 127.83, 128.23, 128.35, 128.41, 128.53, 136.83, 137.19, 137.43, 171.20 δ ; IR (NaCl) 3409, 3088, 3031, 2869, 1645, 1455, 1250, 1074 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_5$ m/z 447.2046, found m/z 447.2046.

Formation of 5. To a solution of **53** (0.06 g, 0.13 mmol) in NH_3 (4 mL) was added Li metal at −78 °C until the solution turned a persistent deep blue. After 3 h at reflux, the solution was cooled to −78 °C and then the reaction was quenched by the addition of solid NH_4Cl. The mixture was then allowed to warm to rt. Once NH_3 removal was complete, the reaction mixture was extracted with 10 × 2 mL of a 2:1 solution of $CHCl_3$/MeOH and then filtered. Solvent removal under reduced pressure produced a solid, which was dissolved in a minimum amount of MeOH and purified by chromatography (90:10 $CHCl_3$/MeOH) to give **5** (0.010 g, 0.057 mmol) in 44% yield: mp 163–168 °C (from $CHCl_3$/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (td, J = 6.3, 3.9 Hz, 1 H), 3.59 (dd, J = 11.9, 5.9 Hz, 1 H), 3.68 (dd, J = 11.7, 5.1 Hz, 1 H), 3.72 (t, J = 6.2 Hz, 1 H), 3.89 (dd, J = 5.7, 3.9 Hz, 1 H), 4.20 (d, J = 3.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 57.30, 61.11, 67.20, 68.14, 71.94, 173.17; IR (oil/NaCl) 3287, 3063, 2941, 2890, 2834, 1609, 1453, 1281, 1175, 1032 cm^{-1}; HRMS calcd for $C_6H_{11}NO_5$ m/z 177.0637, found m/z 176.0481.

Formation of 54. To a solution of **53** (0.07 g, 0.16 mmol) in Et_2O (1.6 mL) was added excess $LiAlH_4$ at rt. After 3 h, the reaction was quenched at 0 °C *via* slow addition of 15% aqueous NaOH until all visible $LiAlH_4$ had been consumed. The reaction was filtered, dried, and concentrated to give a crude oil, which was purified by chromatography (Et_2O) to give **54** (0.069 g, 0.16 mmol) in >98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 2.21 (dd, J = 12.2, 1.5 Hz, 1 H), 2.38 (dt, J = 8.7, 2.6 Hz, 1 H), 2.82 (bs, 2 H), 2.91 (dd, J = 12.2, 4.4 Hz, 1 H), 3.27 (d, J = 12.9 Hz, 1 H), 3.55 (dd, J = 8.4, 3.3 Hz, 1 H), 3.64 (t, J = 8.6 Hz, 1 H), 3.73 (m, 1 H), 3.76 (dd, J = 10.4, 2.6 Hz, 1 H), 3.83 (dd, J = 10.4, 2.6 Hz, 1 H), 4.16 (d, J = 13.2 Hz, 1 H), 4.45 (s, 1 H), 4.56 (d, J = 11.1 Hz, 2 H), 4.90 (d, J = 11.1 Hz, 1 H), 7.20–7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.71, 56.67, 64.76, 66.87, 68.10, 73.26, 74.61, 75.90, 78.42, 127.16, 127.65, 127.74, 127.79, 127.97, 127.99, 128.40, 128.94, 137.85, 138.52, 138.60; IR (oil/NaCl) 3422, 3063, 2923, 1495, 1453, 1098 cm^{-1}; HRMS calcd for $C_{27}H_{31}NO_4$ m/z 433.2253, found m/z 433.2253.

Formation of 4. To a solution of **54** (0.08 g, 0.18 mmol) in EtOH (2 mL) was added 10% Pd on carbon (0.18 g) and concd HCl (1.8 mL), and the mixture was placed under an atmosphere of H_2 and stirred at rt. After 14 h, the reaction mixture was filtered and the solvent removed under reduced pressure to give **4** (0.014 g, 0.094) as a crude solid (52% yield), which was recrystallized to give pure **4** (0.009 g, 0.059 mmol) in 33% yield: mp 184–186 °C (from MeOH/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (ddd, J = 9.9, 6.6, 3.0 Hz, 1 H), 3.10 (dd, J = 13.8, 1.3 Hz, 1 H), 3.27 (dd, J = 13.8, 3.0 Hz, 1 H), 3.55 (dd, J = 9.6, 3.0 Hz, 1 H), 3.70 (dd, J = 12.3, 6.0 Hz, 1 H), 3.74 (t, J = 6.8 Hz, 1 H), 3.85 (dd, J = 12.3, 3.5 Hz, 1 H), 4.10 (m, 1 H).

General Method for the $NaBH_3CN$ Reduction of Enaminoesters. To a solution of the enamino ester (1.0 equiv) and bromocresol green (trace amounts as an indicator) in MeOH (0.2 M) was added $NaBH_3CN$ (1.0 equiv). A 5% methanolic HCl solution was added dropwise until a yellow color persisted in solution. While the reaction mixture was stirred for 2 h, periodic addition of HCl was made to maintain a yellow color. The mixture was then diluted with CH_2Cl_2 (5 times the volume of MeOH), washed with 10% aqueous $NaHCO_3$ (1/2 the volume of CH_2Cl_2), and the organic phase was dried over Na_2SO_4. The solvent was evaporated and chromatography (70:30 petroleum ether/Et_2O) afforded the pure piperidines.

40 and 41: 0.110 g, 0.318 mmol, 100% yield, mixture of **40/41** (>90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major isomer) 0.98 (d, J = 6.9 Hz, 3 H), 1.13 (t, J = 7.1 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H), 1.37 (dq, J = 5.2, 12.4 Hz, 1 H), 1.56 (dq, J = 13.2, 3.0 Hz, 1 H), 1.72–1.92 (m, 2 H), 2.19 (dd, J = 7.4, 14.8 Hz, 1 H), 2.46 (dd, J = 6.9, 14.8 Hz, 1 H), 2.78 (dt, J = 4.9, 11.8 Hz, 1 H), 3.22 (dq, J = 4.7, 6.9 Hz, 1 H), 3.34 (m, 1 H), 3.67 (s, 2 H), 3.93–4.12 (m, 4 H), 7.12–7.31 (m, 5 H); (minor isomer) 0.93 (d, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.3 Hz, 3 H), 1.20 (t, J = 7.3 Hz, 3 H), 1.62–1.77 (m, 3 H), 1.84 (m, 1 H), 2.34 (dd, J = 10.3, 14.2 Hz, 1 H), 2.65 (dd, J = 3.4, 14.2 Hz, 1 H), 2.73 (m, 1 H), 3.22–3.35 (m, 2 H), 3.75 (s, 2 H), 4.06 (q, J = 7.3 Hz, 2 H), 4.08 (q, J = 7.3 Hz, 2 H), 7.17–7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major isomer) 10.4, 14.1, 21.2, 28.2, 40.1, 41.5, 50.7, 51.9, 53.2, 60.1, 60.4, 126.6, 127.8, 128.2, 140.6, 172.1, 174.1; IR (neat) 3087, 3063, 3029, 2980, 2940, 2874, 2853, 1734, 1495, 1453, 1370, 1200, 1152, 1034, 733, 698 cm^{-1}; HRMS calcd for $C_{20}H_{29}NO_4$ m/z 347.2097, found m/z 347.2113.

57: 0.619 g, 1.27 mmol, 88% yield, mixture of isomers (>90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major isomer) 1.17 (t, J = 7.2 Hz, 3 H), 1.53–1.78 (m, 3 H), 1.99 (m, 1 H), 2.43 (dd, J = 8.7, 14.2 Hz, 1 H), 2.60 (dd, J = 5.3, 14.2 Hz, 1 H), 2.95 (dt, J = 7.0, 4.5 Hz, 1 H), 3.24 (m, 1 H), 3.54 (dt, J = 4.2, 7.5 Hz, 1 H), 3.71 (m, 3 H), 4.03 (m, 1 H), 4.04 (q, J = 7.2 Hz, 2 H), 4.36 (s, 2 H), 4.42 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 7.16–7.38 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major isomer) 14.1, 24.7, 25.4, 33.9, 52.7, 59.2, 60.2, 68.8, 70.8, 72.9, 74.2, 126.5, 127.3, 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.4, 138.4, 138.8, 140.7, 172.6; IR (neat) 3087, 3063, 3031, 2980, 2936, 2865, 1732, 1495, 1452, 1368, 1290, 1157, 1096, 1028,

737, 698 cm^{-1}; HRMS calcd for $C_{31}H_{37}NO_4$ m/z 487.2723, found m/z 487.2708.

Reduction of 57 to 59. To a solution of **57** (0.167 g, 0.342 mmol) in Et_2O was added $LiAlH_4$ (0.1 g, 2.63 mmol), and the mixture was stirred for 2 h. The reaction was quenched by addition of H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL), and H_2O (0.3 mL). After the mixture was stirred for 1 h, the solution was filtered, and the solvents were evaporated to give **59** (0.133 g, 0.298 mmol) in 87% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 1 H), 1.27 (s, 1 H), 1.41 (m, 1 H), 1.68 (m, 1 H), 1.94 (m, 1 H), 2.09 (m, 1 H), 2.27 (m, 1 H), 2.91 (m, 1 H), 3.40 (dt, J = 2.2, 10.5 Hz, 1 H), 3.48–3.68 (m, 3 H), 3.62 (d, J = 13.2 Hz, 1 H), 3.74 (dd, J = 8.0, 9.9 Hz, 1 H), 3.86 (dd, J = 3.7, 9.9 Hz, 1 H), 4.11 (d, J = 13.2 Hz, 1 H), 4.41 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 4.58 (d, J = 12.1 Hz, 1 H), 4.61 (d, J = 11.5 Hz, 1 H), 7.20–7.38 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 26.6, 30.9, 50.6, 54.4, 57.1, 62.9, 68.2, 70.4, 72.3, 73.3, 126.9, 127.3, 127.4, 127.6, 128.3, 129.0, 138.2, 138.7, 140.0; IR (neat) 3405, 3087, 3063, 3029, 2936, 2861, 1495, 1455, 1100, 1075, 733, 698 cm^{-1}; HRMS calcd for $C_{29}H_{35}NO_3$ m/z 445.9956, found m/z 445.2619.

Swern Oxidation of 59 to 60. To a solution of oxalyl chloride (0.057 g, 0.45 mmol) in CH_2Cl_2 at −70 °C was added a solution of DMSO (0.070 g, 0.90 mmol) in CH_2Cl_2 (1 mL). After 10 min, a solution of **59** (0.133 g, 0.297 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to stir for 45 min at −65 °C, and then NEt_3 (0.182 g, 1.8 mmol) was added. After the mixture was stirred for 20 min at −65 °C, it was warmed to rt for 1 h. The mixture was quenched with 10% aqueous $NaHCO_3$ and then extracted with 3 × 10 mL of CH_2Cl_2. The solvents were evaporated and the aldehyde was used immediately without further purification.

Wittig Homologation of 60 to 61. A mixture of **65** (0.168 g, 0.6 mmol) and PPh_3 (0.157 g, 0.6 mmol) was heated at reflux in toluene (2 mL) for 48 h. After the solution was cooled to rt, the solvent was removed under vacuum and THF (2 mL) was added. A solution of BuLi (2.5 M in hexane, 0.24 mL, 0.6 mmol) was added to the phosphonium salt at −78 °C and the mixture was stirred for 15 min at −78 °C and then stirred for 1 h at rt. The resulting ylide solution was cooled to −78 °C and **60** (0.137 g, 0.296 mmol) in THF (1 mL) was added. After the mixture was warmed to −45 °C over 2 h, it was stirred at that temperature for an additional 1 h, warmed to 0 °C for 3 h, and stirred an additional 2 h at rt. The reaction was quenched with H_2O (10 mL) and then the solution extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The oil was purified by chromatography (90:10 to 80:20 petroleum ether/Et_2O) to give **61** (0.102 g, 0.163 mmol) in 55% yield (cis/trans 85:15): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3 H), 1.20–1.38 (m, 8 H), 1.44–1.75 (m, 6 H), 1.88–2.20 (m, 4 H), 2.22–2.35 (m, 2 H) 2.58 (m, 1 H, trans isomer), 2.69 (m, 1 H), 2.83 (dt, J = 7.4, 3.8 Hz, 1 H, trans isomer), 3.01 (dt, J = 7.4, 4.3 Hz, 1 H), 3.54 (m, 1 H), 3.68–3.78 (m, 3 H), 3.91 (s, 4 H), 4.06 (d, J = 14.0 Hz, 1 H, trans isomer), 4.08 (d, J = 13.7 Hz, 1 H), 4.39 (s, 2 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.43 (d, J = 11.5 Hz, 1 H, trans isomer), 4.55 (d, J = 11.5 Hz, 1 H, trans isomer), 4.56 (d, J = 11.5 Hz, 1 H), 5.21 (m, 1 H), 5.34 (m, 1 H), 7.16–7.41 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (cis isomer) 8.1, 23.7, 25.0, 25.4, 27.4, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.5, 55.0, 58.9, 64.9, 68.7, 70.8, 72.9, 74.6, 112.1, 126.4, 127.2, 127.3, 127.4, 127.6, 128.0, 128.3, 128.4, 131.1, 138.4, 138.8, 141.1; (trans isomer) 8.1, 23.5, 25.0, 27.2, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.4, 54.8, 58.8, 64.9, 68.7, 70.8, 72.9, 74.6, 112.0, 126.2, 126.9, 127.3, 127.4, 127.7, 127.8, 128.2, 128.3, 128.4, 131.3, 138.4, 138.9, 141.2; IR (neat) 3100, 3080, 3029, 2930, 2855, 1453, 1075, 733, 696 cm^{-1}; HRMS calcd for $C_{41}H_{55}NO_4$ m/z 625.4131, found m/z 625.4112.

Preparation of 7. To a solution of **61** (0.099 g, 0.158 mmol) in THF (8 mL) was added 10% aqueous HCl (4 mL). After the mixture was stirred for 2 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2CO_3) and concentrated. In preparation for hydrogenation, the residue was dissolved in EtOH (10 mL), and concd HCl (20 drops) was added. To this mixture was added 10% Pd on carbon (0.05 g), and the solution was stirred under H_2 (3 atm) for 24 h. The mixture was filtered and concentrated. The residue was dissolved in 20 mL of $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and extracted with 4 × 20 mL of $CHCl_3$, and the combined organic layers were dried over Na_2SO_4. Filtration through basic alumina with $CHCl_3$ and MeOH, followed by removal of solvent, produced crystals, which were washed with a minimum amount of acetone and dried under vacuum to give **7** (0.045 g, 0.142 mmol) in 90% yield as white crystals: mp 88–89 °C (from acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3 H), 1.23–1.41 (m, 13 H), 1.44–1.61 (m, 5 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 2.07 (bs, 3 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.41 (q, J = 7.3 Hz, 2 H), 2.76 (m, 1 H), 2.87 (dt, J = 5.5, 7.7 Hz, 1 H), 3.53 (ddd, J = 4.0, 5.6, 6.9 Hz, 1 H), 3.61 (dd, J = 5.4, 10.5 Hz, 1 H), 3.65 (dd, J = 7.8, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8, 23.9, 26.3, 27.4, 28.6, 29.2, 29.3, 29.4, 29.6, 33.9, 35.8, 42.4, 49.7, 58.1, 62.3, 68.1, 212.0; IR (neat) 3320, 2926, 2855, 1717, 1460, 1377, 1275, 1119, 1073, 723 cm^{-1}; HRMS calcd for M-1 of $C_{18}H_{35}NO_3$ m/z 312.2540, found m/z 312.2540.

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. G.R.C. acknowledges BASF Corporation for a Graduate Research Fellowship. 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: Experimental procedures for **24**, **36**, **37**, **49**, **63**, **64**, and **65** and copies of ^1H NMR spectra of all compounds in the Experimental Section (49 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.