Asymmetric Conjugate Additions to Chiral Bicyclic Lactams. A Stereoselective General Synthesis of Chiral 3-Aminopyrrolidines

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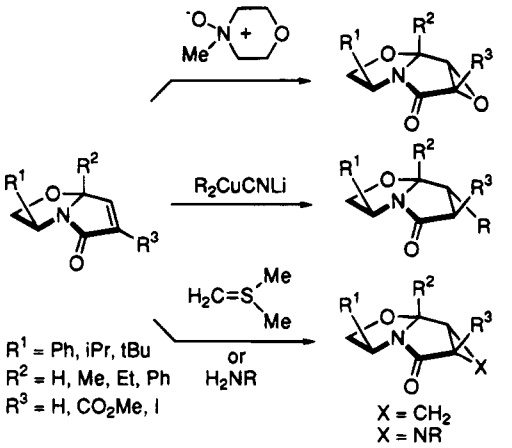
Stereoselective, conjugate additions of primary amines to chiral bicyclic lactams are described. Typical yields ranged from 80% to 90% with facial diastereoselectivities ranging from 95:5 to >98:2. Several optically pure amino bicyclic lactams were transformed by reductive cleavage, in two steps, to chiral 3-aminopyrrolidines.

The 3-aminopyrrolidine moiety is a ubiquitous system found in a diverse number of compounds displaying an impressive range of biological activities.[1] Such compounds include the antitumor complex **1** and the psychotropic drug **2**. A number of syntheses of 3-aminopyrrolidines have been reported; however, these lead to optically impure products,[2] rely on resolution of a racemate,[3] or lack generality.[4] In our continuing efforts to expand the utility of chiral bicyclic lactam chemistry, we envisioned that conjugate addition of amines to bicyclic lactam **3**, followed by subsequent reductive cleavage of the bicyclic system, would yield 3-aminopyrrolidines **4** in a concise fashion. Conjugate addition of other nucleophiles (Scheme 1) to the chiral bicyclic lactams has been previously observed in our laboratory leading to a host of stereospecifically substituted *endo* epoxides,[5a] *endo* alkylations,[5b] *endo* cyclopropanations,[5c] and *endo* aziridines.[5d]

Scheme 1



Although conjugate amine addition to a variety of α,β-unsaturated carbonyl moieties is well precedented, addition of amines to unsaturated lactam systems is less well known.[6] Herein, we report a facile and stereoselective conjugate amine addition to selected bicyclic lactams and the subsequent elaboration of the resulting adducts **5** to yield chiral, nonracemic 3-aminopyrrolidines **11**, **12**, and **16**.

Table 1 displays the results of addition of various amines to the bicyclic lactams **3**. The stereochemistry of the major diastereomer resulting from conjugate amine addition to the lactams was found to be *endo*. This assignment was supported by nuclear Overhauser effect (NOE) correlation of amino lactam **5b** with related lactam **6** which possesses known stereochemistry.[7] Lactam **6** demonstrated a 5.2% C-7 methine hydrogen signal enhancement upon irradiation of the angular methyl group. Similarly, lactam **5b** displayed a 5.6% C-7 methine signal enhancement upon angular methyl group irradiation.

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

(1) For biologically active molecules containing the 3-aminopyrrolidine moiety, see: (a) Iwanami, S.; Mutsuo, T.; Yasufumi, H.; Osamu, H.; Shinji, U. *J. Med. Chem.* **1981**, *24*, 1224. (b) Okada, T.; Ezumi, K.; Yamakawa, M.; Sato, H.; Tsuji, T.; Tsushima, T.; Motokawa, K.; Komatus, Y. *Chem. Pharm. Bull.* **1993**, *41*, 126. (c) Bouzard, D.; Cesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 518. (d) Takamatsu, M.; Matsui, M.; Ikeda, Y. Eur. Pat. Appl. EP 327, 709; *Chem. Abstr. 113,* 71314t. (e) Harrison, B. L.; Baron, B. M. Eur. Pat. Appl. EP 398, 283, 1990; *Chem. Abstr. 114,* 185–466v. (f) Petersen, U.; Krebs, A.; Schenke, T.; Grohe, K.; Schriewer, M.; Haller, I.; Metzger, K. G.; Endermann, R.; Zeiler, H. J. *Eur. Pat. Appl. EP 401, 623,* 1990; *Chem. Abstr. 114,* 207234x.

(2) (a) Gallina, C.; Marta, C.; Colombo, C.; Romeo, A. *Tetrahedron* **1971**, *27*, 4685. (b) Gallina, C.; Koch, V.; Romeo, A. *Tetrahedron Lett.* **1969**, *35*, 3055. (c) Hausler, J. *Liebigs Ann. Chem.* **1981**, 1073.

(3) (a) Takeshi, H.; Yokoyama, T.; Nakazono, K.; Okada, M. Jpn. Kokai Tokkoyo Koho, 02, 218, 664, 1990; *Chem. Abstr. 114,* 81579t. (b) Kogoori, Y.; Wakayama, M.; Tetsuya, S.; Sato, Y. Jpn. Kokai Tokkyo Koho JP 04, 360, 866, 1992; *Chem. Abstr. 119,* 17093b.

(4) (a) Hassner, A.; Eliezer, F.; Nudelman, A.; Albeck, A.; Gottlieb, H. *Tetrahedron Lett.* **1994**, *35*, 2397. (b) Morimoto, Y.; Kazuo, A. *Chem. Pharm. Bull.* **1987**, *35*, 3845. (c) Williams, R. M.; Fegley, G. J. *Tetrahedron Lett.* **1992**, *33*, 6755. (d) Croucher, P. D.; Furneaux, R. H.; Lynch, G. P. *Tetrahedron* **1994**, *50*, 13299.

(5) (a) Andres, C. J.; Spetseris, N.; Norton, J. R.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 1613. (b) Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 36. (c) Romo, D.; Meyers, A. I. *Tetrahedron Lett.* **1989**, *30*, 1745. (d) Andres, C. J.; Meyers, A. I. *Tetrahedron Lett.*, in press.

(6) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: New York, 1992; p 283.

(7) Romo, D. Ph.D. Dissertation, Colorado State University, 1991.

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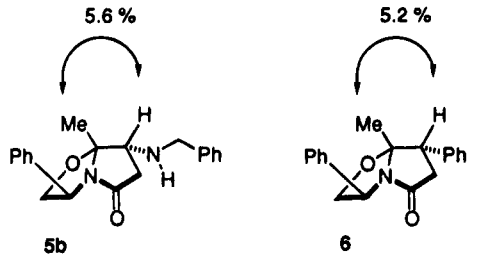
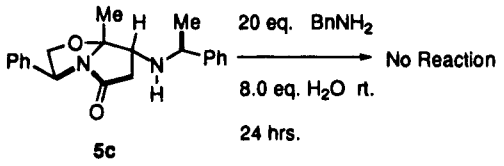
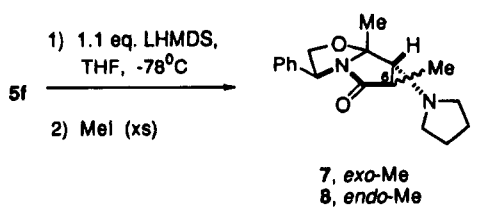


Subsequent experiments revealed two essential features for the optimization of the amine addition: (a) water was essential to drive the amine addition to completion, and (b) complete reaction required 8 equiv of amine. By providing a proton source for the resulting enolate from amine addition, water assists in facile protonation which drives the reaction to completion. The workup conditions also allowed for complete recovery of the excess amine, thus minimizing loss of the amine component.

The product of the amine addition to the lactam appears to be the kinetically controlled product and was shown to be highly resistant to reversal. Thus, when lactam adduct **5c** was treated with 20.0 equiv of benzylamine and 8.0 equiv of water for 24 h, **5c** was recovered, unchanged, in 92% yield. This behavior demonstrates that the amino lactam adduct, once formed, does not appear to undergo reversal to the unsaturated lactam precluding the possibility of thermodynamic factors responsible for the stereochemical result.



In order to ascertain whether the specifically generated enolate would result in reversal of the amine addition, pyrrolidino lactam **5f** was subjected to 1.1 equiv of lithium hexamethyldisilazane (−78 °C) and treated with excess iodomethane. None of the unsaturated lactam **3** (R = Me) was recovered, and only the methylated lactams **7** and **8** were formed as a 2:1 mixture of C-6 epimers. Although alkylation selectivity was low, the diastereomers **7** and **8** were readily separable via chromatography. Thus, amino lactam alkylation at C-6 demonstrates the potential of also functionalizing the 4 position of the 3-aminopyrrolidine moiety which would result from removal of the chiral auxiliary (*vide infra*).



It was also of interest to assess the importance of double diastereoselectivity during the conjugate amine addition. In this regard we examined the behavior of several chiral primary amines. Examination of Table 1 reveals the lack of sensitivity of the lactam addition to stereochemical properties of the amine (entries 2−4). Since we had considered the addition of only primary amines up to this juncture, we also were concerned with

Table 1. Conjugate Addition of Amines to Unsaturated Bicyclic Lactams 5

Entry	R^1	Amine	Yield (%)	Product	Selectivity[a]
1	Me	$tBuNH_2$	82	**5a**	95:5
2	Me	$PhCH_2NH_2$	84	**5b**	95:5
3	Me	H_2N, Ph, Me (S)	83	**5c**	95:5
4	Me	H_2N, Ph, Me (R)	85	**5d**	95:5
5	Ph	H_2N, Ph, Me (S)	89	**5e**	>98:2
6	Me	HN	89	**5f**	>98:2
7	Me	HN, HO	82	**5g**	>98:2
8	Me	H_2N, Me	81	**5h**	95:5
9	Me	H_2N	80	**5i**	95:5

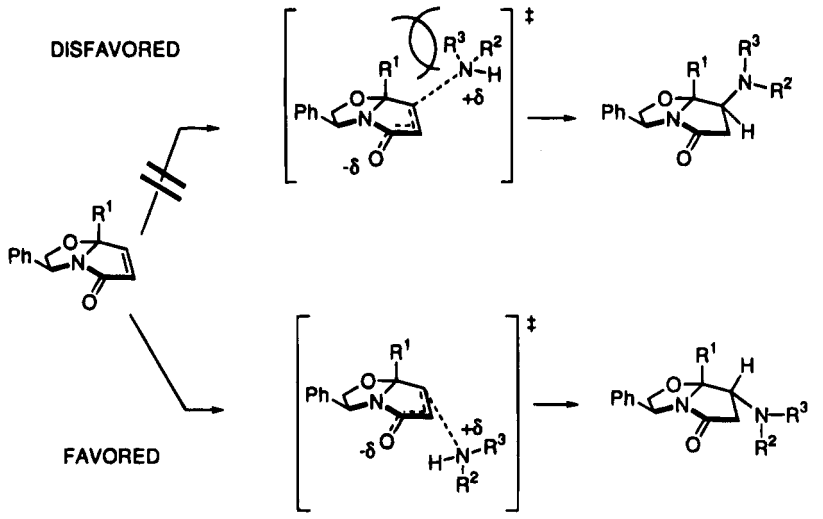
[a] Determined by NMR.

the suitability of using secondary amines and assessing the effect of a more sterically encumbered nucleophile. When the amine was changed from a primary amine (entry 3) to the sterically conjested secondary amine (entry 6), the selectivity of *endo*−*exo* addition increased from 95:5 to >98:2. Thus, bulkier nucleophiles are seemingly sensitive to the facial selectivity. Similarly, when the angular substituent in the lactam was changed from methyl to phenyl (entry 5), the selectivities from the reaction with the same primary amine changed from 95:5 (entry 3) to >98:2 (entry 5). We can now propose a general model to rationalize the observed selectivity, and this is presented in Scheme 2. Increasing the size of the angular substituent (R^1) results in increased interaction with the incoming amine component on the *exo* face. On the other hand, increasing the steric bulk of the amine (R^2 or R^3) also causes increased steric interaction with the angular substituent on the *exo* face thus favoring *endo* entry. For these steric effects to be so critical to the stereochemical outcome suggests strongly that this addition process leading to the amino lactams proceeds through a late (product-like) transition state.

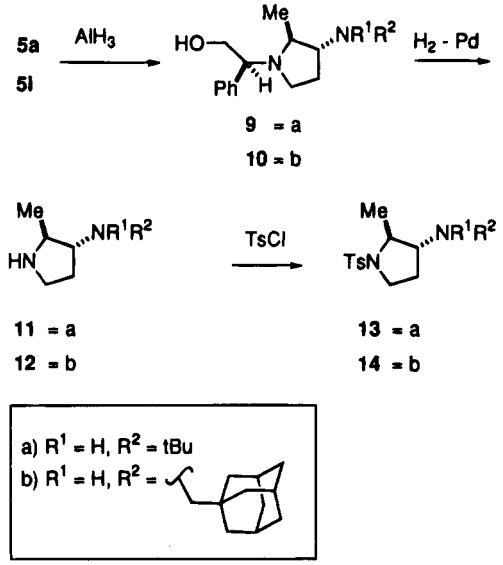
It now was important to demonstrate the synthetic utility of the amine additions above, and in this regard several lactams were transformed into chiral 3-aminopyrrolidines. The method employed was related to a previous procedure used in our laboratory.[8] Thus, reduction of lactam **5a** with $LiAlH_4$−$AlCl_3$ yielded a 20:1 (NMR) mixture of epimeric *N*-(hydroxymethyl)benzylpyrrolidines **9**. Chromatography gave optically pure **9** in 81% yield. Similarly, treatment of the adamantyl

(8) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656.

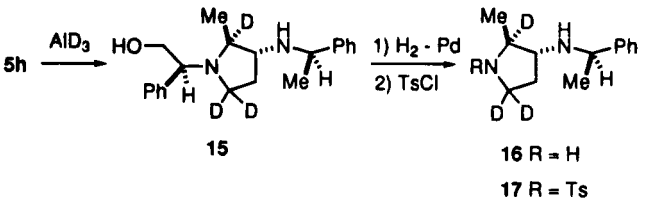
Scheme 2



lactam **5i** with $LiAlH_4$–$AlCl_3$ gave a 20:1 (NMR) mixture of epimeric N-substituted pyrrolidines. Chromatography resulted in a 75% yield of optically pure **10**. The N-substituted pyrrolidines **9** and **10** were transformed into chiral 3-aminopyrrolidines **11** and **12** by hydrogenolysis with palladium hydroxide on carbon. For purposes of characterization, aminopyrrolidines **11** and **12** were converted to their crystalline toluenesulfonamides **13** (62%, two steps) and **14** (56%, two steps) by treatment with Hunig's base/*p*-toluenesulfonyl chloride in anhydrous dichloromethane.[9] The absolute stereochemistry of the aminopyrrolidine **13** was confirmed by anamolous dispersion X-ray crystallographic determination and shown to be as drawn.[10]



Specifically deuteriated chiral aminopyrrolidines were also found to be accessible from chiral amino lactams. Thus, treatment of lactam **5h** with deuterated alane (from $LiAlD_4$–$AlCl_3$) afforded a 15:1 (NMR) mixture of epimeric deuteriobenzylpyrrolidines, **15**. Chromatography provided specifically deuteriated optically pure material in 70% yield. The latter was transformed into chiral 2,5,5-trideuteriated aminopyrrolidine **16** by hydrogenolysis, as above, and converted to the sulfonamide **17** (62%, two steps) to allow for ready characterization.



In summary, facile, stereoselective conjugate amine additions to chiral bicyclic lactams have been demonstrated. These additions tolerated a considerable variety of amines and gave high yields of amine adducts. The resulting amino lactams were readily converted into chiral 2-alkyl-3-aminopyrrolidines or their deuteriated derivative. The wide variety of tolerated amines, coupled with the previously demonstrated ability to vary the angular substituent,[8] and the availability of both lactam antipodes in optically pure form make this an attractive method for the synthesis of chiral 3-aminopyrrolidines.

Experimental Section[11]

Conjugate Amine Additions Using the Amine as a Solvent—General Procedure. (+)-7-(*S*)-*tert*-Butylamino Lactam 5a. A 20 mL scintillation vial was fitted with a small magnetic stirring bar and the unsaturated lactam **3** (R^1 = Me) (0.42 g, 1.95 mmol) was added. *tert*-Butylamine (3.5 mL, 33 mmol) was syringed into the vial, and stirring was initiated. Distilled water (0.3 mL, 16 mmol) was added to the reaction mixture, and the vial was capped. After 12 h, the amine solution was deposited on a silica gel column and eluted with 1:1 hexanes/ether to provide 0.48 g (82%) of lactam **5a** as a colorless solid: $[\alpha]^{23}_D$ = +120.6° (*c* 1.9, $CHCl_3$); mp 122–124

(9) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.
(10) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge, CB2 1EZ, U.K.

(11) THF was distilled from sodium metal, while CH_2Cl_2 was used unpurified or distilled from calcium hydride. Reaction flasks, when specified, were flame-dried under vacuum and placed under dry argon prior to use. Amines were purchased from Aldrich, Fluka, and Lancaster chemical companies and utilized as received. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. All rotations were determined at 589 nm at 23 °C. Flash chromatography was conducted according to the method of Still.[12] Combustion analyses were difficult to obtain on **11**, **12**, and **16**. Instead, compounds **11**, **12**, and **16** were transformed into their sulfonamides **13**, **14**, and **17** and analyzed in this form.
(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

°C; IR (neat) 3313, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 9 H), 1.41 (s, 3 H), 1.65 (s, 1 H), 2.37 (d, 1 H, J = 17 Hz), 2.99 (dd, 1 H, J = 17 Hz), 3.41 (m, 1 H), 4.18 (dd, 1 H), 4.56 (t, 1 H, J = 8.2 Hz), 5.23 (t, 1 H, J = 7.0 Hz), 7.29 (m, 5 H); ^{13}C NMR δ 24.1, 30.1, 44.3, 50.8, 56.4, 58.1, 73.7, 100.6, 126.0, 127.7, 128.9, 140.3, 178.9. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.36. Found: C, 70.54; H, 8.41.

(+)-7-(*S*)-Benzylamino Lactam 5b. 5b was prepared using the same general procedure. Thus, 0.30 g (1.39 mmol) of unsaturated lactam **3** was treated with 3.0 mL (27.8 mmol) of benzylamine and 0.20 mL (11 mmol) of distilled water. Chromatography of the crude product (1:1 hexanes/ether) yielded 0.37 g (84%) of lactam **5b** as a clear liquid: $[\alpha]^{23}_D$ = +96.8° (*c* 2.8, $CHCl_3$); IR (neat) 3328, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 1 H), 1.95 (s, 1 H), 2.42 (d, 1 H, J = 17 Hz), 2.90 (dd, 1 H, J = 17 Hz), 3.33 (d, 1 H, J = 4.6 Hz), 3.79 (q, 2 H, J = 28 Hz), 4.30 (dd, 1 H, J = 8.2 Hz), 4.50 (m, 1 H), 5.23 (m, 1 H), 7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.2, 40.7, 51.6, 57.7, 62.6, 74.3, 100.9, 126.4, 127.4, 127.8, 128.4, 128.8, 128.9, 139.9, 177.3; MS *m*/*z* (rel intensity) 323 (M + 1, 100), 233 (30), 162 (30), 108 (80), 52 (50).

(+)-7-(*S*)-((*S*)-Methylbenzylamino) Lactam (5c). 5c was prepared using the general procedure. Thus, 0.30 g (1.39 mmol) of unsaturated lactam **3** was treated with (*S*)-methylbenzylamine (3.36 mL, 27.8 mmol) and 0.20 mL (11 mmol) of distilled water. Chromatography of the crude product (1:1 hexanes/ether) yielded 0.39 g (83%) of lactam **5c** as a clear yellow liquid: $[\alpha]^{23}_D$ = +72.5° (*c* 3.5, $CHCl_3$); IR (neat) 3326, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.36 (dd, 3 H, J = 6.65 Hz), 2.08 (s, 1 H), 2.45 (dd, 1 H, J = 17 Hz), 2.77 (dd, 1 H, J = 17 Hz), 3.07 (dd, 1 H), 3.77 (q, 1 H, J = 6.6 Hz), 4.27 (dd, 1 H, J = 8.3 Hz), 4.55 (t, 1 H, J = 7.9 Hz), 5.24 (m, 1 H), 7.29 (m, 10 H); ^{13}C NMR δ 24.6, 25.2, 40.2, 55.1, 57.9, 59.5, 74.2, 100.6, 126.2, 126.7, 127.4, 127.8, 128.9, 140.1, 145.2, 178.1; MS *m*/*z* (rel intensity) 337 (M + 1, 10), 162 (10), 122 (40), 52 (100).

(+)-7-(*S*)-((*R*)-Methylbenzylamino) Lactam (5d). 5d was prepared using the same procedure as for **5a**. Thus, 0.30 g (1.39 mmol) of unsaturated lactam **3** was treated with (*R*)-methylbenzylamine (3.36 mL, 27.8 mmol) and 0.20 mL (11 mmol) of distilled water. Chromatography of the crude product (1:1 hexanes/ether) yielded 0.40 g (85%) of lactam **5d** as a white foam: $[\alpha]^{23}_D$ = +156.9° (*c* 1.6, $CHCl_3$); IR (neat) 3321, 1708 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 1.34 (d, 3 H, J = 6.6 Hz), 1.37 (s, 3 H), 1.85 (s, 1 H), 2.14 (dd, 1 H, J = 17 Hz), 2.83 (dd, 1 H, J = 17 Hz), 3.24 (dd, 1 H), 3.95 (q, 1 H, J = 6.6 Hz), 4.28 (dd, 1 H, J = 8.4 Hz), 4.61 (m, 1 H), 5.24 (m, 1 H), 7.27 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 25.2, 41.8, 57.2, 57.7, 60.8, 74.0, 101.1, 126.2, 127.1, 127.4, 127.8, 128.8, 128.9, 140.1, 145.8, 177.6; MS *m*/*z* (rel intensity) 337 (M + 1, 50).

(+)-7-(*S*)-((*S*)-Methylbenzylamino) Lactam 5e. 5e was prepared using the general procedure. Thus, 0.18 g (0.69 mmol) of unsaturated lactam **3a** (R^1 = Ph) was treated with (*S*)-methylbenzylamine (1.68 mL, 13.3 mmol) and 0.10 mL (6 mmol) of distilled water. Chromatography (1:1 hexanes/ether) yielded 0.24 g (89%) of lactam **5e** as a white foam: $[\alpha]^{23}_D$ = +32.2° (*c* 0.6, $CHCl_3$); IR (neat) 3060, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, 3 H, J = 6.7 Hz), 2.25 (s, 1 H), 2.47 (dd, 1 H, J = 17 Hz), 2.91 (dd, 1 H, J = 16 Hz), 3.26 (dd, 1 H, J = 5.8 Hz), 3.85 (q, 1 H, J = 6.6 Hz), 4.01 (m, 1 H), 4.70 (dd, 1 H), 5.22 (t, 1 H, J = 7.70 Hz), 7.25 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 40.6, 55.5, 59.3, 61.2, 74.5, 103.0, 125.9, 126.6, 127.3, 127.4, 127.9, 128.6, 128.8, 129.0, 138.9, 141.6, 145.5, 179.1; MS *m*/*z* (rel intensity) 399 (M + 1, 30).

(+)-7-(*S*)-Pyrrolidino Lactam 5f. 5f was prepared using the general procedure. Thus, 0.30 g (1.39 mmol) of unsaturated lactam **3** was treated with pyrrolidine (2.3 mL, 27.8 mmol) and 0.20 mL (11 mmol) of distilled water. Chromatography of the crude product (ether) yielded 0.35 g (89%) of lactam **5f** as a brown solid: $[\alpha]^{23}_D$ = +147.4° (*c* 1.0, CH_2Cl_2); mp 130−132 °C; IR (neat) 3003, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.76 (m, 4 H), 2.80 (m, 4 H), 2.91 (dd, 1 H, J = 17 Hz), 3.09 (dd, 1 H, J = 7.5 Hz), 4.12 (dd, 1 H, J = 8.7 Hz), 4.64 (m, 1 H), 5.20 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.7, 25.3, 38.7, 52.8, 57.9, 67.5, 73.2, 101.3, 125.9, 127.7, 128.9, 140.5, 178.1. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.74. Found: C, 71.18; H, 7.77.

(+)-7-(*S*)-((*S*)-2′Pyrrolidinemethanol) Lactam 5g. 5g was prepared using the general procedure. Thus, 0.30 g (1.39 mmol) of unsaturated lactam **3** was treated with (*S*)-2-pyrrolidinemethanol (2.74 mL, 27.8 mmol) and 0.20 mL (11 mmol) of distilled water. Chromatography of the crude product (ether) yielded 0.36 g (82%) of lactam **5g** as a brown foam: $[\alpha]^{23}_D$ = +154.5° (*c* 1.5, $CHCl_3$); IR (neat) 3550, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.77 (m, 4 H), 2.66 (m, 3 H), 2.91 (m, 2 H), 3.03 (s, 1 H), 3.44 (m, 1 H), 3.61 (m, 2 H), 3.03 (s, 1 H), 3.44 (m, 1 H), 3.61 (m, 2 H), 4.16 (dd, 1 H), 4.67 (t, 1 H, J = 8.4 Hz), 5.17 (t, 1 H, J = 7.5 Hz), 7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.7, 24.8, 28.0, 35.3, 48.6, 57.5, 63.2, 63.4, 63.9, 74.2, 100.1, 125.8, 127.8, 129.0, 139.8, 177.1. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65. Found: C, 68.45; H, 7.69.

(+)-7-(*S*)-[(*R*)-(1′-Cyclohexylethyl)amino] Lactam 5h. 5h was prepared using the general procedure. Thus, 0.42 g (1.95 mmol) of unsaturated lactam **3** was treated with (*R*)-1-cyclohexylethylamine (4.90 mL, 33.0 mmol) and 0.30 mL (16 mmol) of distilled water. Chromatography of the crude product with 5:1 ether/methanol yielded 0.54 g (81%) of lactam **5h** as a yellow oil: $[\alpha]^{23}_D$ = +65.5° (*c* 0.9, $CHCl_3$); IR (neat) 3322, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 1 H, J = 6.4 Hz), 1.12 (m, 6 H), 1.39 (s, 1 H), 1.73 (m, 5 H), 2.27 (m, 2 H), 2.81 (dd, 1 H, J = 16 Hz), 3.37 (d, 1 H, J = 4.8 Hz), 4.29 (dd, 1 H, J = 8.2 Hz), 4.23 (m, 1 H), 5.20 (m, 1 H), 7.24 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.2, 25.1, 26.8, 26.9, 27.1, 29.4, 29.6, 41.0, 44.3, 54.4, 57.7, 60.8, 74.4, 100.9, 126.4, 127.8, 128.9, 140.1, 177.7; MS *m*/*z* (rel intensity) 343 (M + 1, 100).

Conjugate Amine Addition Using CH_2Cl_2 as a Solvent. (+)-7-(*S*)-(Adamantylmethyl)amino Lactam 5i. Lactam **3** (0.42 g, 1.95 mmol) was added to a 20 mL scintillation vial equipped with a small magnetic stirring bar. Adamantanemethylamine (2.57 g, 15.6 mmol) and 0.30 mL (16 mmol) of distilled water were added to the vial. Dichloromethane (2.0 mL) was added, and the reaction mixture was stirred for 12 h. The solution put on a silica gel column and eluted with 1:1 ether/hexanes to yield 0.59 g (80%) of lactam **5i** as a yellow oil: $[\alpha]^{23}_D$ = +73.0° (*c* 1.7, $CHCl_3$).; IR (neat) 3340, 1709, 1603; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.55, (m, 15 H), 1.92 (m, 1 H), 2.08 (d, 1 H, J = 11 Hz), 2.76 (dd, 1 H, J = 14 Hz), 2.83 (dd, 1 H, J = 14 Hz), 3.17 (d, 1 H, J = 4.9 Hz), 4.32 (dd, 1 H, J = 4.0 Hz), 4.42 (m, 1 H), 5.20 (m, 1 H), 7.23 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.3, 28.8, 33.7, 35.6, 40.9, 41.1, 57.7, 60.2, 64.3, 74.3, 101.0, 126.4, 127.5, 128.9, 140.1, 175.5; MS *m*/*z* (rel intensity) 381 (M + 1, 25).

Epimeric Methyl Lactams 7 and 8. Lactam **5f** (100 mg, 0.35 mmol) was placed in a dry 10 mL flask equipped with a magnetic stir bar. The flask was placed under argon, and 2.0 mL of dry THF was added. Stirring was initiated, the solid dissolved, and the reaction vessel cooled to −78 °C. Lithium hexamethyldisilizane (0.35 mL, 0.35 mmol) was added dropwise to the lactam solution, and the reaction mixture was allowed to stir for 1 h. Iodomethane (1.75 mmol, 0.11 mL) was added dropwise, and the reaction was continued for another hour. The reaction was quenched with saturated NH_4Cl solution (1.0 mL) and allowed to warm to rt. THF was removed under reduced pressure and the resultant aqueous solution extracted (10 mL, 3×) with CH_2Cl_2. The organic layers were combined and dried over K_2CO_3. Rotary evaporation and chromatography of the crude product (1:9 methanol/EtOAc) gave alkylated lactams **7** and **8** as a 2:1 mixture of C-6 epimers in 60% (63.0 mg, 0.21 mmol) overall yield.

(+)-(*S*)-7-Pyrrolidino 6-methyl lactam 7: $[\alpha]^{23}_D$ = +192.5° (*c* 2.2, CH_2Cl_2); IR (neat) 1710, 1450, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 7.4 Hz), 1.52 (s, 3 H), 1.83 (m, 4 H), 2.83 (m, 4 H), 3.11 (m, 1 H), 3.57, (d, 1 H, J = 6.9 Hz), 4.07 (t, 1 H, J = 8.5 Hz), 4.72 (t, 1 H, J = 8.3 Hz), 5.06 (t, 1 H, J = 8.3 Hz), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 9.4, 24.5, 24.6, 43.2, 49.0, 55.9, 67.7, 74.2, 125.7, 127.5, 128.7, 139.8, 178.4; HRMS *m*/*z* (M + 1) calcd 301.1912, found 301.1916.

(+)-(*S*)-7-Pyrrolidino 6-methyl lactam 8: $[\alpha]^{23}_D$ = +175.0° (*c* 1.7, CH_2Cl_2); IR (neat) 1715, 1496, 1450, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, 3 H, J = 7.4 Hz), 1.55 (s, 3 H), 1.87 (m, 4 H), 3.08 (m, 4 H), 3.26 (m, 1 H), 3.86 (d, 1 H, J = 6.4 Hz), 4.10

(t, 1 H, J = 8.7 Hz), 4.75 (t, 1 H, J = 8.9 Hz), 5.09 (t, 1 H, J = 8.2 Hz), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.7, 24.9, 25.4, 43.1, 50.9, 56.4, 68.1, 77.6, 125.9, 128.1, 129.2, 139.4, 177.4; HRMS m/z (M + 1) calcd 301.1912, found 301.1915.

General Procedure for Amino Lactam Alane Reduction. (+)-(*S*)-2-Methyl-(*R*)-3-(*tert*-butylamino)-1-*N*-[2′-(1′-hydroxy-2′-(*S*)-phenylethyl)]pyrrolidine (9). Aluminum trichloride (247 mg, 1.85 mmol) under Ar was cooled to 0 °C. Dry THF (12.5 mL) was added, and stirring was initiated. $LiAlH_4$ (5.45 mL of a 1.0 M THF solution) was added dropwise and the reaction mixture allowed to warm to rt. After stirring for 20 min at rt, the mixture was cooled to −78 °C and amino lactam **5a** (504 mg, 1.75 mmol) was added, via cannula, as a dry THF (10 mL) solution. The reaction was stirred for 1 h at −78 °C, warmed to rt, and allowed to stir for an additional 3 h. The mixture was then cooled to 0 °C, and 1.16 mL of water was added in a dropwise fashion followed by 1.64 mL of a 10% NaOH solution. More water (3.80 mL) was then added, along with ether (30 mL), and the reaction mixture allowed to stir for 30 min. The ether solution was then dried with $MgSO_4$ and evaporated. Chromatography (4:2:1 hexanes/EtOAc/triethylamine) gave 392 mg of benzylpyrrolidine **9** as an orange oil (81%): $[\alpha]^{23}_D$ = +30.4° (c 3.4, $CHCl_3$); IR (neat) 3415 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.15 (m, 1 H), 1.21 (d, 3 H, J = 5.9 Hz), 2.05 (m, 2 H), 2.26 (q, 1 H, J = 8.8 Hz), 2.71 (m, 1 H), 2.82 (m, 1 H), 3.59 (m, 1 H), 3.96 (m, 2 H), 7.08 (m, 2 H), 7.27 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 17.4, 30.4, 43.7, 51.0, 58.9, 60.6, 61.8, 62.0, 128.0, 128.4, 129.5, 134.9; HRMS m/z (M^+) calcd 276.2161, found 276.2160.

(+)-(*S*)-2-Methyl-(*R*)-3-[(adamantylmethyl)amino]-1-*N*-[2′-(1′-hydroxy-2′-(*S*)-phenylethyl)]pyrrolidine (10). The general procedure was used. Treatment of a solution of bicyclic lactam **5i** (100 mg, 0.26 mmol) in dry THF (10 mL) with a solution of alane (prepared from 66.0 mg of anhydrous $AlCl_3$ in 10.0 mL of dry THF with 1.46 mL of 1.0 M $LiAlH_4$ in THF) returned, after chromatography (1:1 toluene/methanol), 67.0 mg (70%) of pyrrolidine **10** as a brown oil: $[\alpha]^{23}_D$ = +34.5° (c 1.1, $CHCl_3$); IR (neat) 3418, 1452 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.16 (d, 3 H, J = 6.0 Hz), 1.42 (m, 7 H), 1.75 (m, 6 H), 2.03 (m, 6 H), 2.35 (m, 2 H), 2.51 (m, 1 H), 2.70 (m, 1 H), 3.71 (dd, 1 H, J = 8.8 Hz), 3.97 (m, 2 H), 7.13 (m, 5 H); ^{13}C NMR (C_6D_6) δ 18.3, 28.8, 30.0, 33.5, 37.5, 40.9, 43.9, 60.9, 61.3, 62.9, 65.7, 129.3, 136.3; MS m/z (rel intensity) 369 (M + 1, 62).

(+)-(*S*)-2-Methyl-2-deuterio-(R)-[(*R*)-(cyclohexylethyl)amino]-5,5-dideuterio-1-*N*-[2′-(1′-hydroxy-2′-(*S*)-phenylethyl)]pyrrolidine (15). The general procedure was used. Treatment of a solution of bicyclic lactam **5h** (178 mg, 0.52 mmol) in dry THF with a solution of deuterated alane (prepared from 132 mg of anhydrous $AlCl_3$ in 20 mL of dry THF with 2.92 mL of 1.0 M $LiAlD_4$ in THF) returned, after chromatography (4:2:1 hexanes/EtOAc/triethylamine), 121 mg (70%) of pyrrolidine **15** as a yellow oil: $[\alpha]^{23}_D$ = +14.5° (c 1.3, C_6H_6); IR (neat) 3433, 1450 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.88 (m, 5 H), 1.10 (m, 8 H), 1.63 (m, 6 H), 2.26 (m, 1 H), 2.67 (dd, 1 H, J = 7.9 Hz), 3.73 (dd, 1 H, J = 8.5 Hz), 3.98 (m, 2 H), 7.10 (m, 5 H); ^{13}C NMR (C_6D_6) δ 16.9, 17.8, 26.8, 26.9, 27.0, 28.5, 29.6, 29.7, 43.1 (pentet), 44.0, 55.5, 61.1, 61.2 (t), 61.7, 62.8, 129.3, 136.2; ^{2}H NMR (C_6D_6) δ 2.09 (s, 1 D), 2.15 (s, 1 D), 2.61 (s, 1 D); MS m/z (rel intensity) 334 (M + 1, 60).

(−)-(*S*)-2-Methyl-3-(*R*)-(*tert*-butylamino)pyrrolidine (11). Benzyl-substituted pyrrolidine **9** (389 mg, 1.41 mmol) was dissolved in 2.0 mL of anhydrous EtOH and placed in a dry pressure tube equipped with a magnetic stirring bar. Palladium(II) hydroxide on carbon (20%, 167 mg) was added to the reaction vessel. The pressure tube was sealed and flushed with hydrogen (3×), and the mixture was allowed to stir for 12 h under 1 atm of hydrogen. Filtration through Celite and evaporation of EtOH under reduced pressure gave the crude pyrrolidine **11**. Chromatography (1:1:1 triethylamine/methanol/chloroform) gave pyrrolidine **11** as a yellow oil (70%). Because of its air and moisture sensitivity, pyrrolidine **11** was directly converted to sulfonamide **13** for purposes of characterization.

(+)-(*S*)-2-Methyl-(*R*)-3-[(adamantylmethyl)amino]-pyrrolidine (12). The same procedure as above for pyrrolidine **11** was used. Thus, treatment of a 2.0 mL anhydrous ethanolic solution containing 140 mg of benzylpyrrolidine **10** with 1 atm of hydrogen, followed by filtration and chromatography (1:1:1 triethylamine/methanol/chloroform), gave pyrrolidine **12** as a brown oil (70%). Aminopyrrolidine **12** was converted to sulfonamide **14** for characterization.

(−)-(*S*)-2-Methyl-2-deutero-3-[(*R*)-(cyclohexylethyl)-amino]-5,5-dideuteropyrrolidine (16). The above procedure for pyrrolidine **11** was used. Thus, treatment of a 1.0 mL anhydrous ethanolic solution containing 78.0 mg of benzylpyrrolidine **15** with 1.0 atm of hydrogen, followed by filtration and chromatography (1:1:1 triethylamine/methanol/$CHCl_3$), gave pyrrolidine **16** as an orange oil (71%). Aminopyrrolidine **16** was converted to sulfonamide **17** for characterization.

(+)-(*S*)-2-Methyl-(*R*)-3-(*tert*-butylamino)-1-*N*-*p*-toluenesulfonamidopyrrolidine (13). To pyrrolidine **11** (32.0 mg, 0.205 mmol) and *p*-toluenesulfonyl chloride (101 mg, 0.53 mmol) under argon was added dry CH_2Cl_2 (1.0 mL) with stirring. Diisopropylethylamine (0.2 mL, 1.15 mmol) was syringed into the flask and the mixture allowed to stir for 24 h. The CH_2Cl_2 solution was then deposited on a silica gel column and eluted with 1:1 hexanes/EtOAc to provide 56 mg of sulfonamide **13** (89%) as a brown oil. Recrystallization from hexanes gave **13** as a clear crystalline solid: mp 67 °C; $[\alpha]^{23}_D$ = +46.7° (c 1.9, C_6H_6); IR (neat) 3341, 1449, 1150 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.73 (s, 9 H), 0.85 (m, 1 H), 1.42 (d, 3 H, J = 6.4 Hz), 1.57 (m, 1 H), 1.94 (s, 3 H), 2.52 (q, 1 H, J = 5.3 Hz), 3.27 (m, 3 H), 6.85 (d, 2 H, J = 8.1 Hz), 7.83 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (C_6D_6) δ 20.9, 21.1, 29.7, 33.4, 47.4, 50.2, 59.2, 64.2, 128.0, 129.3, 135.7, 142.5. Anal. Calcd for $C_{16}H_{26}N_2O_2S$: C, 61.90; H, 8.44. Found: C, 62.17; H, 8.42.

(+)-(*S*)-2-Methyl-(*R*)-3-[(adamantylmethyl)amino]-1-*N*-*p*-toluenesulfonamidopyrrolidine (14). The above procedure was used. Thus, treatment of a 1.0 mL anhydrous CH_2Cl_2 solution containing 20.0 mg of pyrrolidine **12** and 48.0 mg of *p*-toluenesulfonyl chloride with 0.13 mL of diisopropylethylamine yielded, after chromatography (1:1 hexanes/EtOAc), 28.0 mg of pyrrolidine **14** as a yellow oil (88%): $[\alpha]^{23}_D$ = +15.3° (c 0.7, C_6H_6); IR (neat) 3338, 1452, 1159 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.13 (m, 6 H), 1.35 (m, 5 H), 1.68 (m, 9 H), 1.92 (m, 7 H), 3.11 (m, 1 H), 3.38 (m, 2 H), 6.82 (d, 2 H), 7.81 (m, 2 H); ^{13}C NMR (C_6D_6) δ 20.9, 22.4, 28.6, 28.9, 29.4, 32.8, 37.2, 40.4, 46.9, 59.7, 62.3, 65.1, 129.1, 135.6, 142.1; MS m/z (rel intensity) 402 (M^+, 20).

(−)-(*S*)-2-Methyl-2-deutero-(*R*)-[(*R*)-(cyclohexylethyl)-amino]-5,5-dideutero-1-*p*-toulenesulfonamidopyrrolidine (17). The above procedure was used. Thus, treatment of a 0.5 mL anhydrous CH_2Cl_2 solution containing 16.0 mg of pyrrolidine **12** and 72.0 mg of *p*-toluenesulfonyl chloride with 0.2 mL of Hunig's base yielded, after chromatography (1:1 hexanes/EtOAc), 24.0 mg of pyrrolidine **17** as a brown oil (87%): $[\alpha]^{23}_D$ = −2.4° (c 1.2, C_6H_6); IR (neat) 3324, 1439, 1155 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.52 (m, 1 H), 0.63 (d, 3 H, J = 6.4 Hz), 0.72 (m, 2 H), 1.07 (m, 4 H), 1.35 (m, 1 H), 1.65 (m, 3 H), 1.91 (m, 1 H), 1.99 (s, 3 H), 2.59 (q, 1 H, J = 2.5 Hz), 6.85 (d, 2 H, J = 8.4 Hz), 7.81 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (C_6D_6) δ 16.9, 21.0, 22.2, 26.7, 26.9, 28.7, 28.8, 30.0, 43.6, 44.0 (pentet), 54.3, 61.4, 63.0 (t), 99.9, 128.0, 129.3, 135.8, 142.3; MS m/z (rel intensity) 368 (M + 1, 40).

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Supplementary Material Available: ^{1}H NMR spectra for compounds **5a,h,i**, **7−10**, **13−15**, and **17** and the ORTEP presentation of **13** (13 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.

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