Asymmetric Synthesis of 2-Alkyl-Perhydroazepines from [5,3,0]-Bicyclic Lactams

A. I. Meyers,* Susan V. Downing, and Michael J. Weiser

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

aimeyers@lamar.colostate.edu

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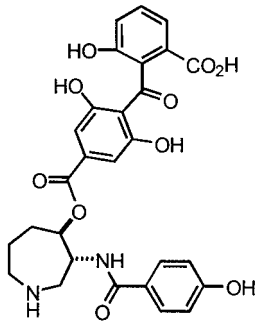
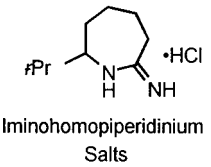
The synthesis and utility of a novel class of [5,3,0]-bicyclic lactams are described. Produced by the cyclodehydration of (*R*)-phenylglycinol with *ω*-keto acids, lactams **4**−**6** were obtained as separable diastereomeric mixtures (∼2:1) in low yields (∼40%). Higher chemical yield (up to 61%) was realized via an alternate route involving ring closure metathesis of 2-allyl-*N*-acroyl oxazolidines, **8**. Stereoselective reductions of the *syn*-bicyclic lactams, **4a** and **5a**, occurred with the use of alane or lithiumaluminum hydride, affording azepine alcohols, **11a** and **15a**, of the *R* configuration at the 2-position, in good to moderate yields (50−88%). High selectivity was also observed in the diisobutylaluminum hydride reduction of the epimeric *anti* lactams, **4b** and **5b**, affording azepine alcohols, **11b** and **15b**, of the *S* configuration at C-2. Hydrogenolytic cleavage of the *N*-benzyl moiety afforded chiral 2-substituted perhydroazepines, (*R*)- and (*S*)-**12**, in good yields and good enantiomeric excesses (84−94%).

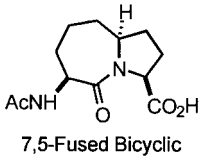
Seven-membered nitrogen heterocycles are constituents of a number of compounds with interesting pharmacological properties. For example, Balanol, the subject of several synthetic efforts,[1] is known to be a potent inhibitor of the protein kinase C enzyme, while iminohomopiperidinium salts are known to be selective inhibitors of inducible nitric oxide synthase[2] and are therefore potential therapeutic agents for inflammatory conditions such as osteo or rheumatoid arthritis. Additionally, substituted seven-membered lactams have been studied as potential peptide turn mimetics,[3] and 7,5-fused bicyclic lactams have been used as conformationally restricted dipeptide surrogates.[4]



Balanol

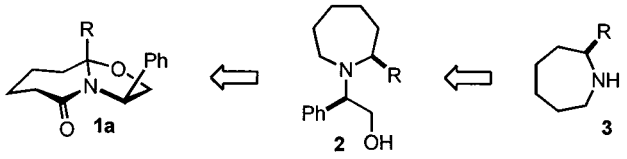


Iminohomopiperidinium Salts



7,5-Fused Bicyclic Lactams

General methods for the direct synthesis of 2-substituted perhydroazepines are few. Racemic products are obtained from the trialkylaluminum-mediated Beckman rearrangement of cyclohexanone oxime sulfonates[5] and the alkylation of dipole stabilized carbanions.[6] Given our earlier successes in the construction of chiral pyrrolidines and piperidines from [3,3,0]- and [4,4,0]-bicyclic lactams,[7] we felt that the [5,3,0]-bicyclic lactam scaffold **1a** could provide access to chiral 2-substituted azepines **3** in a relatively straightforward fashion. We have elected to name the [3,3,0] lactams as "5,5-", the [4,3,0] lactams as "5,6-", and the [5,3,0] lactams as "5,7-". This trivial nomenclature will be used throughout this paper.



Previous methods for accessing the versatile bicyclic lactam template consisted of cyclodehydration of a *γ*- or *δ*-keto acid and a chiral amino alcohol by simply heating the two in toluene overnight with azeotropic removal of water.[7] For the synthesis of *N*-heterocycles, (*R*)- or (*S*)-phenylglycinol was commonly employed as the chiral auxiliary. Employing this protocol with 6-oxooctanoic

(1) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615−617, and references therein.

(2) Hansen, D. W., Jr. et al. *J. Med. Chem.* **1998**, *41*, 1361−1366.

(3) (a) Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385−8386. (b) Nadin, A.; Derrer, S.; McGeary, R. P.; Goodman, J. M.; Raithby, P. R.; Holmes, A. B.; O'Hanlon, P. J.; Pearson, N. D. *J. Am. Chem. Soc.* **1995**, *117*, 9768−9769.

(4) (a) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393−396. (b) Colombo, L.; Di Giacomo, M.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.* **1994**, *35*, 4031−4034.

(5) (a) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368−7370. (b) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831−2843.

(6) (a) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270−3276. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117.

(7) The extensive chemistry of the 5,5- and 5,6-bicyclic lactam systems has been thoroughly reviewed: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569. (b) Meyers, A. I. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Cambridge, MA, 1994; pp 145−161. (c) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1−8. (d) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931−8952. (e) For a recent review on this subject, see: Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, in press.

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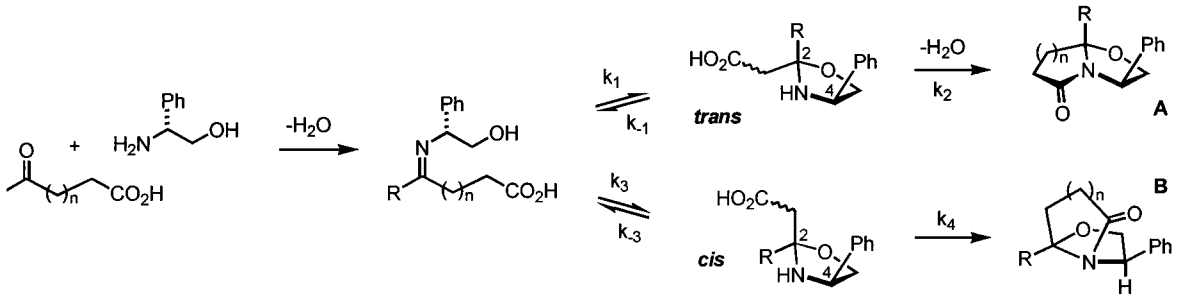
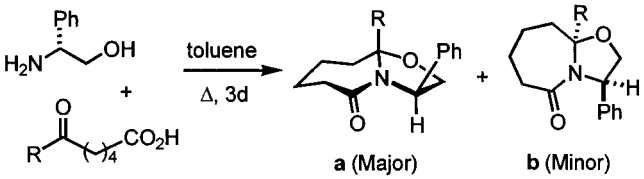
Scheme 1



acid[8] furnished the 5,7-bicyclic lactam diastereomers **5a** and **5b**, as a 2:1 mixture, in very low (11%) yield (**5a**,**b**; R = Et). After extending the reaction time to 5 days, the yield of the angular ethyl lactams **5ab** was improved to 40%, with the remainder of the material consisting of several uncharacterized products.[9] A reaction time of 3 days was then set as the standard, which facilitated purification (fewer side products) without compromising the yield of the desired products. In this way, the angular methyl lactams **4ab** were also obtained in 38% yield (2:1). The keto acid 6-oxo-8-methylnonanoic acid provided a 5:1 mixture of angular isobutyl lactams **6ab** in very low yield (8%).



4ab R=Me, 38%, 2:1
5ab R=Et, 40%, 2:1
6ab R=*i*-Bu, 8%, 5:1

The absolute stereochemistry of the aminal center in lactam diastereomer **4a** was determined from its crystal structure.[10] While assignment of the other lactam products might rest on analogy with **4a**, it was observed for each of the phenylglycinol-derived 5,7-bicyclic lactams (**4a**−**6a**) that the chemical shift of the benzylic proton in the major lactam diastereomers (**5a**, **6a**) was found downfield (5.29 ± 0.04 ppm) from that for the minor epimers (5.19 ± 0.02 ppm). This distinction has also been observed on related bicyclic lactams derived from 4-acetylbutyric acid and phenylglycinol (*syn*-alkyl; 5.38 ppm, *anti*-alkyl; 4.96 ppm), whose stereochemistry has been confirmed to be 4:1 favoring the *syn* methyl.[11]

The rationale to account for the above mixtures of bicyclic lactams of (a,b) products is based upon their mechanism of formation,[12] which is depicted in Scheme 1. In synthesis of the "5,5-bicyclic lactam" (**A**, $n = 1$), $k_2 \gg k_4$, leading to the *syn*-alkyl product **A** to the exclusion of the very strained *anti*-alkyl product **B**. For the "5,6-bicyclic lactam" (**A**, $n = 2$), closure to **B** is more likely to occur since the bicyclic structure can now more easily accommodate the *trans* ring fusion. Products **A** and **B** are both formed as a 4−10:1 mixture, respectively,[11] with $k_2 > k_4$. For the "5,7-bicyclic lactams" ($n = 3$), the ring fusion in **B** is even more accommodated as a result of the increased flexibility of the larger ring size. However, neither k_2 or k_4 are very fast, and a prior equilibrium k_1,k_{-1} and k_3,k_{-3} to oxazolidines is established, with very little preference in the latter for 2,4-*trans* versus 2,4-*cis* geometry.[13] The mixture of lactam **5a** or **5b** could not be altered when heated in wet toluene, but addition of *p*-TsOH caused an enriched sample of **5a** (96% de by ^{1}H NMR) to be reduced to 33% de within 24 h.

Efforts to enhance the chemical yield and diastereoselection of **4**−**6** included the examination of different amino alcohols[14] (valinol, *tert*-leucinol, and *gem*-dimethylphenylglycinol), different solvents that form azeotropes with water, and additives reported to aid in amide bond formation,[15] to name a few. However, these efforts did not lead to any improvements in yield and stereochemistry.

A new approach to these lactams was investigated (Scheme 2) using ring closure metathesis (RCM), to form a 5,7-bicyclic lactam from the bisolefinated oxazolidine **8**. First, azeotropic condensation of 5-hexene-2-one **7** with (*R*)-phenylglycinol formed the 2-butenyl substituted 1,3-oxazolidine, which was immediately treated with acryloyl chloride and triethylamine to afford the bisolefinated oxazolidine **8** in a combined yield of 84% with a diasteriomeric ratio of 3:1 at the C-2 center. The *syn* and *anti* diastereomers of **8** were separated, and the major diastereomer **8b**[10] was then subjected to RCM using 5 mol % of Grubbs' ruthenium catalyst[16] to provide the unsaturated 5,7-bicyclic lactam (98%) as a single product, which was reduced without further purification (H_2−$Pd(OH)_2$) to afford the 5,7-bicyclic lactam **4b** in 99% yield. The overall yield of **4b** from (*R*)-phenylglycinol was 61%. Thus, the RCM route to 5,7-bicyclic lactam systems appear to be much improved over the classical cyclodehydration of a keto acid and amino alcohol. However, the major product **4b** contained the *anti* configuration with respect to the angular methyl and phenyl groups. This, therefore, corresponded to the minor diastereomer of **4**

(8) (a) White, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6605−6607. (b) Kaga, H.; Miura, M.; Orito, K. *Synthesis* **1989**, 864−866.

(9) Starting material was recovered only in very low yields.

(10) Susie Miller of this department is gratefully recognized for solving the X-ray crystal structures of compounds **4a**, **8b**, and **10a**.

(11) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084−7085.

(12) Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, 6701−6706.

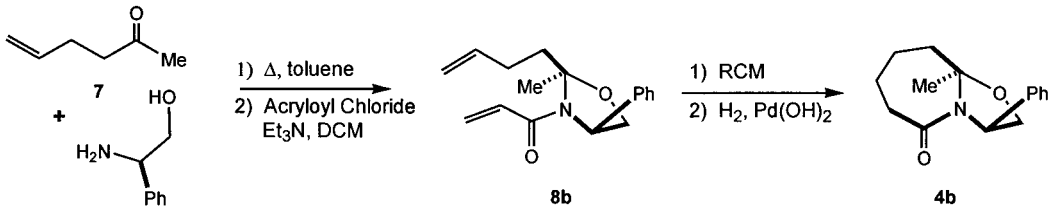
(13) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223−2226.

(14) (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974−7978. (b) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 530. (c) Meyers, A. I.; McKennon, M. J. *J. Org. Chem.* **1993**, *58*, 3568−3571. (d) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.

(15) (a) Yamada, S.; Wagatsuma, M.; Takkeuchi, Y.; Terashima, S. *Chem. Pharm. Bull.* **1971**, *19*, 2380−2388. (b) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. (c) Nadin, A. I. et al. *Mater. Sci. Eng. C* **1996**, *4*, 59.

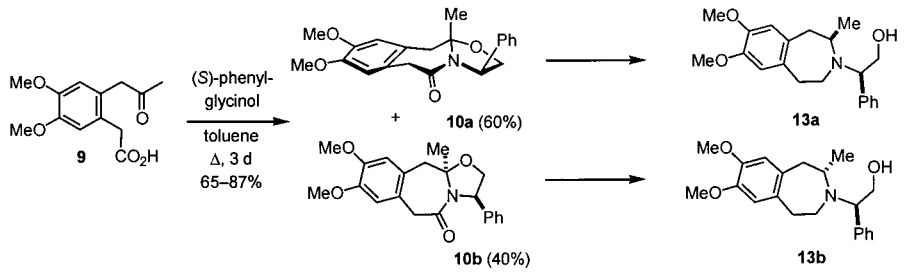
(16) For a review on ring closing metathesis, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

Scheme 2

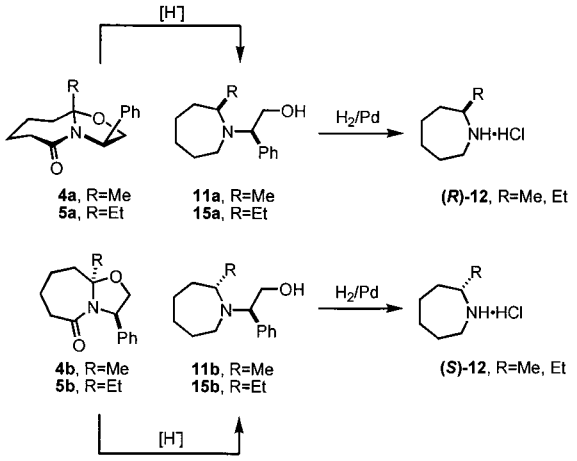


4b: 61% overall yield from *R*-phenylglycinol

Scheme 3



Scheme 4



(**4b**) obtained by azeotropic condensation of the 6-oxo-carboxylic acids and (*S*)-phenylglycinol. As mentioned, the stereochemistry of **4b** was based upon the X-ray data taken for **8b**.

It was next decided to employ a conformational restraint in the keto acid backbone (*cisoid* double bond) to assess if seven-membered ring closure via azeotropic condensation would be facilitated. In this regard, the keto acid, **9**, when subjected to azeotropic condensation with (*S*)-phenylglycinol in toluene, gave the benzo-fused lactams **10a** and **10b** in 65−87% chemical yield as a 1.5:1 mixture, respectively (Scheme 3). Once again, the benzylic proton of the chiral auxiliary in **10a** appeared downfield in the major diastereomer (5.42 ppm) compared to that for the minor epimer **10b** (4.99 ppm), and when both epimers are available, this trend may serve as a diagnostic tool for diastereomer identification for other phenylglycinol-derived 5,7-bicyclic lactams. For further structure proof, the stereochemistry of **10a** was confirmed from a crystal structure.[10]

Hydride reduction of each of the purified bicyclic lactam diastereomers **4a**, **4b**, **10a**, and **10b** was then undertaken (Scheme 4) and these results are summarized in Table 1. Screening of hydride reagents was performed on *syn*-methyl lactam **4a** with lithium aluminum hydride and alane, with both reductions showing good selectivity (retention) and affording predominantly epimer **11a** (entries a and b). Unfortunately, the resulting amino alcohol diastereomers **11a,b** could not be totally freed from the minor amounts of the other epimer. In this regard, conversion of the hydroxyl in **11a,b** to various esters (acyl, naphthoyl), which was a successful remedy in the separation of piperidine-derived amino alcohols,[11] did little to solve the problem. It was, therefore, decided to reductively remove the chiral remnant in **11** and **15** using $Pd(OH)_2-H_2$ and convert the resulting amines **12** (R = Me) to the *p*-bromobenzoyl amides, (*R*)-**14**, using *p*-bromobenzoyl chloride. This could be cleanly separated and allowed accurate ratio data to be obtained. The enantiomeric hydrochloride salts [(*R*)-**12**, (*S*)-**12**; R = Me] could also be separated by HPLC (Regis (*R,R*) Whelk-02 Pirkle covalent chiral column).[17] The absolute stereo-

Table 1. Hydride Reductions of *syn*- and *anti*-5,7-Bicyclic Lactams 4, 5, and 10

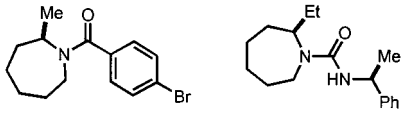
entry	lactam	hydride source	yield of amino alcohol (%)	diastereomeric purity (**a**:**b**)
a	**4a**	$LiAlH_4$	88[b] (**11a**)	94.3:5.7[d]
b	**4a**	AlH_3[a]	80 (**11a**)	95.7:4.3[d]
c	**4a**	*i*-Bu_2AlH	93[b] (**11a**)	1:1[e]
d	**4a**	BH_3	89[b] (**11a**)	3:1[e]
e	**5a**	$LiAlH_4$	83 (**15a**)	88.6:11.4[f]
f	**5a**	AlH_3	51[c] (**15a**)	92.0:8.0[f]
g	**10a**	$LiAlH_4$	50 (**13a**)	95:5[g]
h	**4b**	$LiAlH_4$	70[b] (**11b**)	2:1[e]
i	**4b**	AlH_3	51 (**11b**)	1:1[e]
j	**4b**	*i*-Bu_2AlH	95 (**11b**)	4.5:95.5[d]
k	**5b**	*i*-Bu_2AlH	61 (**15b**)	3.2:96.8[f]
l	**10b**	*i*-Bu_2AlH	53 (**13b**)	3:97[g]

[a] Generated in situ from $AlCl_3$ and $LiAlH_4$. [b] Yield is crude. [c] Reaction did not go to completion; partial reduction product obtained. [d] From HPLC of derivative **14**; value is ±0.5. [e] From integration of ^1H NMR signals (methyl doublets) at 1.17 and 0.97 ppm, respectively; values are approximate as a result of signal-obscuring impurity in samples. [f] From HPLC of derivative **15c**; value is ±0.5. [g] From integration of ^1H NMR signals (methyl doublets) at 0.78 and 0.72 ppm, respectively; value is ±2%.

(17) While an $[\alpha]_D$ value was not recorded for enantiomers (*S*)-**12** or (*S*)-**17**, the proton NMR spectra for each of these were identical to those for compounds (*R*)-**12** and (*R*)-**17**, respectively.

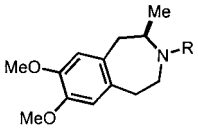
chemistry at the C-2 methyl group of the major product (**12**), obtained from the hydride reduction of lactam **4a**, was determined to be *R* from a crystal structure solved for azepine hydrochloride salt (*R*)-**12**, R = Me.[18]

For the 2-ethyl compound **5** (a and b), the *p*-bromobenzoyl derivative of azepines **15a** and **15b** could not be separated after acylation of the amino group as was done previously for **14**. However, the urea derivative **15c** from (*S*)-α-methylbenzylisocyanate (50% yield) allowed separation of the diastereomers of **15a** and **15b** by HPLC (CHIRACEL OD column). Again, lactam reduction of **5a** with alane (entry f) was slightly more selective than with lithium aluminum hydride (entry e). However, in this case, the reaction with alane was much slower, and 20% of starting material was obtained wherein only carbonyl reduction in the lactam had occurred (not shown).



(*R*)-**14**

(*R*)-**15c**



16, R = COC_6H_4Br
17, R = H . HCl

To restate, the derivatives (*R*)-**14** and **15c** derived from the cyclodehydration condensation were formed primarily to establish accurate enantiomer ratios, which could not be determined from proton NMR shift reagents because of signal overlapping or the presence of impurities that were not removed by flash chromatography, and not for the purpose of obtaining stereochemically pure product. The ratio of amino alcohols **13a**,**b**, obtained from reduction of benzo-fused lactam **10a** with LAH, was easily discerned by proton NMR, and the products, therefore, need not be derivatized for HPLC separation.

Prior to this study, the stereochemistry of hydride reductions of *anti*-bicyclic lactam diastereomers (**4b**, **5b**) had not been investigated. In view of the fact that the ring closure metathesis gave good yields of the *anti*-bicyclic lactams, **4b**, several hydride reagents were screened, and it was found that diisobutylaluminum hydride provided selectivity far superior to that of alane or LAH (Table 1, entries h−j). That the stereochemistry at C-2 in **15b** was found to be opposite of that obtained from reduction of *syn*-lactam **4a** was verified once the *N*-substituent was removed by hydrogenolysis. The products, **12**, from each lactam **4a** and **4b** were found to be enantiomers.[19]

Some comments on the stereoselectivity of the hydride reductions of the lactams **4**−**6** and **10** are appropriate.

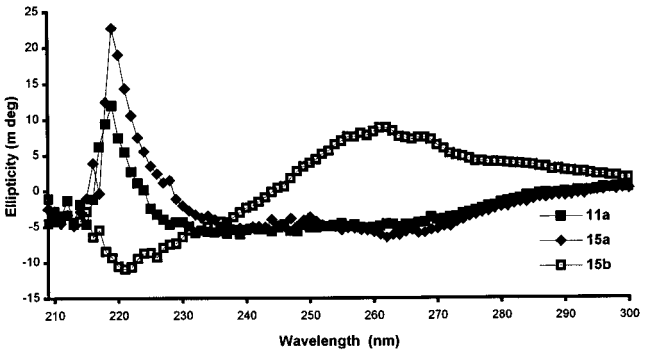
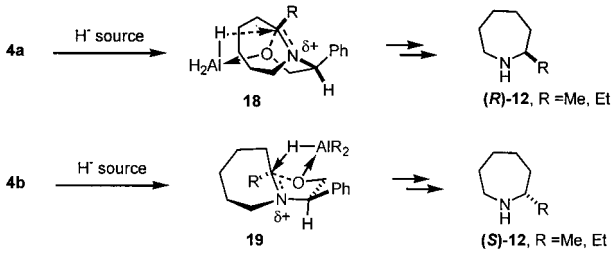


Figure 1. Circular dichroism (CD) spectra of amino alcohols **11a**, **15a**, and **15b** in CH_3CN.

The reduction was found to occur with the same stereochemical sense on each of the *anti*-bicyclic lactams studied. This was determined from comparison of the circular dichroism spectra of amino alcohols **11a** and **15a** and **15b**. Because there are two stereo centers in **11a** and **15a**, the spectrum of **15b** from DIBAL reduction of *endo*-lactam **5b** was also obtained to ascertain that the CD characteristics weren't simply due to the stereochemistry at the aryl group of the chromophore. As observed in Figure 1, the Cotton effects of **11a** and **15a** are quite similar, while that for **15b** is quite consistent with its enantiomer.

Rationalization for the stereochemical outcome in hydride reductions of the *syn*-5,7-bicyclic lactams follows directly from retention, which was reported for the reduction of 5,5- and 5,6-bicyclic lactams with alane.[11,20] Following reduction of the carbonyl group, complexation of the Lewis acidic aluminum reagent to the sterically less congested α-face weakens the angular C−O bond and promotes formation of the iminium ion species, **18**. Hydride delivery from aluminum, in an intramolecular sense, follows prior to formation of a discreet, planar intermediate. The observed result is that hydrogen occupies the site previously held by the oxygen, and retention of the stereochemistry predominates. For the *anti*-lactams, the *β*-face is the more accessible one, and reaction in the above manner, as in **19**, accounts for the retention of the orientation of the angular alkyl group.



In summary, stereoselective reductions of the 5,7-bicyclic lactams **4a**, **4b**, **10a**, and **10b** proceeded smoothly with the use of alane or lithium aluminum hydride, affording the corresponding perhydroazepines with *R* configuration at C-2 in good to moderate yields (50−88%) from the *syn* epimers. Good selectivity was also observed in the diisobutylaluminum hydride reduction of the *anti* lactam epimers, **4b**, **5b**, and **10b**, affording perhydroazepines of the opposite configuration at C-2. Hydrogenolytic cleavage of the *N*-benzyl moiety then produced

(18) Agnete la Cour is gratefully recognized for solving the X-ray crystal structure of compound (*R*)-**12**·HCl (R = Me), for which the absolute structure parameter is 0.00 ± 0.19. After refinement of the structure as the (*S*)-enantiomer, the flack parameter was 1.20 ± 0.18. Designation of C-5 as nitrogen and N as C-5 resulted in an unreliable temperature factor and a rise of the conventional R-factor from 0.0764 to 0.0839. Upon refinement of the crystal structure as a racemic twin, the data converged to 100% of the (*R*)-enantiomer of **12** (R = Me), with a confidence level of 95%.

(19) (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem*. **1991**, *56*, 2294−2296. (b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem*. **1992**, *57*, 1656−1662.

(20) Beugelmans, R.; Ginsburg, H. *Heterocycles*, **1985**, *23*, 1197.

chiral 2-substituted perhydroazepines in good yields and good enantiomeric excesses (84−94%).

Experimental Section

General. (*R*)-Phenylglycinol was generously provided by The Pharmacia Company. The synthesis of 8-methyl-6-oxononanoic acid was adapted from Koga;[8b] 6-oxooctanoic acid[8a] and benzo-fused keto acid **9**[20] were synthesized according to literature procedures. All other reagents were commercially available (Aldrich) and used without further purification.

8-Methyl-6-oxononanoic Acid. Isovaleryl chloride (9.3 mL, 76.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise (addition funnel) over the course of 30 min to a solution of 1-morpholinocyclopentene (10.4 mL, 65.3 mmol) and Et_3N (10.9 mL, 78.4 mmol) in CH_2Cl_2 (35 mL) at 0 °C. This mixture was allowed to warm to room temperature, and stirring was maintained for 4 days. Then, 6 M HCl (35 mL) was added, the mixture was heated to reflux for 5 h, and then it was cooled to room temperature. The phases were separated, and the organic one was washed with brine and dried (Na_2SO_4).

The crude diketone was dissolved in water (15 mL), NaOH (9.0 g, 225 mmol) was added, and the solution was heated to reflux for 1 h. The mixture was poured into ice water (70 mL), acidified to pH 3 with concentrated HCl, and extracted with CH_2Cl_2 (2 × 35 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and triturated with hexanes to provide 3.6 g (29%) of 8-methyl-6-oxononanoic acid as a light tan solid, mp 37.5−39.5 °C. The aqueous material was further acidified to pH 2, saturated with solid NaCl, and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated to provide an additional 5.0 g (41%) of the keto acid as an impure oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, J = 6.5 Hz, 6H), 1.64 (apt s, 4H), 2.15 (m, 1H), 2.30 (d, J = 7.4 Hz, 2H), 2.39−2.43 (m, 4H), 11.73 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 22.8, 23.2, 24.4, 24.9, 34.0, 43.0, 52.1, 179.8, 210.7; IR (neat) 1698 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{10}H_{18}O_3$ (M + H)$^+$ 187.1334, found 187.1338. This material was used without further purification.

General Procedure for the Azeotropic Synthesis of 5,7-Bicyclic Lactams. Angular Methyl Lactams 4. 6-Oxoheptanoic acid (2.0 g, 13.7 mmol) and (*R*)-phenylglycinol (1.9 g, 13.7 mmol) were combined in 137 mL of toluene, heated to reflux with azeotropic removal of water for 3 days, cooled, and concentrated, and the residue was dissolved in EtOAc (100 mL). The solution was washed with 2 M NaOH (25 mL), 1 M HCl (25 mL), and saturated (aqueous) $NaHCO_3$ (25 mL) and then dried ($MgSO_4$). Flash chromatography of the residue (hexanes/EtOAc 2:1) provided 630 mg of *syn*-methyl **4a** as a yellow oil that solidified upon standing (19%), 285 mg of *anti*-methyl **4b** as a pale yellow solid (8%), and 61 mg (2%) of **4a**/**4b** as an epimeric mixture (1:1.4). **4a:** mp 96−98 °C; R_f = 0.21 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = −65.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66−2.11 (m, 9H), 2.57−2.68 (m, 2H), 4.03 (dd, J = 5.2 and 9.0 Hz, 1H), 4.38 (dd, J = 7.0 and 9.0 Hz, 1H), 5.33 (dd, J = 5.0 and 6.9 Hz, 1H), 7.26−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 24.4, 37.3, 39.7, 62.0, 70.3, 95.7, 126.6, 127.5, 128.7, 140.5, 171.39; IR (neat) 1643, 1403 cm^{-1}; MS *m*/*z* 245. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 7.79; N, 5.71. **4b:** mp 103−104 °C; R_f = 0.14 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = 1.18 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61−2.08 (m, 8H), 2.25−2.31 (m, 1H), 2.60−2.64 (m, 2H), 4.05 (dd, J = 1.5 and 9.2 Hz, 1H), 4.41 (dd, J = 6.7 and 9.0 Hz, 1H), 5.21 (br d, J = 6.1 Hz, 1H), 7.25−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 24.4, 24.9, 38.2, 40.1, 61.5, 70.3, 95.3, 126.8, 127.5, 128.7, 142.2, 171.0; IR (neat) 1629, 1412 cm^{-1}; MS *m*/*z* 245. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.37; H, 7.81; N, 5.74.

Angular Ethyl 5,7-Bicyclic Lactams 5. Prepared from 6-oxooctanoic acid[8a] (500 mg, 3.16 mmol) and (*R*)-phenylglycinol (434 mg, 3.16 mmol) in 50 mL of toluene using the general procedure described above. Flash chromatography of the residue (hexanes/EtOAc 5:2) provided 330 mg (40%) of **5** as an epimeric mixture (**5a**/**5b** 2.3:1). Recrystallization from Et_2O provided purified *anti*-ethyl **5b**, as a 12:1 mixture, as long colorless needles. While under aspirator pressure during collection of **5b**, *syn*-ethyl **5a** precipitated from the mother liquor as a white solid, essentially free from the minor diastereomer. **5a:** mp 137−138 °C; R_f = 0.34 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = −49.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J = 7.3 Hz, 3H), 1.63−2.04 (m, 6H), 2.13−2.31 (m, 2H), 2.48−2.67 (m, 2H), 3.94 (dd, J = 5.9 and 9.0 Hz, 1H), 4.34 (dd, J = 7.2 and 9.2 Hz, 1H), 5.29 (dd, J = 5.9 and 7.2 Hz, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 23.7, 24.2, 29.3, 35.3, 37.1, 61.7, 70.1, 98.0, 126.5, 127.4, 128.7, 140.3, 171.6; IR (neat) 1634 cm^{-1}; MS *m*/*z* 259. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.20; H, 8.10; N, 5.43. **5b:** mp 92−94 °C; R_f = 0.30 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ = −4.67 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.5 Hz, 3H), 1.50−1.67 (m, 2H), 1.74−2.09 (m, 4H), 2.26−2.35 (m, 2H), 2.50−2.54 (m, 2H), 3.88 (dd, J = 2.1 and 9.1 Hz, 1H), 4.25 (dd, J = 6.9 and 9.1 Hz, 1H), 5.19 (dd, J = 1.9 and 6.7 Hz, 1H), 7.16−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 21.2, 24.3, 26.9, 35.8, 38.2, 61.6, 70.5, 97.6, 126.8, 127.4, 128.6, 142.2, 171.0; IR (neat) 1637 cm^{-1}; MS *m*/*z* 259. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.65; H, 8.19; N, 5.26.

2-(*R*)-*N*-Acroyl Oxazolidine 8b. A solution of (*R*)-(−)-phenylglycinol (8.88 g, 64.7 mmol) and 5-hexene-2-one **7** (7.50 mL, 64.7 mmol) in toluene (200 mL) was heated to reflux through a Dean Stark trap for 24 h. The solution was concentrated without workup to a yellow oil. The crude oil was then taken up in 200 mL of dichloromethane and placed in an ice bath. Triethylamine (18.0 mL, 129 mmol) and acryloyl chloride (5.28 mL, 65.0 mmol) were subsequently added. After 10 min, the ice bath was removed, and the solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated (aqueous) NH_4Cl (20 mL), and the phases were separated. The organic phase was washed with brine, and the combined aqueous layers were extracted with dichloromethane. The organics were then dried (Na_2SO_4) and concentrated to a tan oil. Flash column chromatography (40:60, ether/hexanes) provided 14.75 g of **8a** and **8b** (84%) containing 11.06 g of the (2*R*)-diastereomer **8b** as a yellow solid, and 3.69 g of the crude (2*S*)-diastereomer **8b** as a yellow oil (dr = 3:1). (2*R*)-**8b:** mp 65−67 °C; $[\alpha]^{23}_D$ = −29.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 2.06 (m, 1H), 2.22 (dd, J = 6.6 Hz, 7.5 Hz, 2H), 2.62 (m, 1H), 3.90 (dd, J = 3.0 Hz, 3.0 Hz, 1H), 4.36 (dd, J = 6.6 Hz, 6.6 Hz, 1H), 4.95 (m, 3H), 5.41 (dd, J = 2.1 Hz, 1.5 Hz, 1H), 5.82 (m, 1H), 6.04 (dd, J = 10.2 Hz, 10.2 Hz, 1H), 6.25 (dd, J = 2.4 Hz, 1.5 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 28.8, 37.1, 61.0, 71.6, 114.5, 125.9, 127.7, 127.8, 128.8, 129.8, 138.1; IR (neat) 1653, 1613, 1418, 1361 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.43; H, 7.78. The minor diastereomer, **8a**, was not characterized further because of impurities.

Angular Methyl 5,7-Bicyclic Lactam 4b. A solution of the (2*R*)-diastereomer of **8b** (3.25 g, 12.0 mmol) in toluene (1.6 L) was heated to reflux. The high dilution was necessary as a result of dimerization at higher concentrations. A solution of Grubbs' catalyst,[16] $Cy_2Ru(PPh_3)_2CHPh$, (493 mg, 0.60 mmol) in toluene (10 mL) was added through the condenser via a syringe pump set at a rate of 0.397 mL/h. TLC (EtOAc, $KMnO_4$) confirmed completion after 25 h. The cooled solution was washed with brine, and the combined aqueous layers were extracted with EtOAc. The organics were dried (Na_2SO_4) and concentrated to a light brown solid. Flash column chromatography (EtOAc) afforded 2.87 g of the unsaturated lactam (98%) as a white crystalline solid. **α,β-unsaturated lactam:** mp 128−130 °C; $[\alpha]^{23}_D$ = +92.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3H), 2.27 (m, 2H), 2.45 (m, 2H), 3.98 (dd, J = 8.1 Hz, 8.1 Hz, 1H), 4.39 (dd, J = 6.6 Hz, 6.6 Hz, 1H), 5.12 (dd, J = 6.6 Hz, 6.6 Hz, 1H), 5.85 (m, 1H), 6.14 (m, 1H), 7.15−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 26.1, 36.5, 61.5, 70.3, 93.2, 126.2, 126.5, 127.1, 128.1, 139.9, 141.5; IR (neat) 1653, 1592 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 74.02; H, 7.18. To a solution of the α,β-

unsaturated lactam (500 mg, 2.06 mmol) in ethanol (10 mL) was added $Pd(OH)_2$ (20% on carbon) (21.9 mg, 0.0411 mmol). A balloon of H_2 gas was fitted to the reaction flask, and the solution was allowed to stir at room temperature. Reaction progress was monitored by NMR because of TLC co-spotting. After 24 h, NMR indicated completion. The reaction solution was filtered directly through a Celite pad and concentrated to a white solid. The crude solid was passed through a plug of silica to afford 498 mg of **4b** (99%) as a colorless crystalline solid. **4b:** mp 99−101 °C. This proved to be identical to **4b** obtained by the cyclodehydration route.

Benzo-Fused 5,7-Bicyclic Lactams 10. Synthesized from keto acid **9**[20] (300 mg, 1.19 mmol) and (*R*)-phenylglycinol (163 mg, 1.19 mmol) in 50 mL of toluene using the general procedure for azeotropic cyclocondensation. Flash chromatography of the residue, after solvent evaporation, (hexanes/EtOAc 1:1) provided 166 mg (39%) of the *syn*-diastereomer **10a** and 109 mg (26%) of the *anti*-diastereomer **10b** as solids. **10a:** mp 138−139 °C; $R_f = 0.19$ (hexanes/EtOAc 1:1); $[\alpha]^{23}_D = -48.5$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 3.17 (d, $J = 14.8$ Hz, 1H), 3.43 (d, $J = 15.0$ Hz, 1H), 3.80−3.93 (m, 9H), 4.47 (t, $J = 8.7$ Hz, 1H), 5.42 (apt t, 1H), 6.72 (s, 1H), 6.75 (s, 1H), 7.16−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 21.3, 25.4, 42.9, 43.8, 56.3, 60.9, 69.2, 94.6, 112.9, 113.7, 125.6, 125.8, 126.5, 127.3, 128.8, 140.6, 148.3, 167.4; IR (neat) 1639 cm^{-1}; MS *m*/*z* 353. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.68; H, 7.12; N, 3.60. **10b:** mp 147−148 °C; $R_f = 0.11$ (hexanes/EtOAc 1:1); $[\alpha]^{23}_D = +79.6$ (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H), 3.29 (d, $J = 15.4$ Hz, 1H), 3.42 (d, $J = 15.2$ Hz, 1H), 3.50 (d, $J = 15.5$ Hz, 1H), 3.72−3.84 (m, 5H), 3.92 (s, 3H), 4.38 (dd, $J = 7.4$ and 9.1 Hz, 1H), 4.99 (dd, $J = 1.9$ and 7.4 Hz, 1H), 6.67 (s, 1H), 6.80−6.83 (m, 3H), 7.07−7.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 42.9, 44.4, 56.2, 56.3, 60.3, 70.6, 94.0, 112.8, 113.8, 125.7, 126.5, 127.2, 127.3, 128.4, 141.8, 148.1, 148.2, 167.4; IR (neat) 1652 cm^{-1}; MS *m*/*z* 353. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.17; H, 6.60; N, 3.95.

***N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*R*)-methyl-hexahydrozepine 11a.** Alane was generated as follows. THF (4 mL) was added slowly to $AlCl_3$ (48 mg, 0.36 mmol) at 0 °C. After stirring for5 min, a solution of $LiAlH_4$ (41 mg, 1.07 mmol) in 1 mL of THF was added slowly via syringe. The mixture was stirred at room temperature for 20 min and then cooled to −78 °C. To the alane solution was added a precooled (−78 °C) solution of lactam **4a** (73 mg, 0.30 mmol) in 3 mL of THF via cannula. After 45 min, the solution was warmed to room temperature, stirred an additional 1 h, and then recooled to 0 °C. The mixture was quenched by the careful addition of 1 M HCl (5 mL), the phases were separated, and the aqueous was extracted with CH_2Cl_2. The combined organic phases were washed with 2 M NaOH (10 mL, back extracted with 10 mL of CH_2Cl_2) and brine (10 mL) and then dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 76 mg (80%) of **11a** shown to be a mixture of diastereomers (22.0:1) by HPLC analysis of derivative (*R*)-**14**. **11a:** ^{1}H NMR (300 MHz) δ 1.17 (d, $J = 6.3$ Hz, 3H), 1.30−1.46 (m, 2H), 1.56−1.74 (m, 6H), 2.42−2.50 (m, 1H), 2.87−2.95 (m, 1H), 3.16−3.22 (m, 1H), 3.38 (br s, 1H), 3.69 (dd, $J = 5.2$ and 10.3 Hz, 1H), 3.92 (appt t, 1H), 4.06 (dd, $J = 5.0$ and 10.3 Hz, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 20.5, 23.7, 29.3, 31.7, 35.6, 44.9, 54.1, 61.0, 65.0, 127.8, 128.5, 128.8, 138.3; MS *m*/*z* 233; HRMS (FAB$^+$) calcd for $C_{15}H_{23}NO$ $(M + H)^+$ 234.1858, found 234.1856. This material was used without further purification.

***N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*R*)-ethyl-hexahydrozepine 15a.** Alane was prepared as described for compound **11a**. To a solution of alane (0.43 mmol) in THF (5.2 mL) at −78 °C was added lactam **5a** (92 mg, 0.35 mmol) as a solution in THF (3.5 mL). This mixture was stirred for 1 h, warmed to −40 °C and stirred for 14 h, and then warmed to −20 °C and stirred for an additional 4 h. The reaction was quenched by the careful addition of 1 M HCl (3 mL), brine (1 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with 1 M NaOH (10 mL, back extracted with 10 mL of CH_2Cl_2) and brine (10 mL) and then dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 59 mg (68%) of **15a**, shown to be a mixture of diastereomers (11.5:1) by HPLC analysis of its urea derivative, **15c**. **15a:** ^{1}H NMR (300 MHz) δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.31−1.81 (m, 10H), 2.49−2.57 (m, 1H), 2.86−2.93 (m, 2H), 3.45 (br s, 1H), 3.68 (dd, $J = 5.0$ and 10.1 Hz, 1H), 3.93 (apt t, 1H), 4.04 (dd, $J = 5.0$ and 10.1 Hz, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 11.4, 23.9, 26.4, 29.4, 30.3, 31.1, 45.1, 61.0, 61.1, 65.8, 127.8, 128.4, 128.8, 138.4; MS *m*/*z* 247; HRMS (FAB$^+$) calcd for $C_{16}H_{25}NO$ $(M + H)^+$ 248.2014, found 248.2021. This material was used without further purification.

***N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*R*)-methyl-benzazepine 13a.** To a stirred solution of lactam **10a** (70 mg, 0.20 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (27 mg, 0.71 mmol) as a solid in one portion. The heterogeneous mixture was allowed to reach room temperature, stirred for 29 h, and then heated to reflux for 15 min. The mixture was cooled to 0 °C, quenched by the careful addition of 1 M HCl (3.0 mL), and made alkaline (pH 11) by the addition of 2 M NaOH. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with 1 M NaOH (10 mL, back extracted with 10 mL of EtOAc) and brine (10 mL) and dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 10:1, then EtOAc) provided 34 mg (50%) of pure **13a** as an oil and a 20:1 mixture of diastereomers. **13a:13b:** ^{1}H NMR (400 MHz) δ 0.78 (d, $J = 6.1$ Hz, 3H), 2.56 (dd, $J = 6.1$ and 15.0 Hz, 1H), 2.64 (dd, $J = 7.0$ and 14.0 Hz, 1H), 2.68−2.76 (m, 1H), 2.89 (br dd, $J = 8.7$ and 14.0 Hz, 1H), 3.01 (br dd, $J = 9.3$ and 11.0 Hz, 1H), 3.10 (apt d, $J = 13.9$ Hz, 1H), 3.17 (apt t, $J = 5.5$ Hz, 1H), 3.73 (dd, $J = 5.1$ and 10.5 Hz, 1H), 3.80 (s, 6H), 3.90 (apt t, $J = 9.2$ Hz, 1H), 3.99 (dd, $J = 4.7$ and 7.7 Hz, 1H), 6.51 (s, 1H), 6.55 (s, 1H), 7.24−7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 16.3, 36.9, 43.2, 45.8, 52.2, 56.2, 56.3, 61.4, 66.9, 112.9, 114.2, 128.0, 128.5, 128.7, 131.0, 133.3, 139.3, 147.0, 147.2; HRMS (FAB$^+$) calcd for $C_{21}H_{27}NO_3$ $(M + H)^+$ 342.2069, found 342.2071. This material was used without further purification in the next step.

General Procedure for the Reduction of *anti*-Bicyclic Lactams with DIBAL. *N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*S*)-methyl-hexahydroazepine 11b. To a solution of *anti*-bicyclic lactam **4b** (82 mg, 0.33 mmol) in THF (5 mL) at −78 °C was added diisobutylaluminum hydride (0.60 mL, 3.34 mmol) dropwise. The solution was stirred, with gradual warming to room temperature, for 12 h. The mixture was cooled to 0 °C and quenched by the careful addition of 1 M HCl (5.0 mL). It was made alkaline (pH 11) by the addition of 2 M NaOH and stirred for 0.5 h with warming to room temperature. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with 1 M NaOH (10 mL, back extracted with 10 mL EtOAc) and brine (10 mL) and dried (Na_2SO_4). The crude residue was purified by chromatography (hexanes/EtOAc 10:1, then EtOAc) to provide 73 mg (95%) of **11b**, shown to be a mixture of diastereomers (21.2:1) by HPLC analysis of the *N*-(*p*-bromobenzyoyl) derivative (*S*)-**14**, obtained from (*S*)-**12** (R = Me). **11b:** ^{1}H NMR (300 MHz) δ 1.00 (d, $J = 6.4$ Hz, 3H), 1.26−1.50 (m, 4H), 1.51−1.80 (m, 4H), 2.52−3.08 (bs, 1H), 2.76−2.89 (m, 2H), 3.17−3.30 (m, 1H), 3.78 (apt t, $J = 6.2$ Hz, 2H), 3.95 (dd, $J = 8.1$ and 14.6 Hz, 1H), 7.26−7.38 (m, 5H). This material was used without further purification in the next step.

***N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*S*)-ethyl-hexahydroazepine 15b.** Prepared from lactam **5b** (47 mg, 0.18 mmol) using the general procedure for DIBAL reduction. Flash chromatography of the crude product (hexanes/EtOAc 10:1, then EtOAc) provided 27 mg (61%) of **15b** shown to be a mixture of diastereomers (30.5:1) by HPLC analysis of the urea derivative **15c**. **15b:** ^{1}H NMR (300 MHz) δ 0.84 (t, $J = 7.4$ Hz, 3H), 1.30−1.81 (m, 10H), 2.78−2.95 (m, 3H), 3.70−3.85 (m, 2H), 4.0 (apt t, $J = 6.8$ Hz, 1H), 7.31−7.45 (m, 5H); ^{13}C NMR (100 MHz) δ 11.6, 24.3, 26.3, 29.2, 29.6, 32.9, 45.2, 61.7, 62.7, 68.6, 127.6, 128.5, 128.9, 140.7; MS *m*/*z* 247; HRMS (FAB$^+$)

calcd for $C_{16}H_{25}NO$ $(M + H)^+$ 248.2014, found 248.2013. This material was used without further purification in the next step.

***N*-(1′-(*R*)-Phenyl-2′-hydroxy-ethyl)-2-(*S*)-methyl-benzazepine 13b.** Prepared from *anti*-lactam **10b** (77 mg, 0.22 mmol) using the general procedure for DIBAL reduction. Flash chromatography of the crude product (hexanes/EtOAc 10:1, then 1:1) provided 40 mg (53%) of **13b** as an oil and a 30:1 mixture of diastereomers: ^{1}H NMR (300 MHz) δ 0.72 (d, J = 6.6 Hz, 3H), 2.56 (dd, J = 6.6 and 14.7 Hz, 1H), 2.63−2.77 (m, 2H), 2.98−3.10 (m, 2H), 3.32 (apt d, J = 14.9 Hz, 1H), 3.37−3.44 (m, 1H), 3.68 (dd, J = 5.1 and 10.9 Hz, 1H), 3.83−3.90 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.99 (dd, J = 5.2 and 8.2 Hz, 1H), 6.59 (s, 1H), 6.64 (s, 1H), 7.31−7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 13.9, 37.0, 42.4, 43.2, 55.2, 56.2, 56.3, 62.1, 70.3, 113.0, 114.3, 127.9, 128.7, 129.0, 131.0, 133.5, 140.1, 147.0, 147.1; MS *m*/*z* 341; HRMS (FAB$^+$) calcd for $C_{21}H_{27}NO_3$ $(M + H)^+$ 342.2069, found 342.2078. This material was used without further purification in the next step.

General Procedure for Hydrogenolysis of the Phenethyl Moiety. 2-(*R*)-Methyl-hexahydroazepine Hydrochloride (*R*)-12 (R = Me). A solution of amino alcohol **11a** (25 mg, 0.11 mmol) in EtOH (2 mL) was hydrogenated over 5 mg of $Pd(OH)_2$. After 4 h, the mixture was filtered over Celite, and the pad was rinsed with Et_2O. Concentrated HCl (5 drops) was added to the filtrate prior to concentration. The crude solid was triturated with Et_2O to provide 13 mg (85%) of (*R*)-**12** (R = Me) as a white solid that was used without further purification: $[\alpha]^{23}_D = -1.8$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 1.56 (d, J = 6.4 Hz, 3H), 1.63−2.13 (m, 8H), 3.18 (br s, 1H), 3.31 (br s, 1H), 3.43 (br s, 1H), 9.30 (br s, 1H), 9.65 (br s, 1H); ^{13}C NMR (100 MHz) δ 20.6, 25.0, 25.2, 27.0, 33.8, 44.9, 55.1.

2-(*R*)-Ethyl-hexahydroazepine Hydrochloride (*R*)-12 (R = Et). Prepared from **15a** (37 mg, 0.15 mmol) in 86% yield using the general procedure for hydrogenolysis: $[\alpha]^{23}_D = -5.8$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 1.07 (t, J = 7.2 Hz, 3H), 1.55−2.13 (m, 10H), 3.17 (m, 2H), 3.31 (br s, 1H), 9.26 (br s, 1H), 9.57 (br s, 1H); ^{13}C NMR (100 MHz) δ 10.7, 25.1, 25.2, 27.2, 27.2, 30.3, 45.3, 60.5. This material was used without further purification in the next step.

2-(*S*)-Methyl-benzazepine Hydrochloride (*S*)-17. Prepared from **13a** (40 mg, 0.15 mmol) in 65% yield using the general procedure for hydrogenolysis: $[\alpha]^{23}_D = -4.7$ (*c* 1.3, CH_2Cl_2). Anal. Calcd for $C_{13}H_{20}ClNO_2$: C, 60.58; H, 7.82; N, 5.43. Found: C, 58.66; H, 7.55; N, 5.03.

***N*-(*p*-Bromobenzoyl)-2-(*R*)-methyl-hexahydroazepine (*R*)-14.** To a solution of 4-bromobenzoyl chloride (29 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added azepine hydrochloride (*R*)-**12** (R = Me) (13 mg, 0.09 mmol) as a solution in CH_2Cl_2 (5 mL) and 2 M NaOH (2 mL), dropwise. The mixture was stirred vigorously for 4 h with gradual warming to room temperature. The phases were separated, and the aqueous one was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried (Na_2SO_4). The crude material was purified by flash chromatography (hexanes, then hexanes/EtOAc 10:1) twice to provide 16 mg (60%) of (*R*)-**14** as a mixture of rotamers. HPLC analysis ((*R*,*R*) Whelk-02 Pirkle covalent, hexanes/2-propanol 90:10, 1 mL/min) showed (*R*)-**14** to be a 20:1 mixture of enantiomers, with the major one eluting as the second peak: $[\alpha]^{23}_D = -28.4$ (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 1.02 (d, J = 6.9 Hz, 2H), 1.15−1.40 (m, 5H), 1.52−1.60 (m, 0.4H), 1.71−1.98 (m, 4H), 2.03−2.13 (m, 0.4 H), 2.73−2.92 (m, 0.6 H), 2.99 (dd, J = 11.8 and 14.9 Hz, 0.4H), 3.40 (br d, J = 15.0 Hz, 0.4H), 3.55−3.67 (m, 0.6H), 4.21 (br d, J = 13.1 Hz, 0.6 H), 4.62−4.66 (m, 0.4 H), 7.17−7.24 (m, 2H), 7.50−7.53 (m, 2H); ^{13}C NMR (75 MHz) δ 19.6, 21.0, 25.0, 25.3, 27.0, 29.1, 31.1, 30.8, 35.3, 36.3, 40.0, 43.4, 50.4, 53.6, 122.7, 127.6, 127.7, 131.6, 131.7, 136.6, 136.8, 170.0; IR (neat) 1628, 1589, 1422 cm^{-1}; MS *m*/*z* 295 (M − 1), 297 (M + 1); HRMS (FAB$^+$) calcd for $C_{14}H_{18}$79BrNO $(M + H)^+$ 296.0650, found 296.0637.

***N*-(*p*-Bromobenzoyl)-2-(*S*)-methyl-hexahydroazepine (*S*)-14.** Prepared from **11b** (after hydrogenolysis) as described for compound (*R*)-**12** (R = Me). HPLC analysis ((*R*,*R*) Whelk-02 Pirkle covalent, hexanes/2-propanol 90:10, 1 mL/min) showed (*S*)-**14** to be a 21.2:1 mixture of enantiomers: $[\alpha]^{23}_D = +29.8$ (*c* 1.1, CH_2Cl_2).

***N*-(1′-(*S*)-Methyl-benzylamino-carbonyl)-2-(*R*)-ethyl-hexahydroazepine 15c.** Azepine salt (*R*)-**12** (R=Et) (20 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (5 mL), washed with 2 M NaOH (2.5 mL, back extracted with CH_2Cl_2), and dried (Na_2SO_4). The filtered solution was cooled to 0 °C, and (*S*)-α-methylbenzyl isocyanate (0.03 mL, 0.21 mmol) was added. The mixture was stirred for 6 h with gradual warming to room temperature and was quenched with brine. The phases were separated, and the aqueous one was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), and the crude solid was purified by flash chromatography (hexanes, then hexanes/EtOAc 10:1) to provide 21 mg (64%) of **15c** as an off-white waxy solid. HPLC analysis (Chiracel OD, hexanes/2-propanol 97.5:2.5, 1 mL/min) showed **15c** to be an 11.5:1 mixture of diastereomers: mp 72−75 °C; $[\alpha]^{23}_D = -17.4$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.3 Hz, 3H), 1.15−1.36 (m, 4H), 1.40−1.66 (m, 4H), 1.53 (d, J = 6.5 Hz, 3H), 1.66−1.92 (m, 4H), 2.09−2.19 (m, 1H), 2.82−2.97 (m, 1H), 3.53 (br s, 1H), 4.01 (br s, 1H), 4.64 (br d, J = 6.3 Hz, 1H), 5.10 (quintet, J = 7.0 Hz, 1), 7.26−7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 11.0, 14.3, 23.1, 25.0, 28.1, 28.9, 30.1, 34.4, 41.4, 50.2, 126.2, 127.1, 128.7, 145.2, 157.4; IR (neat) 3344, 1617, 1528, 1494 cm^{-1}; MS *m*/*z* 274; HRMS (FAB$^+$) calcd for $C_{17}H_{26}N_2O$ $(M + H)^+$ 275.2123, found 275.2120.

***N*-(1′-(*S*)-Methyl-benzylamino-carbonyl)-2-(*S*)-ethyl-hexahydroazepine (*S*)-15c.** Prepared from **15b** (after hydrogenolysis) in 50% yield (two steps) as described for compound (*R*)-**12** (R = Et). HPLC analysis (Chiracel OD, hexanes/2-propanol 97.5:2.5, 1 mL/min) showed (*S*)-**15c** to be a 30.5:1 mixture of diastereomers: mp 97−102 °C; $[\alpha]^{23}_D = +30.8$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 0.84 (t, J = 6.8 Hz, 3H), 1.16−1.82 (m, 12H), 1.46 (d, J = 6.8 Hz, 3H), 2.08 (m, 1H), 2.82 (m, 1H), 4.52 (br d, 1H), 5.05 (m, 1H), 7.19−7.34 (m, 5H); ^{13}C NMR (100 MHz) δ 11.1, 14.4, 23.0, 25.1, 28.2, 28.9, 30.1, 34.6, 41.4, 50.0, 126.3, 127.2, 128.8, 145.2, 157.4; IR (neat) 3333, 1622, 1528, 1494 cm^{-1}; MS *m*/*z* 274; HRMS (FAB$^+$) calcd for $C_{17}H_{26}N_2O$ $(M + H)^+$ 275.2123, found 275.2120.

***N*-(*p*-Bromobenzoyl)-2-(*R*)-methyl-benzazepine 16.** Prepared from (*R*)-**17** (8 mg, 0.02 mmol) in 33% yield, as a mixture of rotamers, as described for compound (*R*)-**14**: $[\alpha]^{23}_D = -38.4$ (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 1.06−1.50 (br d, 3H), 2.65−3.12 (m, 4.6H), 3.24 (br t, 0.4H), 3.61 (br d, 0.4H), 3.81 (s, 2.4H), 3.86 (s, 3.6H), 3.96 (br s, 0.6H), 4.62 (br d, 0.6H), 5.14 (br s, 0.4H), 6.49 (s, 0.6H), 6.57 (s, 0.4H), 6.64 (s, 0.4H), 6.69 (s, 0.6H), 6.99 (d, J = 6.8 Hz, 1.2H), 7.18 (d, J = 7.2 Hz, 0.8H), 7.47 (d, J = 7.6 Hz, 1.2H), 7.52 (d, J = 7.6 Hz, 0.8H); ^{13}C NMR (100 MHz) δ 16.4, 17.6, 30.0, 35.0, 36.5, 37.4, 41.3, 41.7, 43.1, 46.9, 53.3, 56.2, 56.4, 113.3, 113.6, 114.0, 114.4, 123.5, 128.1, 128.6, 128.8, 132.0, 136.2, 147.8, 170.7; IR (neat) 1628, 1518, 1429 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{20}H_{22}$79BrNO$_3$ $(M + H)^+$ 404.0861, found 404.0852.

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Supporting Information Available: X-ray data and selected ^{1}H and ^{13}C spectra and CD curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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