Method C. Bis(diphenylphosphine)palladium Chloride. The reaction was carried out as described in method A except that 1.43 mmol of the iodopyrrole 1, bis(diphenylphosphine)-palladium chloride (0.075 g, 0.288 mmol), and cuprous iodide (0.027 g, 0.143 mmol) were used.

Cross Coupling of 1-(Triisopropylsilyl)-3,4-diiodopyrrole (10) with Monosubstituted Acetylenes. Method D. The reaction (10 mmol scale) was carried out exactly as in method B except that the amount of all the other reagents was doubled. The amounts of acetonitrile and triethylamine were the same as these of method B. The reaction time was 2 h.

Desilylation of 1-(Triisopropylsilyl)-3-pyrrolylacetylenes 8 and 11. The desilylation was effected as described above for a 10-min period (45 min for 8, R = Me_3Si). The solution was diluted with ether, washed with water, dried over magnesium sulfate, and evaporated in vacuo. Compound **9** (R = H) was obtained as a very unstable oil which was not manipulated further. The other crude acetylenic pyrroles were purified by column chromatography on Act II neutral alumina using hexane–ethyl acetate (85:15) as the eluting solvent. The yields, mps, etc. for those compounds are found in Table III. The ^1H NMR and infrared spectra are found in Table IV (supplementary material).

Supplementary Material Available: ^1H NMR, IR, and analytical data for 3-substituted pyrroles (6 pages). Ordering information is given on any current masthead page.

A Simple Asymmetric Synthesis of 2-Substituted Pyrrolidines and 5-Substituted Pyrrolidinones

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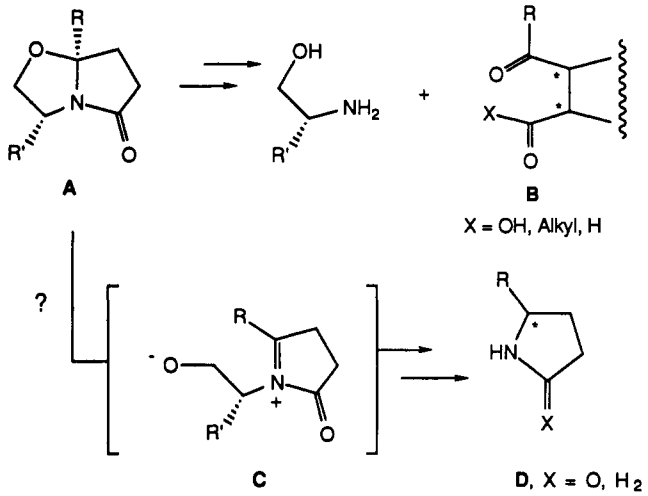
Received October 16, 1991

An efficient procedure for the preparation of the title compounds in high enantiomeric purity has been realized starting from 3-acylpropionic acids. Stereoselective reduction of chiral bicyclic lactams **2a–h**, prepared from the corresponding γ-keto acid and (*R*)-phenylglycinol, using alane or triethylsilane with titanium tetrachloride provided the N-substituted pyrrolidines and pyrrolidinones, respectively. Subsequent cleavage of the phenylglycinol returned the desired amines and lactams. The enantiomeric purity of these compounds was determined to be >98% by chiral stationary-phase HPLC.

Introduction

The pyrrolidine ring system is common to many naturally occurring[1] and medicinally important compounds.[2] Furthermore chiral auxiliaries,[3] chiral bases,[4] and chiral ligands[5] for asymmetric synthesis often employ this heterocyclic moiety. Although there are several procedures for the preparation of chiral pyrrolidines and pyrrolidinones, the majority of these exhibit poor enantiomeric excesses, lack versatility, suffer low yields or some com-

Scheme I



(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (b) Hart, D. J. *Ibid.* 1988; Vol. 6; Chapter 3. (c) Elbein, A. D.; Molyneux, R. J. *Ibid.* 1987; Vol. 5, Chapter 1. (d) Gellert, E. *Ibid.* 1987; Vol. 5, Chapter 2. (e) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, Chapter 4. (f) Massiot, G.; Delaude, C. *Ibid.* 1986; Vol. 27, Chapter 3. (g) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949. (h) Jones, T. H.; Blum, M. S.; Howard, R. W.; McDaniel, C. A.; Fales, H. M.; Dubois, M. B.; Torres, J. *J. Chem. Ecol.* **1982**, *8*, 285. (i) Rüger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331. (j) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (k) Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 439.

(2) (a) Psychotropic agents: Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 7057. (b) Muscarinic acid agonists: Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580. (c) Lundkvist, J. R.; Wistrand, L.-G.; Hacksell, U. *Tetrahedron Lett.* **1990**, *31*, 719. (d) Peptide mimics: Garvey, D. S.; May, P. D.; Nadzan, A. M. *J. Org. Chem.* **1990**, *55*, 936. (e) Heffner, R. J.; Joullié, M. M. *Tetrahedron Lett.* **1989**, *30*, 7021. (f) Novel amino acids: Silverman, R. B.; Nanavati, S. M. *J. Med. Chem.* **1990**, *33*, 931. (g) Anti cancer: Bick, I. R. C.; Hai, M. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 24, Chapter 3. (h) Neuromuscular transmission blocker: Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albequerque, E. X. *Neurochemical Res.* **1986**, *11*, 1227. (i) Immunoregulator: Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohasaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926. (j) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410. (k) Anti fungal: Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; Part 2, Vol. 5, pp 1–19 and references cited therein.

(3) (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590. (b) See: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2.

(4) (a) Tomioka, K. *Synthesis* **1990**, 541 and references therein. (b) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *42*, 523. (c) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

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Scheme II

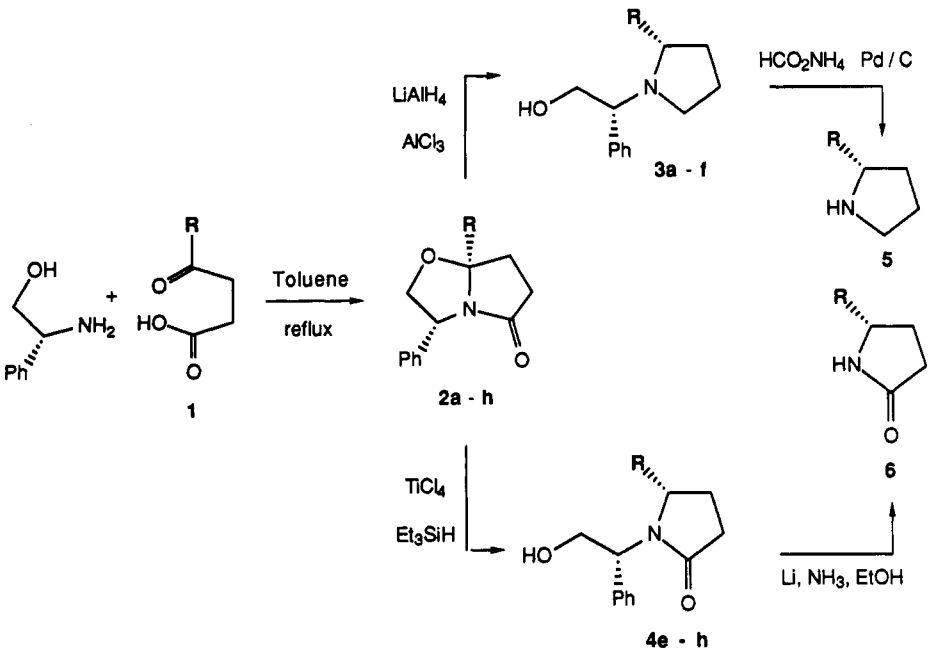


Table I. Formation of Pyrrolidines 5 and Pyrrolidinones 6 from Keto Acid 1 and Phenylglycinol

				pyrrolidines, 5		
R	% yield 2	$[\alpha]_D$,[b] deg	% yield 3	% yield	confn	$[\alpha]_D$,[d] deg
a, $PhCH_2$	77	−181.8	85[c]	60	*S*	+13.3 (CH_2Cl_2)[f]
b, *n*-butyl	91	−152.6	87	62	*R*	−12.0 ($CHCl_3$)
c, *n*-propyl	84	−145.2	75	78	*R*	−18.0 (MeOH)
d, phenyl	98	−99.6	95	51[d]	*S*	−22.0 (MeOH)
e, *n*-heptyl	76[a]	−142.2	90	75	*R*	−15.7 ($CHCl_3$)
f, cyclopentyl	83	−183.4	87	65	*S*	−6.0 (MeOH)
				pyrrolidinones, 6		
R	% yield 2	$[\alpha]_D$,[b] deg	% yield 4[h]	% yield	confn	$[\alpha]_D$,[e] deg
e, *n*-heptyl	76[a]	−142.2	87	93	*R*[j]	+9.0 (CH_2Cl_2)
f, cyclopentyl	83	−183.4	88	89[i]	*S*	+9.6 (CH_2Cl_2)
g, isobutyl	89	−170.3	85	65	*S*	+9.6 (CH_2Cl_2)
h, isopropyl	84	−207.6	94[k]	81[i]	*S*	−18.2 (CH_2Cl_2)[l]

[a] Obtained using dichloroethane as solvent; all other entries in this column were obtained using toluene. [b] All rotations taken in dichloromethane (c = 2.0). [c] Prepared from **2a** using only $LiAlH_4$; all other entires in this column were obtained using $LiAlH_4$–$AlCl_3$. [d] Obtained in two steps via LiDBB-induced elimination of sulfide **7**. [e] All products are >98% ee via HPLC analysis (except **6h** which is 97% enantiomerically pure) or comparison with literature values. [f] Also $[\alpha]_D$ = +20.0° (MeOH), +31.0° (2 N HCl(aq)). [g] Also $[\alpha]_D$ = −13.8° (THF). [h] Isolated yield of major diastereomer. [i] Obtained using Na instead of Li. [j] Reduced to the corresponding pyrrolidine and checked by specific rotation. [k] These diastereomers (97:3) were inseparable. [l] Also $[\alpha]_D$ = −5.0° (EtOH).

bination thereof.[6] Herein, we describe an efficient asymmetric synthesis of substituted pyrrolidines[7] and pyrrolidinones that should find general applicability to a variety of modern synthetic challenges.

In recent years a number of reports have originated from this laboratory concerning the construction of chiral nonracemic compounds via chiral bicyclic lactams (A).[8] These lactams, once properly functionalized, were stripped of the amino alcohol moiety to expose a latent 1,4-dicarbonyl compound B (Scheme I) which were then easily transformed to carbocyclic products. We wished to explore the possibility of preserving the existing pyrrolidine skeleton in A to provide access to a functionalized heterocycle D. The key to this plan was to generate and trap a reactive *N*-acyliminium ion (C) in a highly stereoselective manner. By use of phenylglycinol (A, R′ = phenyl) as the chiral auxiliary, it should be possible to eventually cleave the C–N bond to D.

Results and Discussion

Typically,[9] chiral bicyclic lactams are produced from the cyclodehydration of a γ-keto acid and amino alcohol. The starting keto acid 1, if not commercially available, is readily prepared using the procedure of Larson and co-workers.[10]

(6) (a) Georgiadis, M. P.; Haroutounian, S. A.; Apostolopoulos, C. D. *Synthesis* **1991**, 379. (b) Baldwin, J. E.; Maloney, M. G.; Shim. S. B. *Tetrahedron Lett.* **1991**, *32*, 1379. (c) Shiosaki, K.; Rappoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (d) Arseniyadis, S.; Huang, P. Q.; Diveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457. (e) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (f) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (g) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (h) Liotta, L. J.; Ganem, B. *SynLett* **1990**, 503. (i) Wanner, K. Th.; Höfner *Arch. Pharm.* (*Weinheim*) **1989**, *32*, 93 and 99. (j) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1989**, *30*, 2801. (k) Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 29. (l) Norlander, J. E.; Njoroge, F. G.; Payne, M. J.; Warman *J. Org. Chem.* **1985**, *50*, 3481. (m) Arseniyadis, S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 631. (n) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (o) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775. (p) Maryanoff, B. E.; McComsey, *J. Heterocycl. Chem.* **1985**, *22*, 911. (q) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.

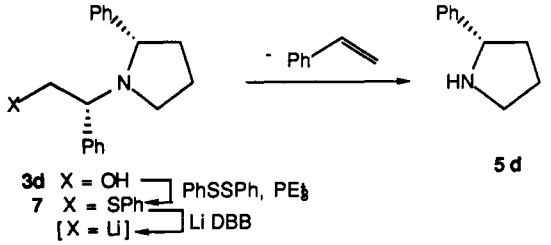
(7) For a preliminary communication, see: Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294.

(8) Romo, D.; Meyers, A. I. *Tetrahedron*, in press, and references cited therein.

(9) For alternative procedures, see: Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.

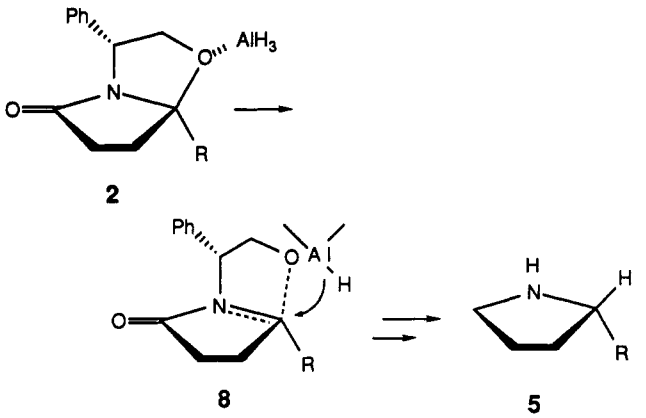
Simply heating an equimolar mixture of the requisite keto acid and (*R*)-phenylglycinol in toluene or dichloroethane overnight provided the desired bicyclic lactams **2a–h**, following silica gel chromatography (Scheme II). The lactams, thus obtained, were shown (NMR) to be comprised of a single diastereomer with the absolute configuration as depicted. It should be noted that the R group in the γ-keto acid **1** will ultimately become the 2-substituent in the pyrrolidines **5** and the 5-substituent in the pyrrolidinones **6**. With a reliable route to bicyclic lactams in hand, studies addressing the preparation of the substituted pyrrolidines and pyrrolidinones were initiated.

The requisite *N*-acyliminium ion C was smoothly generated under Lewis acid conditions, and subsequent hydride trapping of this reactive intermediate in a stereoselective fashion was realized (Scheme II). For example, treatment of **2a–f** with excess alane, prepared in situ from aluminum trichloride and lithium aluminum hydride, furnished the N-substituted 2-alkylpyrrolidines **3a–f** in >97% diastereomeric excess (NMR).[11] In this transformation the alane acts not only as the Lewis acid necessary to form the *N*-acyliminium ion C, but also acts as the hydride source to produce **3**. Of even more synthetic value was the observation made from exposure of lactams **2e–h** to triethylsilane in the presence of titanium tetrachloride. Under these conditions, the N-substituted 5-alkylpyrrolidinones **4e–h** were obtained in >94% diastereomeric excess.[12] Thus, selective and specific reduction of the *N*-acyliminium ion C in the presence of the lactam carbonyl had been accomplished. Hydrogenolysis[13] or dissolving metal conditions gave the corresponding free amines **5a–f** or lactams **6e–h** (Table I). In the case of the 2-phenyl derivative **3d**, which obviously could not tolerate benzylic cleavage, an alternative procedure for benzyl–N bond cleavage was devised. Diphenyl disulfide and triethylphosphine converted the primary alcohol **3d** to the corresponding phenyl sulfide **7**.[14] This was followed by treatment of the crude sulfide with lithium di-*tert*-butyl biphenylide[15] which resulted in lithiation and spontaneous elimination of styrene to generate the 2-phenylpyrrolidine (**5d**) in 51% yield over the two steps.



The assignment of the absolute configuration of pyrrolidines **5a–f** and pyrrolidinone **6h** were based on comparison of the observed optical rotation with those published. Thus, from the sign of these rotations the designation of R or S was made. Additionally, the stereochemistry of the pyrrolidinones **6e–g** were also assigned in this manner once they had been converted to their corresponding pyrrolidines **5** (LAH reduction). Although the sign of rotation had proved valuable in the assignment of configuration for these compounds, they proved less than ideal as a test of enantiomeric purity. For example, the ee's of the pyrrolidines **5** were calculated to range from 72 to 120% based on measured specific rotations. As a more reliable and accurate technique for evaluation of enantiomeric purity, analyses of naphthamide derivatives via chiral stationary-phase HPLC,[16] determined enantiomeric excesses to be ≥98% for the pyrrolidines **5** and pyrrolidinones **6**.[17]

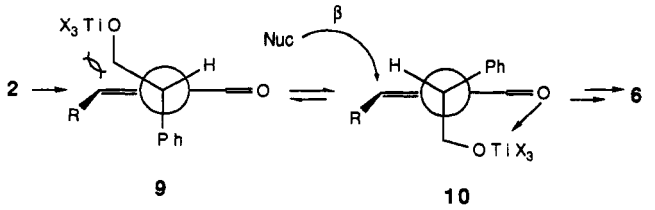
With these configurational assignments on firm ground, it became evident that each of the reductions on **2** had delivered hydride from the congested β-face to furnish the product containing the *R*-substituent with retained configuration. For the alane reduction, this is readily rationalized in accordance with analogous studies on *O,O*-acetal cleavage.[18] The alane, acting as a Lewis acid, weakens the C–O bond in **2** promoting *N*-acyliminium ion formation to **8**. Subsequent delivery of the hydride from the same face as the departing oxygen then provides the observed products **5** (after removal of the chiral auxiliary).



In the reduction of **2**, employing titanium tetrachloride and triethylsilane, the product with inversion of configuration should have been formed,[18] but *this was not observed*. What was obtained instead was also the product of retention (**4**), which was shown after lactam reduction to be identical to **5**. When this incongruity was noted, a reevaluation of the factors governing the reduction of the *N*-acyliminium ion was undertaken and shown to be dependent on the nature of the chiral auxiliary.[19] If one considers the proposed acyliminium ion C (depicted as **9** in a Newman projection viewed down the acylcic C–N bond), it becomes apparent that an allylic 1,3-interaction exists between the electrophilic carbon and the asymmetric center.[20] Subsequent counterclockwise rotation (120°) about the C–N bond minimizes this strain and places the large alkoxytitanium group antiperiplanar to the reactive π-system producing rotamer **10**.[21] From **10**, an opportunity for chelation involving the alkoxytitanium and amide carbonyl also emerges. Hydride addition to **10**, on the

(10) Bentacourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039.
(11) No other diastereomer could be detected by 300-MHz ^{1}H NMR.
(12) These diastereomeric ratios are based on isolated yields of each diastereomer.
(13) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.
(14) (a) Hata, T.; Sekine, M. *Chem. Lett.* **1974**, 837. (b) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. (c) Cleary, D. G. *Synth. Commun.* **1989**, 737.
(15) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Freeman, P. K.; Hutchinson, L. L. *Ibid.* **1983**, *48*, 4705.
(16) Both racemic and chiral *N*-naphthoylpyrrolidines were subjected to analytical HPLC using the Chiralcel OJ and OD cellulose based columns (Diacel Chemical Industries, see: Okamoto, Y.; Hatada, K. *J. Chromatogr.* **1987**, *95*, 389).
(17) For the pyrrolidinones **6**, the ee is dependent on separation of diastereomers **4** by flash chromatography. If left unpurified, the crude mixture **4** produces an ee of 94% in pyrrolidinone **6**.
(18) (a) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595. (b) Mori, I.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (c) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.
(19) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858.
(20) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860 and references cited therein.
(21) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

β-face opposite the large group, furnishes the observed pyrrolidinone **6**.



9 10

To summarize, an efficient and simple procedure has been devised for the preparation of 2-substituted pyrrolidines **5** and 5-substituted pyrrolidinones **6** in high enantiomeric purity. Although the destruction of the chiral auxiliary is required so that the nitrogen of the initial phenyl glycinol is retained in the final products, the low cost of both antipodes of phenylglycine make this methodology still synthetically attractive.

Experimental Section

THF and ether were distilled from sodium, while CH_2Cl_2, $ClCH_2CH_2Cl$, and toluene were distilled from calcium hydride immediately prior to use. Methanol was distilled from magnesium methoxide and stored under argon over 3-Å sieves. The reaction flasks were flame-dried under vacuum then placed under dry argon via Firestone valve prior to use.

All nuclear magnetic resonance spectra were obtained with 32K data sets. Infrared spectra were obtained on a FT-IR as thin films on NaCl plates unless indicated otherwise. All rotations were determined at 589 nm at ~26 °C. Melting points were determined with a capillary melting point apparatus and are uncorrected. Flash chromatography was conducted according to the procedure of Still.[22] Due to their air and moisture sensitivity, elemental analyses on the free pyrrolidines **5a–f** were not obtained.

(−)-(3*R*,7a*R*)-3-Phenyl-5-oxo-7a-(phenylmethyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2a). To a stirred solution of (*R*)-(−)-2-phenylglycinol (54 mg, 0.39 mmol) in dry toluene (5 mL) was added 5-phenyl-4-oxopentanoic acid[10] (75 mg, 0.39 mmol). The resulting clear, light yellow solution was heated to reflux under an argon atmosphere for 22 h. The resulting solution was allowed to cool to room temperature and then was concentrated at reduced pressure. The residual yellow oil was purified by flash chromatography on silica gel employing 1:1 hexane–ethyl acetate as the eluent to provide 88 mg (77%) of lactam **2a** as a clear, colorless oil: $[\alpha]_D$ −181.8° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 1 H), 2.35–2.42 (c, 3 H), 2.86 (d, 1 H, *J* = 13.8 Hz), 3.02 (d, 1 H, *J* = 13.8 Hz), 4.40 (dd, 1 H, *J* = 7.0, 8.8 Hz), 4.69 (dd, 1 H, *J* = 8.2, 8.7 Hz), 5.28 (t, 1 H, *J* = 7.5 Hz), 7.18–7.47 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 33.1, 42.2, 57.4, 72.3, 102.0, 125.9, 126.7, 127.3, 128.0, 128.5, 129.9, 135.3, 139.4, 178.9; IR (thin film) 3062–2856, 1714, 1360, 1240, 1033, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.82; H, 6.55; N, 4.82.

(−)-(3*R*,7a*S*)-3-Phenyl-5-oxo-7a-butyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2b). **2b** was prepared using the same procedure for **2a**. (*R*)-(−)-2-Phenylglycinol (132 mg, 0.96 mmol) and 4-oxo-4-octanoic acid[10] (160 mg, 1.0 mmol) in toluene (8 mL) provided, following flash chromatography with 2:1 hexanes–ethyl acetate, 213 mg (85%) of lactam **2b** as a clear, colorless oil: $[\alpha]_D$ −152.6° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, 3 H, *J* = 7.1 Hz), 1.22–1.71 (c, 6 H), 2.16 (m, 1 H), 2.37 (m, 1 H), 2.59 (ddd, 1 H, *J* = 2.4, 10.3, 17.2 Hz), 2.83 (m, 1 H), 4.07 (dd, 1 H, *J* = 7.4, 8.5 Hz), 4.63 (dd, 1 H, *J* = *J'* = 8.5 Hz), 5.18 (dd, 1 H, *J* = 7.4, 8.5 Hz), 7.22–7.36 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.6, 26.0, 30.9, 33.3, 35.9, 57.5, 72.8, 102.7, 125.4, 127.3, 128.6, 140.1, 179.3; IR (thin film) 2989–2944, 1711, 1360, 1028, 700 cm^{-1}.

(−)-(3*R*,7a*S*)-3-Phenyl-5-oxo-7a-propyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2c). **2c** was prepared using the same procedure for **2a**. (*R*)-(−)-2-Phenylglycinol (130 mg, 0.95 mmol) and 4-oxoheptanoic acid[10] (150 mg, 1.00 mmol) in toluene (7 mL) returned, following flash chromatography with 1:1 hexanes–ethyl acetate, 195 mg, (84%) of lactam **2c** as a light yellow oil: $[\alpha]_D$ −145.2° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3 H, *J* = 7.2 Hz), 1.32–1.71 (c, 4 H), 2.13 (m, 1 H), 2.34 (m, 1 H), 2.55 (ddd, 1 H, *J* = 2.5, 10.2, 17.2 Hz), 2.78 (m, 1 H), 4.04 (dd, 1 H, *J* = 7.4, 8.6 Hz), 4.60 (t, 1 H, *J* = 8.5 Hz), 5.15 (t, 1 H, *J* = 7.7 Hz), 7.20–7.34 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 17.1, 30.8, 33.1, 38.3, 57.4, 72.7, 102.5, 125.3, 127.2, 128.5, 140.1, 179.1; IR (thin film) 3061–2850, 1710, 1449, 1363, 1298, 1237, 1021 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.83; N, 5.71.

(−)-(3*R*,7a*R*)-3-Phenyl-5-oxo-7a-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2d). The same procedure as for **2a** was used. (*R*)-(−)-2-Phenylglycinol (548 mg, 4.0 mmol) and 3-benzoylpropionic acid[23] (750 mg, 4.2 mmol) in toluene (20 mL) returned, following flash chromatography on silica gel employing 3:1 hexane–ethyl acetate as the eluent, lactam **2d** (1.10 g; 98%) as a light yellow solid: mp 72–76 °C; $[\alpha]_D$ −99.6° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.30–2.39 (m, 1 H), 2.59–2.71 (c, 2 H), 2.91–3.04 (m, 1 H), 3.88 (t, 1 H, *J* = 8.8 Hz), 4.66 (dd, 1 H, *J* = 7.9, 8.9 Hz), 5.15, (t, 1 H, *J* = 8.3 Hz), 7.05–7.49 (c, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.1, 36.0, 59.2, 73.6, 102.8, 125.1, 126.8, 127.4, 128.2, 128.4, 128.6, 138.5, 142.1, 180.0; IR (thin film) 3060–2800, 1712, 1343, 1018 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.18; H, 6.09; N, 5.01.

(−)-(3*R*,7a*S*)-3-Phenyl-5-oxo-7a-heptyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2e). **2e** was prepared using the same procedure for **2a**, except that dichloroethane was used in place of toluene. (*R*)-(−)-2-Phenylglycinol (64 mg, 0.47 mmol) and 4-oxoundecanoic acid[10] (140 mg, 0.70 mmol) in dichloroethane (5 mL) gave, following flash chromatography with 2:1 hexanes–ethyl acetate, 106 mg (76%) of lactam **2e** as a clear, colorless oil: $[\alpha]_D$ −142.2° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, 3 H, *J* = 6.7 Hz), 1.18–1.66 (c, 12 H), 2.11 (m, 1 H), 2.31 (ddd, 1 H, *J* = 2.5, 9.7, 13.4 Hz), 2.53 (ddd, 1 H, *J* = 2.5, 10.3, 17.2 Hz), 2.78 (m, 1 H), 4.03 (dd, 1 H, *J* = 7.3, 8.6 Hz), 4.58 (t, 1 H, *J* = 8.5 Hz), 5.14 (t, 1 H, *J* = 7.7 Hz), 718–7.32 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 23.7, 28.9, 29.3, 30.8, 31.4, 33.1, 36.1, 57.4, 72.6, 102.5, 125.3, 127.1, 128.4, 140.0, 179.1; IR (thin film) 3029–2820, 1716, 1452, 1358, 1303, 1028, 697 cm^{-1}.

(−)-(3*R*,7a*R*)-3-Phenyl-5-oxo-7a-cyclopentyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2f). **2f** was prepared using the same procedure for **2a**. (*R*)-(−)-2-Phenylglycinol (89 mg, 0.65 mmol) and 4-oxo-4-cyclopentylbutanoic acid[10] (135 mg, 0.79 mmol) in toluene (7 mL) returned, following flash chromatography with 2:1 hexanes–ethyl acetate, 146 mg (83%) of lactam **2f** as a white solid: mp 122–124 °C; $[\alpha]_D$ −183.4° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.76 (c, 8 H), 2.03–2.38 (c, 3 H), 2.57–2.87 (c, 2 H), 4.11 (dd, 1 H, *J* = 7.2, 8.6 Hz), 4.66 (t, 1 H, *J* = 8.5 Hz), 5.22 (t, 1 H, *J* = 7.8 Hz), 7.20–7.37 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.2, 27.4, 27.5, 27.7, 33.7, 43.5, 57.6, 72.6, 105.2, 125.2, 127.2, 128.6, 140.5, 179.8; IR (CH_2Cl_2 solution) 3063–2857, 1706, 1380, 1342 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.09; H, 7.80; N, 5.16.

(−)-(3*R*,7a*R*)-3-Phenyl-5-oxo-7a-(2-methylpropyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2g). The same procedure as for **2a** was used. (*R*)-(−)-2-Phenylglycinol (452 mg, 3.3 mmol) and 6-methyl-4-oxoheptanoic acid[10] (550 mg, 3.5 mmol) in dry toluene (10 mL) returned, following flash chromatography on silica gel employing 2:1 hexane–ethyl acetate as the eluent, bicyclic lactam **2g** (758 mg; 89%) as a light yellow oil: $[\alpha]_D$ −170.3° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3 H, *J* = 6.7 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz), 1.51 (dd, 1 H, *J* = 4.9, 14.3 Hz), 1.65 (dd, 1 H, *J* = 7.5, 14.3 Hz), 1.79 (m, 1 H), 2.18 (dt, 1 H, *J* = 10.1, 13.4 Hz), 2.41 (ddd, 1 H, *J* = 2.7, 9.7, 13.3 Hz), 2.59 (ddd, 1 H, *J* = 2.6, 10.2, 17.3 Hz), 2.84 (dt, 1 H, *J* = 9.8, 17.3 Hz), 4.04 (dd, 1 H, *J* = 7.7, 8.6 Hz), 4.64 (t, 1 H, *J* = 8.5 Hz), 5.15 (t, 1 H, *J* = 7.8 Hz), 7.23–7.37 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 24.3, 24.7, 31.3, 33.0, 44.1, 57.5, 72.7, 102.8, 125.5, 127.3, 128.6, 140.0, 179.1; IR (thin film) 2975–2856, 1714, 1453, 1365, 1349, 1289, 1028 cm^{-1}.

(−)-(3*R*,7a*R*)-3-Phenyl-5-oxo-7a-isopropyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2h). **2h** was prepared ac-

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(23) Aldrich Chemical Co.

cording to the procedure for **2a**. Thus, 185 mg (1.30 mmol) of 4-oxo-5-methylhexanoic acid[10] and 176 mg (1.30 mmol) (*R*)-phenylglycinol were dissolved in toluene (8 mL) and heated at reflux for 18.5 h. Workup as before, followed by flash chromatography with 2:1 hexane–ethyl acetate, provided the bicyclic lactam **2h** (265 mg; 84%) as a white solid: mp 81–82 °C; $[\alpha]_D$ −207.6° (*c* = 2.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, 3 H, *J* = 6.8 Hz), 1.0 (d, 3 H, *J* = 6.8 Hz), 1.84–2.04 (c, 2 H), 2.40 (ddd, 1 H, *J* = 2.4, 9.8, 13.7 Hz), 2.60 (ddd, 1 H, *J* = 2.4, 10.5, 17.3 Hz), 2.76 (m, 1 H), 4.09 (dd, 1 H, *J* = 7.4, 8.6 Hz), 4.65 (t, 1 H, *J* = 8.5 Hz), 5.20 (t, 1 H, *J* = 7.9 Hz), 7.20–7.39 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 17.0, 26.2, 31.9, 33.9, 57.6, 72.5, 105.7, 125.4, 127.3, 128.6, 140.5, 179.8; IR (thin film) 2987–2867, 1709, 1365, 1327, 1077, 1044, 1017 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.35; H, 7.78; N, 5.65.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-benzyl-2-pyrrolidine (3a). To a stirred, cooled (−78 °C) solution of bicyclic lactam **2a** (35 mg, 0.12 mmol) in dry THF (1 mL) was added the lithium aluminum hydride (0.24 mL 1.0 M in ether; 0.24 mmol) dropwise via syringe under an argon atmosphere. Bubbling was observed. The resulting clear, colorless solution was allowed to stir at −78 °C for 40 min then allowed to warm to room temperature over 20 min and stir overnight (15 h). The reaction was then recooled to 0 °C and quenched by the careful addition of 1 N aqueous hydrochloric acid (2 mL) via syringe under an argon atmosphere (**Caution**: hydrogen gas evolution!). The resulting mixture was then extracted with CH_2Cl_2 (4 × 10 mL), and combined organic layers were washed with 10 mL 1 N aqueous NaOH (back-extracted with 5 mL of CH_2Cl_2) and 10 mL of brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated in vacuo to afford tertiary amine **3a** as a clear, colorless oil (29 mg; 86%). This material was carried on without further purification: $[\alpha]_D$ −115.0° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.41–1.70 (c, 4 H), 2.32 (m, 1 H), 2.46 (dd, 1 H, *J* = 9.4, 13.1 Hz), 2.87–2.96 (c, 2 H), 3.18 (dd, 1 H, *J* = 4.0, 13.2 Hz), 3.68 (dd, 1 H, *J* = 5.1, 10.1 Hz), 3.97 (t, 1 H, *J* = 10.2 Hz), 4.12 (dd, 1 H, *J* = 5.0, 10.2 Hz), 7.12–7.43 (c, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 29.8, 40.8, 45.7, 60.7, 61.5, 63.0, 126.0, 127.8, 128.2, 128.3, 129.2, 135.7, 139.7; IR (thin film) 3400 (br), 3050–2800, 1491, 1447, 1054, 1028 cm^{-1}.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*R*)-butyl-2-pyrrolidine (3b). Preparation of Alane. To a cooled (0 °C) quantity of anhydrous $AlCl_3$ (45 mg, 0.33 mmol) was added dry THF (2.5 mL) via syringe under a static argon atmosphere. The resulting clear, colorless solution was allowed to stir at 0 °C for 5 min, and lithium aluminum hydride (1.0 mL 1.0 M in THF, 1.0 mmol; 3 equiv) solution was added via syringe. Bubbling was observed. The resulting clear, colorless solution was allowed to warm to room temperature and stir for 20 min to give a solution of alane (1.33 mmol).

To a stirred, cooled (−78 °C) solution of alane in dry THF was added a solution of bicyclic lactam **2b** (94 mg, 0.36 mmol) in dry THF (3 mL) via cannula under an argon atmosphere. The resulting cloudy solution was allowed to stir at −78 °C for 45 min and then warmed to room temperature over 20 min and stirred an additional 15 min. The resulting clear, colorless solution was recooled to 0 °C and quenched with the careful addition of 1 N aqueous HCl (5 mL) via syringe (**Caution**: vigorous hydrogen gas evolution!). The resulting slurry was diluted with water (5 mL) and extracted with CH_2Cl_2 (5 × 15 mL). Combined organic layers were then washed with 10 mL of 1 N aqueous NaOH (back-extracted with 10 mL of dichloromethane) and 10 mL of brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 78 mg (87%) of pyrrolidine **3b** as a clear, colorless oil: $[\alpha]_D$ −123.3° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3 H, *J* = 6.9 Hz), 1.22–1.88 (c, 10 H), 2.17 (m, 1 H), 2.55 (m, 1 H), 2.90 (m, 1 H), 3.29 (br s, 1 H), 3.64 (dd, 1 H, *J* = 4.7, 9.7 Hz), 3.96 (t, 1 H, *J* = 10.2 Hz), 4.06 (dd, 1 H, *J* = 4.7, 10.7 Hz), 7.15–7.38 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.1, 23.1, 28.3, 29.8, 33.8, 45.4, 61.0, 62.2, 127.7, 128.0, 129.2, 135.3; IR (thin film) 3428 (br), 2978–2802, 1452, 1058, 1031 cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.49; H, 10.21; N, 5.63.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*R*)-propyl-2-pyrrolidine (3c). The same procedure as for pyrrolidine **3b** was used. Treatment of a solution of bicyclic lactam **2c** (37 mg, 0.15 mmol) in dry THF (3 mL) with a solution of alane (prepared from 24 mg of anhydrous $AlCl_3$ in 2 mL of dry THF with 0.54 mL of 1.0 M lithium aluminum hydride in THF) returned 26 mg (75%) of pyrrolidine **3c** as a clear, colorless oil: $[\alpha]_D$ −118.2° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3 H, *J* = 7.1 Hz), 1.23–1.84 (c, 8 H), 2.18 (m, 1 H), 2.57 (m, 1 H), 2.91 (m, 1 H), 3.47 (br s, 1 H), 3.64 (dd, 1 H, *J* = 4.7, 9.7 Hz), 3.97 (t, 1 H, *J* = 10.2 Hz), 4.06 (dd, 1 H, *J* = 4.7, 10.6 Hz), 7.13–7.39 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.3, 22.0, 29.7, 36.3, 45.4, 58.9, 61.0, 127.7, 128.0, 129.2, 135.2; IR (thin film) 3422 (br), 2986–2790, 1453, 1060, 1028 cm^{-1}.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-phenyl-2-pyrrolidine (3d). The same procedure as for pyrrolidine **3b** was used. Treatment of a solution of bicyclic lactam **2d** (550 mg, 1.97 mmol) in dry THF (10 mL) with a solution of alane (prepared from 580 mg of anhydrous $AlCl_3$ in 25 mL of dry THF with 13.1 mL of 1.0 M lithium aluminum hydride in THF) returned 494 mg (95%) of pyrrolidine **3d** as a light yellow oil: $[\alpha]_D$ −205.1° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–2.11 (c, 4 H), 2.33 (q, 1 H, *J* = 8.6 Hz), 3.03 (br s, 1 H), 3.15 (m, 1 H), 3.47 (t, 1 H, *J* = 7.9 Hz), 3.53 (dd, 1 H, *J* = 5.3, 10.3 Hz), 3.77 (dd, 1 H, *J* = 5.1, 10.5 Hz), 3.99 (t, 1 H, *J* = 10.4 Hz), 7.10–7.44 (c, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 34.6, 45.4, 61.5, 62.2, 64.6, 127.3, 127.7, 127.7, 128.1, 128.8, 129.4, 134.8, 143.5; IR (thin film) 3433 (br), 3085–2800, 1485, 1447, 1055, 1028 cm^{-1}.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*R*)-heptyl-2-pyrrolidine (3e). The same procedure as for pyrrolidine **3b** was used. Treatment of a solution of bicyclic lactam **2e** (90 mg, 0.30 mmol) in dry THF (4 mL) with a solution of alane (prepared from 52 mg of anhydrous $AlCl_3$ in 3 mL of dry THF with 1.2 mL of 1.0 M lithium aluminum hydride in THF) returned 78 mg (90%) pyrrolidine **3e** as a light yellow solid: mp 68–69.5 °C; $[\alpha]_D$ −126.2° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3 H, *J* = 6.5 Hz), 1.11–1.85 (c, 16 H), 2.19 (m, 1 H), 2.56 (m, 1 H), 3.59 (br s, 1 H), 3.64 (dd, 1 H, *J* = 4.6, 9.7 Hz), 3.94–4.09 (c, 2 H), 7.15–7.37 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.0, 22.6, 26.1, 29.3, 29.7, 29.9, 31.8, 33.9, 45.4, 59.2, 61.0, 62.3, 127.7, 128.0, 129.2, 135.1; IR (CH_2Cl_2) 3400, 2975–2812, 1453, 1028 cm^{-1}. Anal. Calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.80; N, 4.84. Found: C, 78.76; H, 10.84; N, 4.81.

(−)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-cyclopentyl-2-pyrrolidine (3f). The same procedure was used as for pyrrolidine **3b**. Treatment of a solution of bicyclic lactam **2f** (92 mg, 0.34 mmol) in dry THF (3 mL) with a solution of alane (prepared from 31 mg of anhydrous $AlCl_3$ in 5 mL of dry THF with 0.7 mL of 1.0 M lithium aluminum hydride in THF) returned 76.4 mg (87%) of tertiary amine **3f** as a clear, colorless oil: $[\alpha]_D$ −106.3° (*c* = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15–1.85 (c, 12 H), 2.19–2.42 (c, 2 H), 2.80–2.94 (c, 2 H), 3.47 (br s, 1 H), 3.60 (dd, 1 H, *J* = 4.9, 9.9 Hz), 3.98 (dd, 1 H, *J* = 10.0, 10.9 Hz), 4.11 (dd, 1 H, *J* = 4.8, 11.0 Hz), 7.16–7.38 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.6, 26.0, 26.0, 26.4, 30.5, 41.6, 45.5, 61.0, 61.9, 62.3, 127.7, 128.0, 129.3, 135.2; IR (thin film) 3422 (br), 2965–2847, 1450, 1031 cm^{-1}.

(+)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*R*)-heptyl-2-pyrrolidinone (4e). To a cooled (−78 °C), stirred solution of triethylsilane (0.78 mL, 4.9 mmol) and bicyclic lactam **2e** (460 mg, 1.53 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of titanium(IV) tetrachloride (3.4 mL of 1.0 M in CH_2Cl_2; 3.4 mmol) via syringe under an argon atmosphere. The resulting clear, orange solution was allowed to stir at −78 °C for 1.5 h and then gradually allowed to warm to room temperature over 3 h. The reaction was allowed to stir at room temperature overnight (~12 h) and then was recooled to 0 °C and carefully quenched via syringe (vigorous reaction!) with saturated aqueous ammonium chloride (35 mL). The resulting mixture was diluted with 20 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were treated, via syringe, with a solution of concentrated HF in dry acetonitrile (1.0 mL of a 2 N solution; 2 mmol). The resulting solution was allowed to stir at room temperature for 0.5 h. The acidic solution was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to give 421 mg of the crude product. Flash chromatography with 1:2 hexane–ethyl acetate provided the major diastereomer **4e** (403 mg; 87%) as a clear, colorless oil along with a small amount of

the minor diastereomer (~14 mg).

For major diastereomer **4e**: $[\alpha]_D$ +24.5° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 6.7 Hz), 1.15–1.44 (c, 11 H), 1.59 (m, 1 H), 1.76 (m, 1 H), 2.09 (m, 1 H), 2.40–2.61 (c, 2 H), 3.36 (m, 1 H), 3.95 (dd, 1 H, J = 3.2, 12.3 Hz), 4.26 (dd, 1 H, J = 7.9, 12.2 Hz), 4.42 (dd, 1 H, J = 3.0, 7.7 Hz), 7.22–7.38 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.3, 23.9, 24.3, 28.8, 29.2, 30.9, 31.4, 32.3, 58.9, 61.2, 63.6, 127.0, 127.5, 128.4, 137.4, 176.6; IR (thin film) 3381 (br), 2958–2840, 1663, 1447, 1418, 1285, 1064 cm^{-1}; mass spectrum, m/z 272 (M − 31), 184, 174, 84.

(+)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-cyclopentyl-2-pyrrolidinone (4f). **4f** was prepared according to the procedure given for **4e**. Thus, 102 mg (0.38 mmol) of bicyclic lactam **2e** and 0.21 mL (1.3 mmol) triethylsilane with 0.94 mL (1.0 M in CH_2Cl_2; 0.94 mmol) of titanium(IV) tetrachloride in dry CH_2Cl_2 (5 mL) returned following workup and treatment with hydrofluoric acid, 104 mg of the crude product. Flash chromatography with 1:2 hexane–ethyl acetate provided the major diastereomer **4e** (90 mg; 88%) as a white solid along with a small amount of the minor diastereomer (~3 mg).

For major diastereomer **4f**: mp 93–95 °C; $[\alpha]_D$ +32.5° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09–1.27 (c, 2 H), 1.54–1.68 (c, 6 H), 1.81 (m, 1 H), 2.02 (m, 1 H), 2.27 (m, 1 H), 2.42–2.62 (c, 2 H), 3.53 (dt, 1 H, J = 4.8, 8.4 Hz), 3.98 (dd, 1 H, J = 3.2, 12.3 Hz), 4.28 (dd, 1 H, J = 7.7, 12.2 Hz), 4.47 (dd, 1 H, J = 3.0, 7.6 Hz), 7.21–7.38 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 25.4, 25.6, 26.1, 28.9, 31.5, 41.1, 61.9, 62.3, 64.3, 127.1, 127.7, 128.6, 137.5, 177.1; IR (thin film) 3379 (br), 2965–2845, 1660, 1447, 1420, 1278, 1060 cm^{-1}; mass spectrum, m/z 242 (M − 31), 204, 174, 154, 84. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.40; H, 8.47; N, 5.04.

(+)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-(2-methylpropyl)-2-pyrrolidinone (4g). **4g** was prepared according to the procedure given for **4e**. Thus, 195 mg (0.75 mmol) of bicyclic lactam **2g** and 0.42 mL (2.6 mmol) of triethylsilane with 1.9 mL (1.0 M in CH_2Cl_2; 1.9 mmol) of titanium(IV) tetrachloride in dry CH_2Cl_2 (10 mL) returned, following workup and treatment with HF, 192 mg of a clear, colorless, viscous oil. This crude material was purified via flash chromatography on silica gel (2:1 EtOAc–hexane) to give the major diastereomer **4g** as a clear, colorless, viscous oil (167 mg; 85%) along with a small amount of the minor diastereomer (~7 mg).

For the major diastereomer **4g**: $[\alpha]_D$ +31.8° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, 3 H, J = 6.3 Hz), 0.86 (d, 3 H, J = 6.4 Hz), 1.27 (m, 1 H), 1.39 (dt, 1 H, J = 3.0, 13.7 Hz), 1.52 (m, 1 H), 1.70 (m, 1 H), 2.07 (m, 1 H), 2.39 (ddd, 1 H, J = 5.0, 9.5, 17.0 Hz), 2.50 (m, 1 H), 3.35 (m, 1 H), 3.92 (dd, 1 H, J = 3.5, 12.2 Hz), 4.24 (dd, 1 H, J = 8.0, 12.2 Hz), 4.43 (dd, 1 H, J = 3.5, 7.9 Hz), 4.83 (br s, 1 H), 7.21–7.34 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 23.8, 24.5, 24.7, 30.8, 41.4, 61.8, 63.9, 127.1, 127.6, 128.5, 137.4, 176.4; IR (thin film) 3373 (br), 2970–2859, 1662, 1466, 1450, 1423, 1368, 1292, 1270, 1172, 1063 cm^{-1}.

(+)-*N*-[2-(1-Hydroxy-2(*R*)-phenylethyl)]-5(*S*)-isopropyl-2-pyrrolidinone (4h). **4h** was prepared according to the procedure given for **4e**. Thus, 97 mg (0.36 mmol) of bicyclic lactam **2h** and 0.22 mL (1.4 mmol) of triethylsilane with 0.99 mL (1.0 M in CH_2Cl_2, 0.99 mmol) of titanium(IV) tetrachloride in dry CH_2Cl_2 (5 mL) returned following workup and treatment with HF, 103 mg of the crude product. Flash chromatography with 1:2 hexane–ethyl acetate provided the major diastereomer **4h** (92 mg; 94%) as a clear, colorless oil (no trace of another diastereomer could be detected): $[\alpha]_D$ +53.1° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, 3 H, J = 6.8 Hz), 0.83 (d, 3 H, J = 6.6 Hz), 1.74–2.13 (c, 3 H), 2.44–2.50 (c, 2 H), 3.35 (p, 1 H, J = 4.2 Hz), 3.96 (ddd, 1 H, J = 3.1, 6.4, 12.0 Hz), 4.28 (dt, 1 H, J = 7.7, 12.0 Hz), 4.37 (dd, 1 H, J = 3.0, 7.8 Hz), 4.86 (t, 1 H, J = 7.1 Hz), 7.21–7.36 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.0, 18.5, 27.8, 31.7, 62.1, 63.6, 64.3, 127.1, 127.7, 128.6, 137.3, 177.3; IR (thin film) 3371 (br), 2968–2860, 1658, 1462, 1442, 1422, 1388, 1368, 1324, 1285, 1250, 1167, 1063 cm^{-1}; mass spectrum, m/z 242 (M − 31), 204, 174, 154, 84. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.40; H, 8.47; N, 5.04.

(+)-2(*S*)-Benzylpyrrolidine (5a).[6k,l] To a stirred solution of anhydrous ammonium formate (72 mg, 1.1 mmol) and tertiary amine **3a** (40 mg, 0.14 mmol) in anhydrous methanol (2 mL) was added 10% palladium on carbon catalyst (25 mg). The resulting black slurry was stirred vigorously at room temperature under an argon atmosphere for 19 h. [Note: The reaction time varied with the quality and quantity of the catalyst and formate salt. Thus, with pure, dry reagents and extended reaction times (>2 h) the N-acylated product (formamide) was obtained instead of the free amine.] The reaction mixture was then concentrated at reduced pressure, and the residue was subjected to flash silica gel chromatography with CH_2Cl_2/CH_3OH (4:1) eluent to afford 13.5 mg (60%) of 2(*S*)-benzylpyrrolidine (**5a**) as a light yellow oil: $[\alpha]_D$ +13.3° (c = 1.8, CH_2Cl_2), +20.0° (c = 0.3, MeOH), +31.0° (c = 0.8, 2 N aqueous HCl); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52–1.95 (c, 4 H), 2.81 (dd, 1 H, J = 8.0, 13.4 Hz), 2.97–3.05 (c, 2 H), 3.16 (m, 1 H), 3.44 (m, 1 H), 5.78 (br s, 1 H), 7.18–7.30 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 30.6, 40.1, 45.1, 60.6, 126.5, 128.6, 129.0, 138.4; IR 3550–3100, 3019–2790, 1632, 1600, 1491, 1447, 1403 cm^{-1}.

(−)-2(*R*)-*n*-Butylpyrrolidine (5b).[6m,o] The same procedure was used as for pyrrolidine **5a**. Thus, 37 mg of tertiary amine **3b** along with 57 mg of ammonium formate and 13 mg of 10% Pd on C in 2 mL of anhydrous CH_3OH gave, following isolation via flash silica gel chromatography with CH_2Cl_2/CH_3OH (4:1) eluent, 11.8 mg of 2(*R*)-*n*-butylpyrrolidine **5b** (62%) as a clear, colorless oil which became light yellow when exposed to air: $[\alpha]_D$ −12.0° (c = 0.6, $CHCl_3$), −8.2° (c = 0.7, MeOH); ^1H NMR δ 0.89 (t, 3 H, J = 6.9 Hz), 1.16–1.92 (c, 10 H), 2.77–3.05 (c, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.9, 25.4, 29.7, 31.9, 36.1, 46.6, 59.4; IR (thin film) 3420 (br), 2965–2834 cm^{-1}.

(−)-2(*R*)-*n*-Propylpyrrolidine (5c).[6q] The same procedure as for pyrrolidine **5a** was used. Thus, 50 mg of tertiary amine **3c** along with 200 mg of ammonium formate and 20 mg of 10% Pd on C in 2 mL of anhydrous CH_3OH gave, following isolation via flash silica gel chromatography with CH_2Cl_2/CH_3OH (4:1) eluent, 16.5 mg of 2(*R*)-*n*-propylpyrrolidine (**5c**) (68%) as a clear, colorless oil which became light yellow when exposed to air: $[\alpha]_D$ −18.0° (c = 0.1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3 H, J = 7.0 Hz), 1.14–1.47 (c, 5 H), 1.63–1.88 (c, 4 H), 2.76–3.03 (c, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.7, 25.4, 31.9, 38.8, 46.6, 59.1.

(−)-2(*R*)-*n*-Heptylpyrrolidine (5e).[6m–o] The same procedure was used as for pyrrolidine **5a**. Thus, 68 mg of tertiary amine **3e** along with 220 mg of ammonium formate and 50 mg of 10% Pd on C in 1.5 mL of anhydrous CH_3OH gave, following isolation via flash silica gel chromatography with CH_2Cl_2/CH_3OH (4:1) eluent, 26 mg of 2(*R*)-*n*-heptylpyrrolidine (**5e**) (65%) as a clear, colorless oil which became light yellow when exposed to air: $[\alpha]_D$ −15.7° (c = 1.1, $CHCl_3$), −13.8° (c = 2.0, THF); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 6.7 Hz), 1.14–1.47 (c, 12 H), 1.65–1.89 (c, 4 H), 2.76–3.04 (c, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 27.5, 29.3, 29.8, 31.8, 31.9, 36.5, 46.6, 59.4; IR (thin film) 3340 (br), 2290–2800, 1538, 1455, 1402 cm^{-1}.

(−)-2(*S*)-Cyclopentylpyrrolidine (5f). The same procedure was used as for pyrrolidine **5a**. Thus, 70 mg of tertiary amine **3f** along with 255 mg of ammonium formate and 60 mg of 10% Pd on C in 2 mL of anhydrous methanol returned following isolation via flash silica gel chromatography with CH_2Cl_2/CH_3OH (4:1) eluent, 24 mg of 2(*S*)-cyclopentylpyrrolidine **5f** (65%) as a clear, colorless oil which became light yellow when exposed to air: $[\alpha]_D$ −6.0° (c = 0.2, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86–2.00 (c, 13 H), 2.78–3.03 (c, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 25.5, 29.5, 29.7, 30.2, 30.9, 31.1, 46.1, 64.8.

(+)-5(*R*)-*n*-Heptyl-2-pyrrolidinone (6e). Ammonia (~40 mL) was condensed into a stirred (glass-covered stir bar) solution of pyrrolidinone **4e** (375 mg, 1.24 mmol) in dry THF (10 mL) and anhydrous ethyl alcohol (0.73 mL, 12.4 mmol) via cold finger (dry ice–acetone), under a static argon atmosphere. To the resulting cold (−33 °C), stirred solution was added enough lithium to produce a dark blue color that persisted for a total of 3 min. The blue reaction was then quenched by the careful addition of a small amount of ammonium chloride (solid). The cold finger was then removed, and the resulting white solution was allowed to warm to room temperature over ~4 h (**Caution**: ammonia gas is evolved). The residual milky solution was concentrated at reduced pressure, and the resulting semisolid was diluted with water (10 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The combined organics were dried (Na_2SO_4) and concentrated at reduced pressure, and the residue was subjected to flash chromatography

(ethyl acetate, on silica gel) to return 211 mg (93%) of **6e** as a white solid: mp 42–44 °C; $[\alpha]_D$ +9.0° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, 3 H, J = 6.7 Hz), 1.17–1.61 (c, 13 H), 2.06–2.25 (c, 3 H), 3.52 (p, 1 H, J = 6.6 Hz), 7.64 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.4, 25.5, 27.0, 28.9, 29.2, 30.3, 31.5, 36.5, 54.6, 178.6; IR (thin film) 3204 (br), 2968–2830, 1698, 1457, 1383, 1349, 1309, 1265 cm^{-1}. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.14; H, 11.53; N, 7.61.

(+)-5(*S*)-Cyclopentyl-2-pyrrolidinone (6f). **6f** was prepared according to the procedure given for **6e**, except sodium was substituted for lithium. Thus, 48 mg (0.18 mmol) of lactam **4f** and 0.10 mL (1.8 mmol) ethanol with ~20 mL dry ammonia in dry THF (3 mL) returned, following workup and purification by flash chromatography (EtOAc on silica gel), 24 mg (89%) of **6f** as a white solid: mp 111–113 °C; $[\alpha]_D$ +9.6° (c = 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.11–1.24 (c, 2 H), 1.51–1.89 (c, 8 H), 2.16–2.34 (c, 3 H), 3.44 (q, 1 H, J = 7.2 Hz), 6.82 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 25.4, 26.4, 28.8, 29.7, 46.1, 59.5, 178.5; IR (thin film) 3172 (br), 2954–2834, 1692, 1458, 1355, 1311, 1267 cm^{-1}. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.63; H, 9.83; N, 9.09.

(+)-5(*S*)-(2-Methylpropyl)-2-pyrrolidinone (6g). **6g** was prepared according to the procedure given for **6e**. Thus, 190 mg (0.73 mmol) of lactam **4g** and 0.43 mL (7.3 mmol) ethanol with ~35 mL of dry ammonia in dry THF (5 mL) returned, following workup and purification by flash chromatography on silica gel (ethyl acetate as eluent), the free pyrrolidinone **6g** as a white solid (67 mg; 65%): mp 61–62 °C; $[\alpha]_D$ +9.6° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3 H, J = 6.6 Hz), 0.88 (d, 3 H, J = 6.6 Hz), 1.26 (m, 1 H), 1.43 (m, 1 H), 1.62 (m, 1 H), 2.16–2.31 (c, 4 H), 3.67 (p, 1 H, J = 6.9 Hz), 7.26 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.8, 25.1, 27.6, 30.3, 45.9, 52.7, 178.6; IR (thin film) 3194 (br), 2955–2871, 1683, 1464, 1388, 1367, 1293, 785 cm^{-1}. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.93; H, 10.66; N, 9.93.

(-)-5(*S*)-Isopropyl-2-pyrrolidinone (6h).[6k] **6h** was prepared according to the procedure given for **6e**, except sodium was substituted for lithium. Thus, 65 mg (0.26 mmol) of lactam **4h** and 0.15 mL (2.6 mmol) ethanol with ~20 mL of dry ammonia in dry THF (4 mL) returned, following workup and flash chromatography (ethyl acetate), 27 mg (81%) of **6h** as a white solid: mp 64–65 °C; $[\alpha]_D$ -18.2° (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3 H, J = 6.7 Hz), 0.93 (d, 3 H, J = 6.7 Hz), 1.61 (p, 1 H, J = 6.8 Hz), 1.74 (m, 1 H), 2.15 (m, 1 H), 2.28–2.37 (c, 2 H), 3.36 (q, 1 H, J = 6.9 Hz), 6.81 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 18.7, 24.7, 30.5, 33.5, 60.6, 178.6; IR (thin film) 3200 (br), 2968–2875, 1702, 1657, 1385, 1314, 1292, 1269 cm^{-1}. Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.97; H, 10.34; N, 11.01.

(+)-*N*-[2-(2(*R*)-Phenyl-1-(phenylthio)ethyl)]-5(*S*)-phenyl-2-pyrrolidine (7). To a stirred solution of diphenyl disulfide (56 mg, 0.25 mmol) and tertiary amine **3f** (34 mg, 0.13 mmol) in dry pyridine (3 mL) was added triethylphosphine (0.06 mL, 0.41 mmol) via syringe under an argon atmosphere. The resulting clear, colorless solution was heated at reflux for 14 h. The resulting yellow solution was allowed to cool to room temperature and was concentrated in vacuo for several hours to remove solvent and phosphine. The residual oil was diluted with 2 mL of 1 N aqueous NaOH and stirred vigorously for 1 h. The resulting mixture was extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give sulfide **7** (41 mg; 90%) as a clear, yellow oil which, due to its instability to silica gel, was carried on to the next step in crude form. Purification could be effected via flash chromatography on silica gel to give a clear, colorless oil: $[\alpha]_D$ +26.2° (c = 2.0 CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 1 H), 1.72–1.87 (c, 2 H), 2.05 (m, 1 H), 2.30 (q, 1 H, J = 8.6 Hz), 2.67 (dd, 1 H, J = 4.7, 12.3 Hz), 3.06 (dd, 1 H, J = 10.8, 12.3 Hz), 3.23–3.39 (c, 2 H), 4.28 (dd, 1 H, J = 4.7, 10.7 Hz), 7.01–7.51 (c, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 35.3, 52.0, 53.4, 59.3, 70.0, 126.7, 126.8, 126.9, 127.6, 128.0, 128.1, 128.1, 128.6, 131.6, 135.3, 140.7, 143.5; IR (thin film) 3070–2750, 1490, 1480, 1452, 1436 cm^{-1}.

(-)-2(*S*)-Phenylpyrrolidine (5d).[6p] Preparation of lithium di-*tert*-butylbiphenylide: To a stirred (glass-covered stir bar), cooled (0 °C) solution of di-*tert*-butylbiphenyl (144 mg, 0.54 mmol, recrystallized from methanol and dried under high vacuum) in dry THF (5 mL, freshly distilled from sodium and oxygen free) was added a small piece of lithium metal (~7 mg, cut from wire over oil, pressed flat with pliers, and washed with pentane) under a static argon atmosphere. The resulting mixture was sonicated for ~100 s until a dark green color persisted. The resulting dark green solution was stirred at 0 °C for 4 h to produce a solution of lithium di-*tert*-butylbiphenylide in THF. To a stirred, cooled (-78 °C) solution of lithium di-*tert*-butylbiphenylide in dry THF (~0.10 M) was added a solution of sulfide **7** (62 mg, 0.17 mmol) in dry THF (3 mL) via cannula under an argon atmosphere. During addition the color went from dark green to dark red. The resulting solution was allowed to stir at -78 °C for 1 h then warmed to 0 °C over 5 min. The solution was allowed to stir at 0 °C for 50 min (color went from dark red back to dark green) then was diluted with reagent grade ether (5 mL). The excess lithium was removed with tweezers, and the resulting colorless cloudy solution was concentrated at reduced pressure. The residue was diluted with 1 N aqueous NaOH and extracted with CH_2Cl_2 (3 × 10 mL). Combined organics were dried (Na_2SO_4) and concentrated at reduced pressure to give a considerable quantity of yellow solid (di-*tert*-butylbiphenyl present). Bulb-to-bulb distillation of this solid (~100 °C at <0.5 mmHg) returned 2-phenylpyrrolidine (**5d**) (13 mg, 51%) as a clear, light yellow, pungent oil: $[\alpha]_D$ -22.0° (c = 0.3, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.61–2.27 (c, 4 H), 3.02 (m, 1 H), 3.21 (m, 1 H), 4.12 (t, 1 H, J = 7.7 Hz), 7.15–7.43 (c, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 34.4, 47.0, 62.6, 126.5, 126.7, 128.3, 144.9; IR (thin film) 3300 (br), 3019–2780, 1600, 1485, 1447, 1066 cm^{-1}.

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