The Synthesis of Aracemic 4-Substituted Pyrrolidinones and 3-Substituted Pyrrolidines. An Asymmetric Synthesis of (−)-Rolipram

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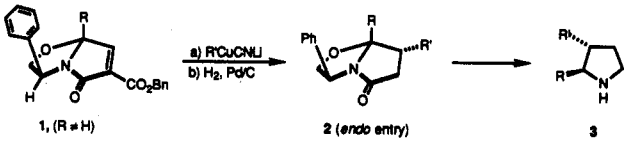
Conjugate additions of RCuCNLi to the chiral α,β-unsaturated lactam 4 gives almost exclusive exo addition—a reversal in stereochemistry when cuprates were added to chiral lactam 1. The lactams 5 were transformed into 4-substituted pyrrolidinones 8 via a three-step sequence which involved decarbalkoxylation, silane reduction and metal–ammonia benzylamine cleavage. The chemical yields as well as the enantiomeric purity were very high for this process. As an example of the usefulness of this scheme, the antidepressant (−)-Rolipram was prepared in good overall yield. Furthermore, the bicyclic lactams 6 were readily transformed, using alane as the reducing agent, to 3-substituted pyrrolidines 11. Absolute configurations of 8 and 11 were confirmed by comparison with literature assignments which also gave strong support to the facial addition of the cuprates to 4.

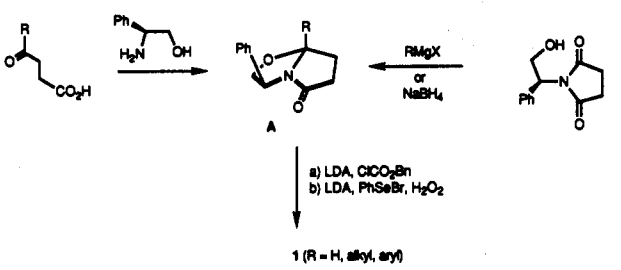
We recently described[1] the conjugate addition of cuprates to the chiral unsaturated lactam 1 which proceeded predominantly from the endo face. Upon decarbalkoxylation, the lactam 2 was reduced sequentially with alane and then hydrogen to product the *trans*-2,3-disubstituted pyrrolidines 3. In this fashion it was possible to generate



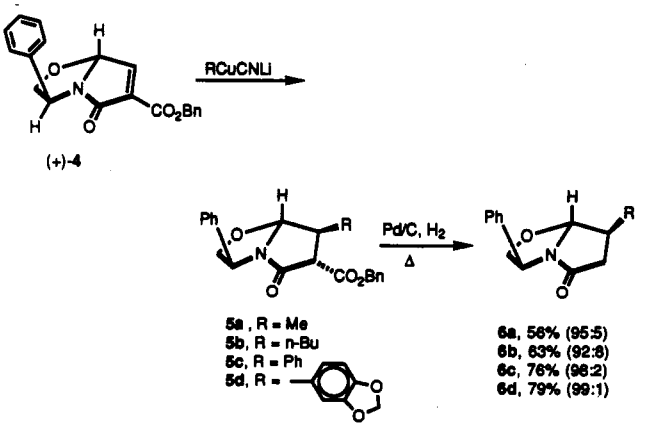
a variety of aracemic pyrrolidines from simple γ-keto carboxylic acids or succinimides and Grignard reagents which furnished the precursors (A) to the lactam 1 (Scheme I).[2]

As an extension to the above, we examined the behavior of the angular H lactam 4 toward cuprate additions also available through the route given in Scheme I. Thus, treatment of 4 with various lower order cyanocuprates (−78 °C, THF) gave good yields of 5 (85–95%) with the major product (>90%) resulting from addition to the exo (β) face. This is in sharp contrast to the stereochemical outcome with lactams (1) whose major conjugate addition products were derived by endo (α) face addition. This result is most likely due to the steric effect of the angular substituent since similar behavior was noted earlier in our laboratory when lactams 1 and 4 were subjected to cyclopropanations,[2] (3 + 2) cycloadditions,[3] and Diels–Alder additions.[4] Since it was observed earlier[1] that the cuprate additions were not possible without the presence of the α-carboxy function in 4 (or 1), removal of the latter was necessary before proceeding. This was accomplished

Scheme I



as described earlier[1] using hydrogenolysis[5] followed by heating in toluene which furnished **6a–d** in overall yields of 56–79% (based on 4). Concern arose over the possibility of 6 suffering epimerization during the reduction–decarboxylation sequence, an event observed earlier[1] (Scheme II). However, the integrity of the stereochemical center in 6 was confirmed when **6c** (R = Ph) was metalated and acylated with benzyl chloroformate producing **5c** which was identical in all respects to **5c** obtained via cuprate additions to 4.



Cleavage of the bicyclic systems 6 to the pyrrolidinones 7 was achieved using triethylsilane and $TiCl_4$ which smoothly cleaved the C–O bond in high yield.[6,7] Only in the case of **6d**, containing the methylenedioxy substituent,

(1) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814.
(2) Romo, D.; Meyers, A. I. *Tetrahedron Rep.* **1991**, *47*, 9503. For the preparation of 1 (R = H), see: Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243. We are studying the procedure to reach 1 (R = H) by reduction of the corresponding succinimide with $LiEt_3BH$ in THF at −78 °C. The earlier route ($NaBH_4$) gave the stated yields on smaller scale (<100 mg), but when scale-up was attempted subsequent to the publication, the yields were erratic and generally low (25–35%) (B. Newhouse, research in progress).
(3) Meyers, A. I.; Fray, A. H. *Tetrahedron Lett.* **1992**, *33*, 3575.
(4) Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299. Meyers, A. I.; Burgess, L. E. Unpublished results.
(5) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.
(6) For review on $TiCl_4$ see Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.
(7) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858.

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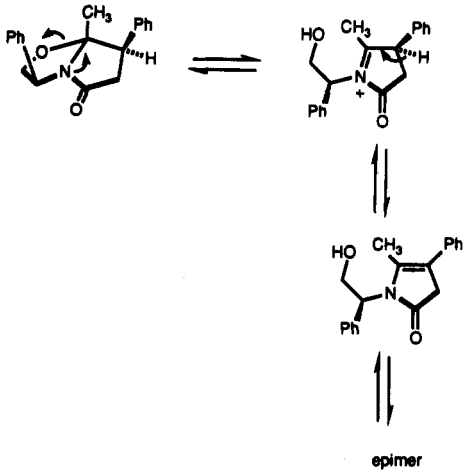
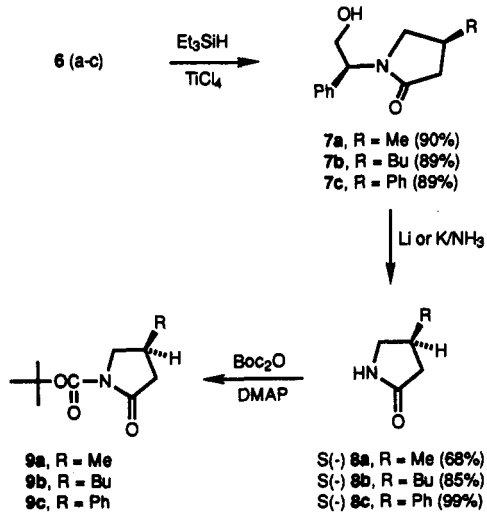
Scheme II

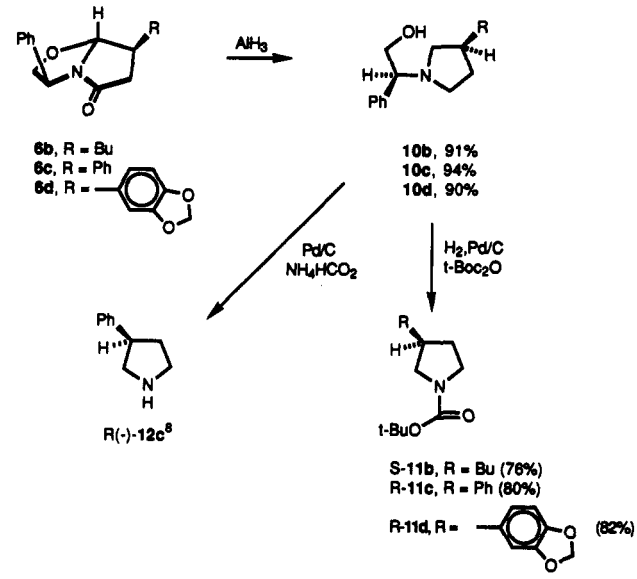


did the reductive cleavage proceed poorly. It was concluded that the oxygen substituents in **6d** were incompatible with the $TiCl_4$–Et_3SiH reduction conditions. However, this problem was overcome nicely in our synthesis of the antidepressant Rolipram to be discussed at the end of this article.



Removal of the chiral auxiliary was accomplished by dissolving metal reduction (Li or K NH_3) which smoothly cleaved the C–N bond in **7**, providing the pyrrolidinones **8** in good yield. Unlike the alane reductions in our earlier report,[1] the carbonyl group in **6** was not reduced under the $TiCl_4$–Et_3SiH conditions. Of immediate interest was the confirmation of absolute stereochemistry in the pyrrolidinones, **8**. A report by Zelle[8] described optically pure 4-phenylpyrrolidinone **8c** as the *S* enantiomer having a levorotary sign ($[\alpha]_D$ −37.8°). The material prepared in our sequence possessed $[\alpha]_D$ −33.8° (MeOH). We can, therefore, confirm that the cuprate additions to **4** proceed as mentioned earlier—from the exo (β) face which would lead to the *S* configuration in the pyrrolidinones, **8**. The specific rotations indicated that **8c** prepared herein was 89% optically pure. In order to establish, in a more reliable fashion, the enantiomeric purity of **8c**, we prepared the *tert*-butoxycarbonyl derivatives **9** and subjected **9c** to chiral HPLC analysis (Figure 1). It is clear that **9c** (or **8c**) was indeed of very high (>99%) enantiomeric purity (peak B) when compared to the racemate (A). Mixing the racemic and synthetic sample confirmed that both peaks matched very well. Since the enantiomeric purity of **8c** was quite convincing, the other derivatives prepared in the same manner should also be of comparable purity. It is difficult to envision any loss in stereochemical purity during the metal–ammonia reduction of **7a–c**, and if any was to occur, the phenyl derivative would have been the most likely candidate to epimerize or racemize. The HPLC data nicely precludes this possibility.

In order to prepare 3-substituted pyrrolidines, the possibility existed to simply reduce the above pyrrolidinones **8**. However, it was felt that it would be more expedient to transform the bicyclic lactams **6** in a two-step procedure to pyrrolidines **10**. In this manner, **6b–d** were treated with lithium aluminum hydride–$AlCl_3$ as reported earlier[1,9] and furnished good yields of the N-substituted pyrrolidines **10b–d**. The single diastereomers were subjected to catalytic transfer hydrogenolysis affording the pyrrolidines, but the yields were low to moderate due to volatility, particularly in the case of the 3-*n*-butyl derivative. However, utilizing the clever procedure of Saito et al.[10] wherein di-*tert*-butyl dicarbonate was added to the N-substituted pyrrolidines **10** prior to catalytic hydrogenolysis, the *N*-Boc derivatives **11** were all formed in good yield (isolated and purified material). Furthermore, the 3-phenylpyrrolidine **12c** compared well to the previously prepared *R* enantiomer,[8] once again confirming that the cuprates added to the exo face of **4**.



In order to further demonstrate some of the interesting synthetic potential[2] of these conjugate additions to the chiral lactams, we examined a route to the known antidepressant and phosphodiesterase inhibitor, Rolipram, **13**,[11] manufactured by Schering AG. The synthetic route envisioned would simply require that a cyanocuprate of **14** be efficiently added to the bicyclic lactam **4**. Following the 3-step sequence mentioned above should afford Rolipram (**13**) in high enantiomeric purity. The required

(8) Zelle, R. E. *Synthesis* **1991**, 1023.

(9) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294.
(10) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.
(11) Schmiechen, R.; Horowski, R.; Palenschat, D.; Paschelke, G.; Wachtel, H.; Kehr, W. U.S. Patent 4 193 926, 1980.
(12) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339.
(13) Green, K. *J. Org. Chem.* **1992**, *56*, 4325.

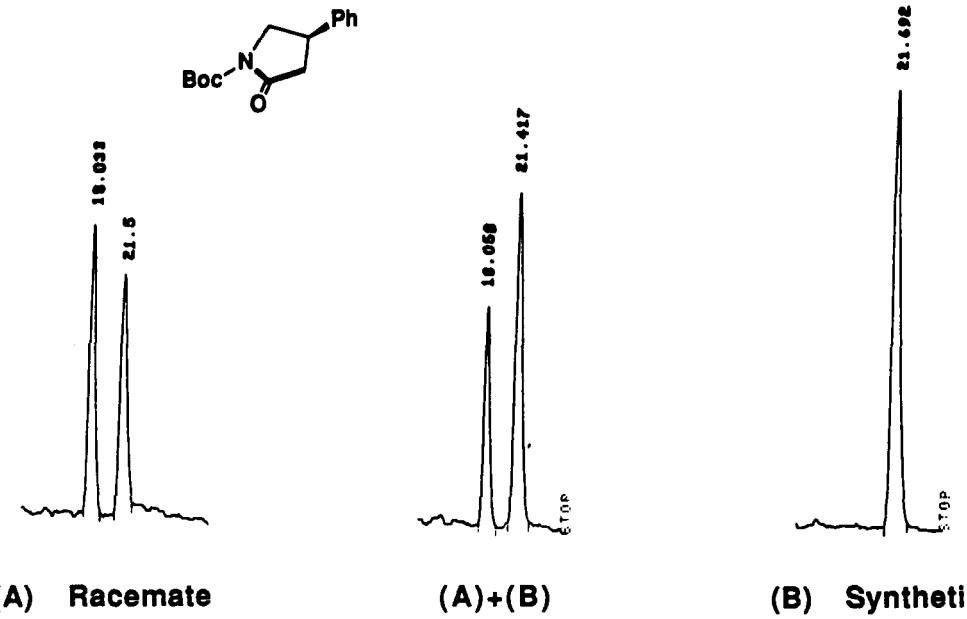
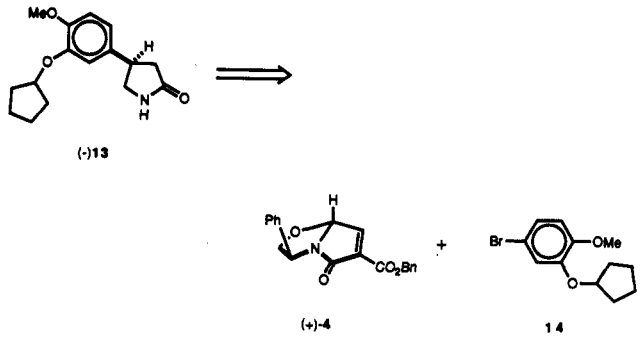


Figure 1. Chiral HPLC analysis of (*S*)-(−)-**8** using Chiralcel *OJ* in hexane–ethanol (95:5) at 254 nm. Flow rate = 0.8 mL/min.

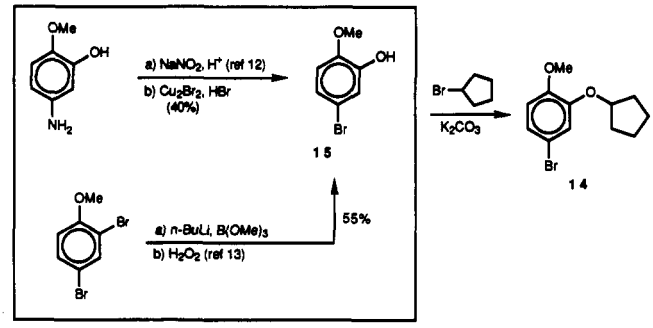


bromoarene, **14**, was prepared as shown in Scheme III. Two routes to 2-methoxy-5-bromophenol were taken, each of roughly equal efficiency to furnish the bromophenol **15**. Transformation to the cyclopentyl ether **14** was readily accomplished with bromocyclopentane in acetone containing potassium carbonate.

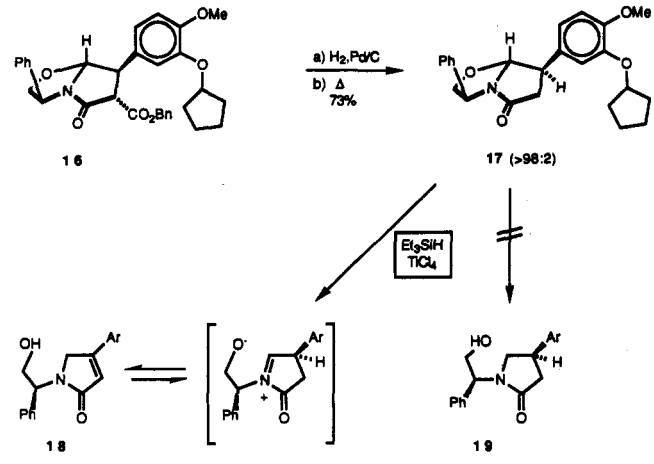
With the requisite aryl bromide in hand, the formation of the aryl cuprate was the next step to be accomplished. Using *tert*-butyllithium the THF solution of **14** cleanly generated the aryllithium which, after introduction of CuCN and addition to a THF solution of (+)-**4**, gave the adduct **16**, which was immediately hydrogenolyzed and decarboxylated as described above to the lactam **17**. The latter was obtained in 73% overall yield from (+)-**4** (after chromatography), and the diastereomeric ratio was assessed at this point to be >98:2 by NMR. The lactam **17** was next subjected to the $TiCl_4$–Et_3SiH reduction in order to reach the pyrrolidinone **19**. However, once again the oxygen substituents on the aromatic moiety interfered dramatically with the Et_3SiH reduction and various unwanted materials were formed (e.g. **18**). This is similar to the earlier experiment involving **6d** (R = 3,4-(methylenedioxy)phenyl) which was also badly decomposed when treated with Et_3SiH–$TiCl_4$.

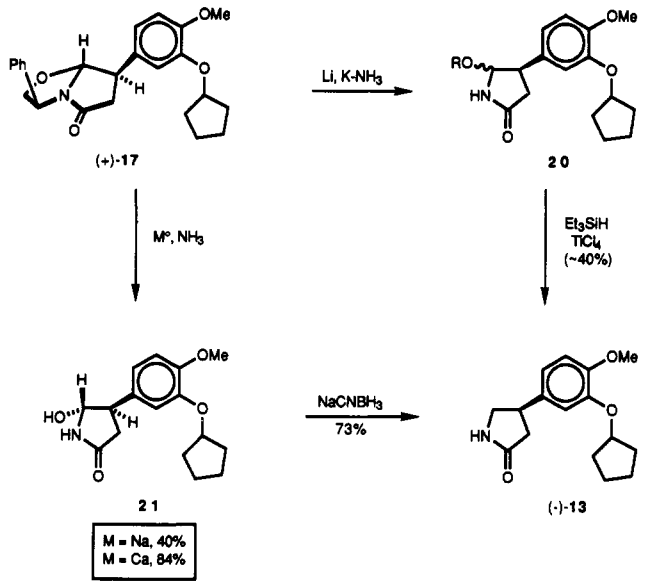
In view of the difficulty in reductively cleaving **17** to the pyrrolidinone **19**, it was decided to reverse the order of the two-step sequence leading to Rolipram, (−)-**13**. In this regard we attempted to reductively cleave the *N*-benzyl group in **17** and then proceed to reduce the alkoxypyrrolidinone moiety, via the acyl iminium salt, to **13**. Reduction in liquid ammonia using lithium or potassium

Scheme III



gave a product which could be tentatively identified as **20** with R = H, $PhCH_2CH_2$, and other materials in a low mass recovery. The crude mixture was subjected to Et_3SiH–$BF_3{\cdot}OEt_2$ and a small amount (30–40%) of Rolipram, **13**, was isolated. The erratic behavior of this sequence was unsatisfactory, and further improvement was sought. Fortunately, the use of sodium–liquid ammonia on **17** increased the yield in the reductive cleavage to 40%, but isolation of pure material was difficult due to instability of the carbinol amide to chromatographic techniques. The increase in yield of **21** in going from Li → K → Na paralleled the reduction potential of the metals Li (3.0), K (2.9), Na (2.7), and it seemed reasonable that calcium, whose





reduction potential is known to be even lower,[14] might provide the optimum reductive cleavage of the bicyclic lactam 17. When the latter was treated with calcium metal (10 equiv) in liquid ammonia and quenched after 4 h, there was obtained an 84% yield of carbinol amide 21. This was subjected to reduction using acidic sodium cyanoborohydride to afford the final product (-)-13 in 73-75% yield.[15] The synthetic material was identical in all respects (NMR, mp, mixed mp) with an authentic sample of Rolipram except the magnitude of $[\alpha]_D$ (observed -19.5° (c 1.15, MeOH); Schering sample -31°). Chiral HPLC analysis (Figure 2) of the *N*-Boc material prepared is shown (B) and when compared to the racemate (provided by Schering AG) indicated >99% enantiomeric purity. Once again, care should be taken when attempting comparison of enantiomeric purities using polarimetric methods.

In summary, an asymmetric route to 3-substituted pyrrolidines and 4-substituted pyrrolidinones has been accomplished[16] using the chiral bicyclic lactam 4 as a convenient template. This now allows access to a wide array of GABA precursors[17] which are important therapeutic agents.[18]

Experimental Section

α-(Carbobenzyloxy)-α,β-unsaturated Lactam (+)-4. To 215 mg (1.06 mmol) of lactam A[2] (R = H) in 15 mL of THF under Ar at -78 °C was added 2.33 mL (2.33 mmol) of lithium hexamethyldisilazane resulting in an orange solution. After 1 h, 0.15 mL (1.06 mmol) of benzyl chloroformate was added neat (passed through a Na_2SO_4 plug prior to use). After an additional 15 min phenylselenyl bromide (prepared in situ from 248 mg (0.79 mmol) of diphenyl diselenide and 38 μL (0.74 mmol) of bromine in 10 mL of THF) was added, the reaction mixture was stirred for 30 min and quenched with excess 1 N HCl. The mixture was allowed to warm to ambient temperature and diluted with ethyl acetate. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and concentrated in vacuo to a viscous red oil which was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. To the red solution was added 0.36 mL (3.18 mmol) of 30% H_2O_2 and after 30 min warmed to ambient temperature over 30 min and quenched with excess 1 N HCl, and the organic solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to 324 mg of a yellow viscous oil which solidified upon standing at ambient temperature. Recrystallization (ethyl acetate/hexane) provided 224 mg of lactam 4 (63%) as colorless needles. Column chromatography (30% ethyl acetate/hexane) of the residue provided an additional 21 mg (6%) of 4 as a white powder: mp 96.5-98.0 °C; $[\alpha]_D$ = +101.8° (c 0.94, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 1.5 Hz, 1 H), 7.43-7.28 (m, 10 H), 5.63 (d, J = 1.4 Hz, 1 H), 5.31 (s, 2 H), 5.06 (app t, J = 7.1 Hz, 1 H), 4.72 (dd, J = 7.4 Hz, J = 8.8 Hz, 1 H), 4.10 (dd, J = 7.1 Hz; 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 160.5, 151.0, 138.8, 135.1, 134.0, 128.8, 128.6, 128.4, 128.2, 127.8, 125.9, 90.7, 77.9, 67.0, 58.2; IR (film) 3064, 3032, 2947, 2876, 1755, 1725, 1624, 1379, 1337, 1228, 735, 698 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11. Found: C, 71.56; H, 5.09.

Cuprate Additions to (+)-4. Phenyl Lactam 5c. To 516 mg (5.73 mmol) of CuCN in 40 mL of THF under Ar at -78 °C was added 2.74 mL (5.37 mmol) of 1.96 M phenyllithium (7:3 cyclohexane-ether). The mixture was warmed to 0 °C when a homogeneous solution resulted (~5 min) and cooled to -78 °C, and 1.20 g (3.58 mmol) of lactam 4 in 10 mL of THF was added slowly. After 30 min the reaction was quenched with 10% NH_4OH/saturated NH_4Cl solution, and the Ar was replaced with air. After 2 h the deep blue solution was diluted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to 1.55 g of a viscous oil. Column chromatography (20% ethyl acetate/hexane) provided 1.25 g (84%) of lactam 5c as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.39-7.25 (m, 15 H), 5.39 (d, J = 4.2 Hz, 1 H), 5.29 (d, J = 12.5 Hz, 1 H), 5.20 (app t, J = 7.1 Hz, 1 H), 5.17 (d, J = 12.4 Hz, 1 H), 4.65 (dd, J = 7.4 Hz, J = 8.9 Hz, 1 H), 4.21-4.06 (m, 2 H), 3.98 (dd, J = 6.9 Hz, J = 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 167.9, 138.5, 137.6, 135.2, 129.1, 128.8, 128.5, 128.2, 128.0, 127.9, 127.8, 127.3, 125.9, 96.5, 75.3, 67.5, 58.0, 57.8, 50.5; IR (film) 3032, 2884, 1742, 1717, 1605, 1406, 1162, 751, 698 cm^{-1}; $[\alpha]_D$ = +50.0° (c 0.40, CH_2Cl_2).

Lactam 6c. To 1.24 g (3.00 mmol) of lactam 5c in 30 mL of methanol under Ar was added 1.51 g (24.0 mmol) of ammonium formate followed by 637 mg (0.60 mmol) of 5% Pd/C. The reaction mixture was stirred for 1.5 h, filtered through Celite, and concentrated in vacuo to a white solid which was heated at reflux in 300 mL of toluene for 1.5 h. The mixture was concentrated in vacuo and passed through a plug of silica gel (ethyl acetate/hexane) providing 754 mg (90%) of lactam 6c as a pale yellow solid: mp 58-59 °C (EtOAc-Hex); ^1H NMR ($CDCl_3$) δ 7.41-7.24 (m, 10 H), 5.30 (d, J = 3.6 Hz, 1 H), 5.18 (app t, J = 7.2 Hz, 1 H), 4.61 (app t, J = 7.8 Hz, 1 H), 3.88 (dd, J = 7.0 Hz, J = 8.7 Hz, 1 H), 3.59 (dt, J = 3.6 Hz, J = 9.5 Hz, 1 H), 3.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.4, 140.2, 139.3, 129.0, 128.9, 127.8, 127.4, 127.1, 125.9, 98.8, 75.0, 57.8, 45.7, 40.6; IR (film) 3061, 3029, 2878, 1718, 1603, 1399, 761, 698 cm^{-1}; $[\alpha]_D$ = +113.3° (c 0.36, CH_2Cl_2).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.19; H, 6.19.

Butyl lactam 5b was prepared from lactam 4 (1.05 g) according to the procedure for the preparation of lactam 5c and was obtained in quantitative yield (1.27 g): ^1H NMR ($CDCl_3$) δ 7.40-7.22 (m, 10 H), 5.27 (d, J = 12.3 Hz, 1 H), 5.20 (d, J = 12.4 Hz, 1 H), 5.11 (app t, J = 7.0 Hz, 1 H), 5.01 (d, J = 4.2 Hz, 1 H), 4.58 (dd, J = 7.4 Hz, J = 8.7 Hz, 1 H), 3.93 (dd, J = 6.9 Hz, J = 8.7 Hz, 1 H), 3.60 (d, J = 10.3 Hz, 1 H), 2.88-2.79 (m, 1 H), 1.65-1.60 (m, 2 H), 1.35-1.24 (m, 4 H), 0.86 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 168.6, 138.8, 135.4, 128.8, 128.5, 128.3, 128.1, 127.8, 125.9, 96.0, 75.3, 67.4, 57.5, 57.4, 45.3, 32.2, 29.3, 22.4, 13.8; IR (film) 3063, 3032, 2956, 2871, 1741, 1716, 1163, 738, 698 cm^{-1}.

Butyl lactam 6b was obtained from lactam 5b (1.25 g) according to the procedure for the preparation of lactam 6c. Column chromatography (5-20% ethyl acetate/hexane) provided diastereomerically pure lactam 6b (519 mg) in 63% yield as a clear colorless oil which solidified at ambient temperature: mp

(14) Hwu, R.; Chua, V.; Schroeder, J. E.; Barans, R. E.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1988**, *53*, 1871.

(15) After this manuscript was submitted for publication, a beautiful asymmetric route to Rolipram was reported: Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 870.

(16) For other methods to prepare 3-substituted pyrrolidines, see: Roussi, G.; Zhang, J. *Tetrahedron* **1991**, *47*, 5161. Becking, L.; Schäfer, H. J. *Tetrahedron Lett.* **1988**, *29*, 2797. Alper, H.; Zhou, J.-Q. *J. Org. Chem.* **1992**, *57*, 3328.

(17) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(18) Bowery, N. G.; Bittiger, H.; Olpe, H. R. *GABA$_B$ Receptors in Mammalian Function*, J. Wiley & Sons: New York, 1990.

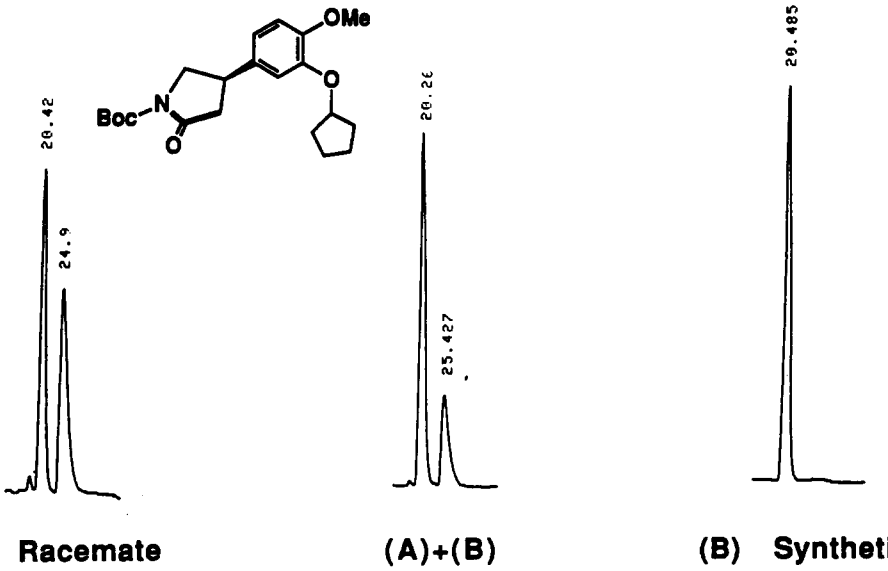


Figure 2. Chiral HPLC analysis of (*S*)-(−)-Rolipram using Chiralcel OD in hexane–2-propanol (9:1) at 254 nm. Flow rate = 0.8 mL/min.

43–45 °C; ^{1}H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5 H), 5.07 (app t, J = 7.3 Hz, 1 H), 4.99 (d, J = 3.3 Hz, 1 H), 4.54 (app t, J = 8.4 Hz, 1 H), 3.84 (dd, J = 7.1 Hz, J = 8.7 Hz, 1 H), 2.70 (dd, J = 9.2 Hz, J = 16.8 Hz, 1 H), 2.45 (dd, J = 8.8 Hz, J = 16.7 Hz, 1 H), 2.37–2.30 (m, 1 H), 1.64–1.55 (m, 2 H), 1.41–1.34 (m, 4 H), 0.91 (app t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.8, 139.5, 128.8, 127.6, 125.8, 98.1, 74.9, 57.4, 40.1, 39.4, 33.1, 29.6, 22.5, 13.9; IR (film) 3062, 3031, 2956, 2871, 1716, 1403, 760, 699 cm^{-1}; $[\alpha]_D$ = +144.2° (c 0.31, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 73.90; H, 8.09.

Methyl lactam 5a was prepared from lactam **4** (208 mg) according to the procedure describing the preparation of lactam **5c** and was obtained in quantitative yield (219 mg) as an inseparable diastereomeric mixture (α- and β-carboxybenzyl groups). Spectral data for the major diastereomer is provided: ^{1}H NMR ($CDCl_3$) δ 7.42–7.17 (m, 10 H), 5.28 (d, J = 12.5 Hz, 1 H), 5.20 (d, J = 12.5 Hz, 1 H), 5.11 (app t, J = 7.3 Hz, 1 H), 4.99 (d, J = 4.4 Hz, 1 H), 4.57 (dd, J = 7.8 Hz, J = 8.7 Hz, 1 H), 3.93 (dd, J = 7.1 Hz, J = 8.7 Hz, 1 H), 3.57 (d, J = 10.4 Hz, 1 H), 2.96–2.82 (m, 1 H), 1.30 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 168.0, 138.5, 135.2, 128.6, 128.3, 128.0, 127.8, 125.7, 125.3, 96.5, 76.4, 67.1, 58.2, 57.4, 40.0, 16.5; IR (film) 3065, 3024, 2963, 2878, 1738, 1716, 1410, 1251, 1167, 739, 698 cm^{-1}. The mixture of epimers was carried on to the decarbalkoxylation without further purification.

Methyl lactam 6a was prepared from lactam **5a** (219 mg) according to the procedure describing the preparation of lactam **6c**. Column chromatography (10–25% ethyl acetate/hexane) provided diastereomerically pure lactam **6a** (76 mg) in 56% overall yield from **4** as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (m, 5 H), 5.09 (app t, J = 7.2 Hz, 1 H), 4.93 (d, J = 2.8 Hz, 1 H), 4.53 (app t, J = 8.5 Hz, 1 H), 3.83 (dd, J = 7.0 Hz, J = 8.7 Hz, 1 H), 2.78–2.68 (m, 1 H), 2.47–2.36 (m, 2 H), 1.28 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.4, 139.5, 128.8, 127.6, 125.8, 99.2, 74.8, 57.7, 40.8, 34.2, 18.5; IR (film) 3063, 3032, 2964, 2876, 1716, 1403, 1059, 761, 700 cm^{-1}; $[\alpha]_D$ = +184.4° (c 0.34, CH_2Cl_2).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 71.76; H, 6.92.

Aryl Lactam 5d. To 106 mL (0.88 mmol) of 4-bromo-1,2-(methylenedioxy)benzene in 6.0 mL of THF under Ar at −78 °C was added 1.03 mL (1.81 mmol) of t-BuLi (pentane, 1.75 M), resulting in a deep yellow solution which turned colorless after 30 min. To the solution was added 85 mg (0.94 mmol) of CuCN, resulting in an orange-red suspension which turned to a dark green solution upon warming to 0 °C for 10 min. The solution was cooled to −78 °C, and 197 mg (0.59 mmol) of lactam **4** in 5 mL of THF was added slowly down the side of the flask. After 1 h the mixture was quenched and worked up according to the procedure described for lactam **5c**. This provided 275 mg of lactam **5d** as a yellow oil which was used without further purification. An analytical sample (oil) was prepared via column chromatography (10–20% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 10 H), 6.78–6.60 (m, 3 H), 5.94 (app s, 2 H), 5.33–5.14 (m, 4 H), 4.63 (dd, J = 7.6 Hz, J = 8.6 Hz, 1 H), 4.07–3.94 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 167.7, 148.3, 147.2, 138.5, 135.3, 131.2, 128.9, 128.5, 128.3, 128.1, 127.9, 125.9, 120.6, 108.7, 107.6, 101.2, 96.5, 75.4, 67.5, 58.3, 57.8, 50.5; IR (film) 3064, 3032, 2890, 1741, 1716, 1504, 1240, 1038, 734, 698 cm^{-1}; $[\alpha]_D$ = +30.4° (c 0.54, CH_2Cl_2).

Anal. Calcd for $C_{27}H_{23}NO_6$: C, 70.89; H, 5.07. Found: C, 70.98; H, 5.09.

Lactam 6d was prepared from lactam **5d** (275 mg) according to the procedure describing the preparation of lactam **6c**. Column chromatography (30–40% ethyl acetate/hexane) provided lactam **6d** (150 mg) in 79% yield from lactam **4**: mp 117–119 °C (EtOAc–Hex); ^{1}H NMR ($CDCl_3$) δ 7.37–7.14 (m, 5 H), 6.81–6.73 (m, 3 H), 5.24 (d, J = 3.6 Hz, 1 H), 5.16 (app t, J = 7.2 Hz, 1 H), 4.59 (dd, J = 7.7 Hz, J = 8.6 Hz, 1 H), 3.87 (dd, J = 7.0 Hz, J = 8.7 Hz, 1 H), 3.50 (dt, J = 3.6 Hz, J = 9.5 Hz, 1 H), 3.03–2.34 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 148.2, 146.8, 139.3, 133.9, 128.9, 127.7, 125.8, 120.3, 108.5, 107.4, 101.1, 98.8, 75.0, 57.8, 45.5, 40.7; IR (film) 3032, 2892, 1716, 1490, 1247, 1038, 757, 697 cm^{-1}; $[\alpha]_D$ = +91.9° (c 0.26, CH_2Cl_2).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30. Found: C, 70.33; H, 5.36.

Pyrrolidinone 7a. To 103 mg (0.47 mmol) of lactam **6a** in 5 mL of CH_2Cl_2 under Ar at −78 °C was added 0.14 mL (0.85 mmol) of triethylsilane followed by 1.04 mL (1.04 mmol) of $TiCl_4$. The resultant solution was allowed to warm to ambient temperature overnight and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with four portions of CH_2Cl_2, and the organic layer was dried over $MgSO_4$, filtered, and concentration in vacuo to 103 mg of colorless oil. Column chromatography (20% ethyl acetate/hexane) provided 94 mg (90%) of **7a** as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.35–7.21 (m, 5 H), 4.98 (dd, J = 4.8 Hz, J = 8.7 Hz, 1 H), 4.13–3.96 (m, 2 H), 3.72 (br s, 1 H), 3.45 (dd, J = 7.7 Hz, J = 9.7 Hz, 1 H), 2.76–2.57 (m, 2 H), 2.46–2.34 (m, 1 H), 2.06 (dd, J = 6.8 Hz, J = 16.5 Hz, 1 H), 1.00 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.9, 136.9, 128.7, 127.9, 127.4, 62.6, 59.5, 52.9, 40.1, 26.7, 19.5; IR (film) 3384, 3019, 2958, 1654, 1437, 1271, 1066, 749, 700 cm^{-1}; $[\alpha]_D$ = +19.9° (c 1.01, CH_2Cl_2).

Lactam 7b was prepared from lactam **6b** (106 mg) according to the same procedure describing the preparation of lactam **7a**. Column chromatography (20% ethyl acetate/hexane) provided **7b** in 89% yield (96 mg) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.35–7.21 (m, 5 H), 4.96 (dd, J = 4.6 Hz, J = 8.7 Hz, 1 H), 4.09 (dd, J = 8.9 Hz, J = 11.9 Hz, 1 H), 3.98 (dd, J = 4.7 Hz, J = 11.9 Hz, 1 H), 3.66 (br s, 1 H), 3.41 (dd, J = 7.8 Hz, J = 9.6 Hz, 1 H), 2.76 (dd, J = 6.7 Hz, J = 9.7 Hz, 1 H), 2.56 (dd, J = 8.4 Hz, J = 16.4 Hz, 1 H), 2.28 (app p, J = 7.5 Hz, 1 H), 2.11 (dd, J = 7.8

Hz, J = 16.5 Hz, 1 H), 1.36–1.14 (m, 6 H), 0.83 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.9, 136.9, 128.7, 127.9, 127.4, 62.6, 59.7, 51.6, 38.5, 34.1, 32.0, 29.4, 22.5, 13.9; IR (film) 3368, 3029, 2924, 1654, 1420, 1066, 750, 699 cm^{-1}; $[\alpha]_D$ = +16.1° (c 0.64, CH_2Cl_2).

Lactam 7c was prepared from lactam **6c** (115 mg) according to the procedure describing the preparation of lactam **7a**. Column chromatography (20% ethyl actate/hexane) provided **7c** in 89% (103 mg) yield as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.36–7.10 (m, 10 H), 5.03 (dd, J = 4.6 Hz, J = 8.9 Hz, 1 H), 4.17 (dd, J = 9.0 Hz, J = 11.8 Hz, 1 H), 4.04 (dd, J = 4.6 Hz, J = 11.9 Hz, 1 H), 3.72 (dd, J = 8.2 Hz, J = 9.6 Hz, 1 H), 3.56 (m, 2 H), 3.18 (dd, J = 7.1 Hz, J = 9.6 Hz, 1 H), 2.90 (dd, J = 8.9 Hz, J = 16.9 Hz, 1 H), 2.64 (dd, J = 8.5 Hz, J = 16.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.2, 141.9, 136.6, 128.8, 128.8, 128.1, 127.5, 127.1, 126.6, 62.7, 60.1, 53.1, 39.6, 37.6; IR (film) 3380, 3030, 2926, 1669, 1435, 760, 700 cm^{-1}; $[\alpha]_D$ = +43.3° (c 0.78, CH_2Cl_2); mp 90–93 °C.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81. Found: C, 76.59; H, 6.86.

Debenzylation to (*S*)-(−)-8a. To 82 mg (0.37 mmol) of lactam **7a** in 0.5 mL of THF, 0.22 mL (3.74 mmol) of absolute ethanol, and ~5 mL of liquid ammonia under Ar was added a lithium silver (ca. 20 mg), resulting in a deep blue solution which was stirred for 10 min and quenched with solid NH_4Cl. The ammonia was allowed to evaporate, and the mixture was diluted with H_2O, extracted with four portions of CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo to near dryness. Column chromatography (25% acetone/ethyl acetate) provided 25 mg (68%) of pyrrolidinone **8a** as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 5.89 (br s, 1 H), 3.49 (app t, J = 8.9 Hz, 1 H), 2.95 (dd, J = 6.1 Hz, J = 9.4 Hz, 1 H), 2.55–2.40 (m, 2 H), 1.93 (dd, J = 7.0 Hz, J = 16.4 Hz, 1 H), 1.12 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.4, 49.5, 38.3, 29.6, 19.6; IR (film) 3242, 2958, 2926, 1696, 1269 cm^{-1}; $[\alpha]_D$ = −6.5° (c 0.26, CH_2Cl_2).

Pyrrolidinone (*S*)-(−)-8b was prepared from lactam **7b** (13.2 mg) according to the same procedure describing the preparation of pyrrolidinone **8a**. Column chromatography (20% acetone/ethyl acetate) provided pyrrolidinone **8b** (6.0 mg) in 85% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.12 (br s, 1 H), 3.46 (app t, J = 8.4 Hz, 1 H), 2.99 (dd, J = 6.5 Hz, J = 9.2 Hz, 1 H), 2.44–2.35 (m, 2 H), 2.02–1.92 (m, 1 H), 1.47–1.40 (m, 2 H), 1.34–1.21 (m, 6 H), 0.88 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.5, 48.1, 36.8, 34.9, 34.3, 29.7, 22.6, 14.0; IR (film) 3225, 2955, 2924, 2855, 1700, 1272 cm^{-1}; $[\alpha]_D$ = −0.67° (c 0.60, CH_2Cl_2).

Pyrrolidinone (*S*)-(−)-8c. To 50.3 mg (0.18 mmol) of lactam **7c** in 2 mL of THF, 0.10 mL (1.79 mmol) of absolute ethanol, and ~25 mL of liquid ammonia under Ar was added ca. 50 mg of potassium slivers until a deep blue color persisted. After 10 min the reaction was quenched by the addition of solid NH_4Cl, and the ammonia was allowed to evaporate as the slurry reached ambient temperature. The residue was taken up in ether, filtered, and concentrated. Column chromatography (ethyl acetate) provided 28.6 mg (99%) of pyrrolidinone **8c** as a white powder: mp 91–93 °C (lit.[8] mp 96–97 °C); ^{1}H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5 H), 6.08 (br s, 1 H), 3.80–3.63 (m, 2 H), 3.41 (dd, J = 6.8 Hz, J = 8.7 Hz, 1 H), 2.72 (dd, J = 8.7 Hz, J = 16.9 Hz, 1 H), 2.49 (dd, J = 8.8 Hz, J = 17.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.9, 142.1, 128.8, 127.0, 126.7, 49.6, 40.2, 38.0; IR (film) 3231, 3033, 2989, 2889, 1686, 1260, 745, 700 cm^{-1}; $[\alpha]_D$ = −33.8° (c 0.89, MeOH) (lit.[8] $[\alpha]_D$ −37.8° (c 0.95, MeOH).

Pyrrolidinone 9a. To 17 mg (0.17 mmol) of pyrrolidinone **8a** in 2 mL of CH_2Cl_2 under Ar was added 24 μL (0.17 mmol) of triethylamine, 21 mg (0.17 mmol) of 4-(dimethylamino)pyridine, and 79 mL (0.34 mmol) of di-*tert*-butyl dicarbonate. After 18 h at ambient temperature the reaction mixture was concentrated in vacuo and pushed through a silica gel plug (ethyl acetate/hexane) providing 29 mg (85%) of pyrrolidinone **9a** as clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.82 (dd, J = 7.6 Hz, J = 10.7 Hz, 1 H), 3.24 (dd, J = 7.0 Hz, J = 10.8 Hz, 1 H), 2.59 (dd, J = 8.0 Hz, J = 16.9 Hz, 1 H), 2.40–2.28 (m, 1 H), 2.10 (dd, J = 8.0 Hz, J = 16.9 Hz, 1 H), 1.48 (s, 9 H), 1.09 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 150.1, 82.7, 53.4, 41.1, 28.0, 25.6, 18.9; IR (film) 2975, 2932, 1786, 1752, 1718, 1317, 1149 cm^{-1}; $[\alpha]_D$ = +1.5° (c 0.33, CH_2Cl_2), +3.1° (c 0.32, MeOH).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.36; H, 8.55.

Pyrrolidinone 9b was prepared from pyrrolidinone **8b** (17 mg) by the same procedure describing the preparation of pyrrolidinone **9a** and was obtained in 83% (24 mg) yield as a low-melting solid: mp 29.5–31.0 °C (EtOAc–Hex); ^{1}H NMR ($CDCl_3$) δ 3.83 (dd, J = 7.6 Hz, J = 10.8 Hz, 1 H), 3.26 (dd, J = 7.6 Hz, J = 10.7 Hz, 1 H), 2.59–2.53 (m, 1 H), 2.22–2.11 (m, 2 H), 1.49 (s, 9 H), 1.44–1.22 (m, 6 H), 0.87 (app t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 150.1, 82.7, 52.0, 39.5, 33.7, 30.8, 29.4, 27.9, 27.7, 22.5, 13.9; IR (film) 2959, 2929, 2874, 1789, 1753, 1715, 1317, 1158 cm^{-1}; $[\alpha]_D$ = +1.2° (c 0.33, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60. Found: C, 64.54; H, 9.64.

Pyrrolidine 10c. To 107 mg (0.80 mmol) of $AlCl_3$ in 4 mL of THF under Ar at 0 °C was added dropwise 2.41 mL (2.41 mmol) of 1 M $LiAlH_4$ THF solution. The reaction was allowed to warm to ambient temperature for 20 min and cooled to −78 °C, and 102 mg (0.37 mmol) of lactam **6c** in 3 mL of THF was added slowly down the side of the flask. After 1 h the solution was quenched by the careful addition of 1 N HCl and extracted with four portions of CH_2Cl_2. The combined organic layer was washed with 10% NaOH, and the aqueous layer was back-extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo to 92 mg (94%) of pyrrolidine **10c** as a white powder: mp 89–91 °C (EtOAc–Hex); ^{1}H NMR ($CDCl_3$) δ 7.35–7.14 (m, 10), 3.91 (dd, J = 6.1 Hz; J = 10.8 Hz, 1 H), 3.82 (dd, J = 5.7 Hz, J = 10.9 Hz, 1 H), 3.56 (app t, J = 5.3 Hz, 1 H), 3.30 (m, 1 H), 3.01 (app t, J = 9.0 Hz, 1 H), 2.99–2.86 (m, 2 H), 2.82–2.73 (m, 1 H), 2.52 (app t, J = 8.2 Hz, 1 H), 2.37–2.25 (m, 1 H), 1.92–1.26 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 144.8, 138.6, 128.6, 128.4, 128.4, 128.3, 127.1, 126.2, 69.8, 64.2, 59.2, 51.7, 42.9, 32.6; IR (film) 3387, 3083, 3027, 2961, 2793, 1949, 1882, 1809, 1602, 1493, 1453, 1057, 759, 700 cm^{-1}; $[\alpha]_D$ = +59.2° (c 0.35, CH_2Cl_2).

Pyrrolidine 10d was prepared from lactam **6d** (52 mg) by the same procedure describing the preparation of pyrrolidine **10c** and was obtained in 90% yield (45 mg) as a clear colorless oil which solidified on standing: mp 118.5–120 °C (EtOAc–Hex); ^{1}H NMR ($CDCl_3$) δ 7.37–7.23 (m, 5 H), 6.72–6.61 (m, 3 H), 5.88 (app s, 2 H), 3.89 (dd, J = 6.0 Hz, J = 10.8 Hz, 1 H), 3.80 (dd, J = 5.7 Hz, J = 10.8 Hz, 1 H), 3.51 (app t, J = 5.9 Hz, 1 H), 3.27–3.16 (m, 1 H), 2.94 (app t, J = 9.0 Hz, 1 H), 2.88–2.70 (m, 3 H), 2.45 (app t, J = 8.0 Hz, 1 H), 2.31–2.19 (m, 1 H), 1.83–1.72 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 147.6, 145.8, 138.9, 138.6, 128.6, 128.4, 127.8, 120.1, 107.9, 107.5, 100.8, 69.8, 64.2, 59.3, 51.7, 42.7, 32.8; IR (film) 3394, 3028, 2961, 2790, 1608, 1504, 1487, 1247, 1038, 702 cm^{-1}; $[\alpha]_D$ = +57.8° (c 0.36, CH_2Cl_2).

Pyrrolidine 10b was prepared from lactam **6b** (102 mg) by the same procedure describing the preparation of pyrrolidine **10c** and was obtained in 91% yield (88 mg) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.35–7.26 (m, 5 H), 3.83–3.71 (m, 2 H), 3.39 (app t, J = 5.9 Hz, 1 H), 2.73–2.65 (m, 3 H), 2.48–2.41 (m, 1 H), 2.03–1.90 (m, 3 H), 1.35–1.13 (m, 7 H), 0.84 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.1, 128.6, 127.5, 69.8, 64.1, 57.5, 50.9, 37.1, 35.2, 30.5, 30.4, 22.7, 14.0; IR (film) 3394, 3061, 3028, 2955, 2789, 2789, 1944, 1878, 1810, 1669, 1452, 1062, 762, 701 cm^{-1}; $[\alpha]_D$ = +59.1° (c 0.44, CH_2Cl_2).

Carbamate 11b. To 23 mg (0.093 mmol) of pyrrolidine **10b** in 5 mL of ethyl acetate under Ar was added 32 μL (0.14 mmol) of di-*tert*-butyl dicarbonate followed by ca. 6 mg (25 wt %) of Pd/C (10%). The mixture was stirred under 1 atm of hydrogen for 16 h, flushed with Ar, filtered through a Celite pad, and concentrated in vacuo to 43 mg of yellow oil. Column chromatography (10% ether/hexane) provided 16 mg of **11b** (76%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.51–3.37 (m, 2 H), 3.25–3.16 (m, 1 H), 2.81 (dd, J = 8.7 Hz, J = 10.5 Hz, 1 H), 2.11–2.00 (m, 1 H), 1.98–1.89 (m, 1 H), 1.43 (s, 9 H), 1.40–1.22 (m, 7 H), 0.87 (app t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.6, 78.9, 51.5, 45.6, 38.7, 32.9, 31.6, 30.4, 28.5, 22.8, 14.0; IR (film) 2961, 2872, 1699, 1404, 1171, 1111, 883, 772 cm^{-1}; $[\alpha]_D$ = −30.5° (c 0.83, CH_2Cl_2).

Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; H, 6.16. Found: C, 68.78; H, 11.07; N, 6.11.

Carbamate 11c was prepared from pyrrolidine **10c** (35 mg) by the same procedure describing the preparation of carbamate **11b** and was obtained in 80% yield (26 mg) as a clear colorless oil after chromatography: ^{1}H NMR ($CDCl_3$) δ 7.32–7.21 (m, 5 H), 3.82–3.77 (m, 1 H), 3.62–3.55 (m, 1 H), 3.43–3.25 (m, 3 H), 2.28–2.19 (m, 1 H), 2.03–1.90 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.5, 141.4, 128.5, 127.0, 126.7, 79.2, 52.2, 45.8, 43.8,

32.8, 28.5; IR (film) 3019, 2974, 2876, 1697, 1403, 1168, 1122, 880, 756, 699 cm^{-1}; $[\alpha]_D$ = +10.3° (*c* 1.03, CH_2Cl_2).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.76; H, 8.61; N, 5.59.

Carbamate 11d was prepared from pyrrolidine **10d** (33 mg) by the same procedure describing the preparation of carbamate **11b** and was obtained in 82% yield (26 mg) as a white solid after chromatography: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 6.74–6.64 (m, 3 H), 5.91 (app s, 2 H), 3.76–3.71 (m, 1 H), 3.59–3.52 (m, 1 H), 3.39–3.32 (m, 1 H), 3.30–3.16 (m, 2 H), 2.22–2.13 (m, 1 H), 1.95–1.82 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.5, 147.8, 146.2, 135.3, 120.0, 108.2, 107.4, 100.9, 79.2, 52.4, 45.7, 43.6, 33.0, 28.5; IR (film) 2974, 2878, 1692, 1406, 1247, 1168, 1124, 1039, 935, 877, 810, 772 cm^{-1}; $[\alpha]_D$ = +16.1° (*c* 1.01, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.85; H, 7.30; N, 4.75.

Bicyclic Lactam 16. To 607 mg (2.24 mmol) bromide **14** in 25 mL of THF under Ar at −78 °C was added 1.92 mL (4.48 mmol) of 2.33 M t-BuLi, resulting in a colorless solution. After 1 h the solution was warmed to 0 °C for 50 min, cooled to −78 °C, and 215 mg (2.39 mmol) of CuCN was added in one portion. The slurry was allowed to warm to 0 °C until a homogeneous solution resulted (~5 min) and cooled to −78 °C, and 500 mg (1.49 mmol) of lactam (+)-**4** was added in 20 mL of THF slowly down the side of the flask. After 1 h the reaction was quenched with 10% NH_4OH/saturated NH_4Cl solution and the Ar replaced with air. After 2 h at ambient temperature a deep blue color resulted, and the mixture was diluted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to 915 mg of lactam **16** as a colorless oil which was used in the next step without further purification. An analytical sample was prepared via column chromatography (10–20% ethyl acetate/hexane) and gave lactam **16** as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37–7.25 (m, 10 H), 6.84–6.75 (m, 3 H), 5.32 (d, *J* = 4.5 Hz, 1 H), 5.27 (d, *J* = 12.4 Hz, 1 H), 5.22–5.14 (m, 2 H), 4.73–4.68 (m, 1 H), 4.63 (dd, *J* = 7.3 Hz, *J* = 8.7 Hz, 1 H), 4.08 (d, *J* = 10.8 Hz, 1 H), 4.02–3.95 (m, 2 H), 3.82 (s, 3 H), 1.88–1.78 (m, 6 H), 1.61–1.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.1, 168.0, 149.6, 148.1, 138.6, 135.3, 130.0, 128.9, 128.5, 128.2, 128.0, 127.9, 126.0, 119.0, 114.2, 112.3, 96.6, 80.5, 75.3, 67.5, 58.1, 57.8, 56.1, 50.2, 32.8, 24.0; IR (film) 3063, 3032, 2956, 2871, 1742, 1717, 1516, 1244, 1164, 734, 698 cm^{-1}; $[\alpha]_D$ = +28.4° (*c* 0.45, CH_2Cl_2).

Lactam 17 was prepared from 900 mg of lactam **16** by the same procedure describing the preparation of lactam **6c** and was obtained (427 mg) as a single diastereomer in 73% yield (from lactam **4**) after column chromatography (20–30% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (m, 4 H), 6.87–6.81 (m, 3 H), 5.24 (d, *J* = 3.5 Hz, 1 H), 5.17 (app t, *J* = 7.2 Hz, 1 H), 4.82–4.75 (m, 1 H), 4.59 (app t, *J* = 8.5 Hz, 1 H), 3.90 (dd, *J* = 7.0 Hz, *J* = 8.5 Hz, 1 H), 3.83 (s, 3 H), 3.51 (app dt, *J* = 3.5 Hz, *J* = 9.3 Hz, 1 H), 3.05–2.87 (m, 2 H), 1.95–1.81 (m, 6 H), 1.68–1.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.7, 149.4, 148.0, 139.4, 132.7, 128.8, 127.8, 125.9, 119.0, 114.1, 112.3, 99.0, 80.6, 74.9, 57.8, 56.1, 45.1, 40.5, 32.8, 24.0; IR (film) 3062, 3019, 2957, 2871, 1716, 1515, 1259, 759, 698, 668 cm^{-1}; $[\alpha]_D$ = +65.6° (*c* 0.43, CH_2Cl_2).

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92. Found: C, 73.10; H, 6.97.

2-Methoxy-5-bromophenol (15). (a) From 2,4-Dibromoanisole. To 500 mg (1.88 mmol) of 2,4-dibromoanisole (Aldrich) in 20 mL of THF under Ar at −78 °C was added 0.79 mL (1.97 mmol) of 2.5 M *n*-BuLi (hexanes). After stirring at 30 min the reaction mixture was warmed to 0 °C and 0.22 mL (1.97 mmol) of neat trimethyl borate was added. After an additional 30 min, 1 mL of H_2O_2 (30%) was added, and the reaction was allowed to stir at ambient temperature overnight, quenched with 1 N HCl, extracted with three portions of ethyl acetate, dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil. Column chromatography (15% ethyl acetate/hexane) provided 210 mg (55%) of bromide **15** as an orange solid: mp 60–62 °C, ^{1}H NMR ($CDCl_3$) δ 7.05 (d, *J* = 2.4 Hz, 1 H), 6.94 (dd, *J* = 2.4 Hz, *J* = 8.6 Hz, 1 H), 6.67 (d, *J* = 8.6 Hz, 1 H), 5.70 (s, 1 H), 3.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.4, 145.8, 122.7, 117.8, 113.2, 111.8, 56.0; IR (film) 3508, 3073, 3008, 2965, 2841, 1503 cm^{-1}.

(b) From Aminophenol. To 6.0 g (43.2 mmol) of 3-amino-6-methoxyphenol (Aldrich) in 36 mL of H_2SO_4/18 mL of MeOH/60 mL of H_2O at 0 °C was added 3.3 g (47.5 mmol) of $NaNO_2$ in 25 mL of H_2O over 30 min. The reaction mixture was allowed to stir 45 min, and 3.5 g (12.1 mmol) of Cu_2Br_2 in 60 mL of H_2O/12 mL of HBr was added over 20 min. The mixture was warmed to reflux for 1.5 h, cooled to ambient temperature, extracted with four portions of ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (20% ethyl acetate/hexane) provided 3.42 g (40%) of **15** as a yellow solid identical to that prepared in a.

2-(Cyclopentyloxy)-4-bromoanisole (14). To 1.50 g (7.39 mmol) of phenol **15** in 100 mL of acetone was added 5.10 g (36.9 mmol) of K_2CO_3, followed by 3.96 mL (36.9 mmol) of cyclopentyl bromide (passed through a plug of basic alumina prior to use). The solution was heated to reflux for 24 h, cooled to ambient temperature, diluted with H_2O, and concentrated in vacuo. Ethyl acetate was added, and the organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to 2.03 g of a yellow oil which was forced through a silica gel plug (10% ethyl acetate/hexane), providing 2.00 g (100%) of ether **14** as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.99–6.95 (m, 2 H), 6.69 (d, *J* = 14.0 Hz, 1 H), 4.73–4.68 (m, 1 H), 3.79 (s, 3 H), 1.94–1.77 (m, 6 H), 1.63–1.56 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 149.2, 148.5, 123.2, 117.9, 113.2, 112.6, 80.7, 56.1, 32.7, 24.0; IR (film) 3073, 2956, 1586, 1498, 1250, 1224, 1131, 1029, 983, 794 cm^{-1}.

Pyrrolidinone 21. To 33.0 mg (0.84 mmol) calcium metal in ca. 15 mL of liquid NH_3 at −78 °C under Ar was added 33.0 mg (0.08 mmol) of lactam **17** in 2 mL of anhydrous THF slowly so as not to totally discharge the blue color. The solution was stirred at −78 °C for 4 h, quenched by the careful addition of solid NH_4Cl, and allowed to warm to ambient temperature under a stream of Ar. After the ammonia had evaporated, the solid residue was filtered (ethyl acetate), and the filtrate was concentrated in vacuo to 20.4 mg (84%) of hydroxypyrrolidinone **21**: ^{1}H NMR ($CDCl_3$) δ 7.44 (br s, 1 H), 6.79–6.68 (m, 3 H), 5.14 (m, 1 H), 4.83–4.80 (m, 1 H), 4.73–4.70 (m, 1 H), 3.79 (s, 3 H), 3.34–3.29 (m, 1 H), 2.94 (dd, *J* = 9.1 Hz; *J* = 17.5 Hz, 1 H), 2.38 (dd, *J* = 5.2 Hz, 17.5 Hz, 1 H), 1.88–1.72 (m, 6 H), 1.58–1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 178.0, 149.3, 147.9, 133.6, 118.7, 114.1, 112.3, 86.7, 80.7, 56.1, 48.9, 37.0, 32.8, 24.0; IR (film) 3380, 3255, 2957, 1716, 1645, 1519, 1250, 1051, 819 cm^{-1}; $[\alpha]_D$ = +2.8° (*c* 0.42, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.74; H, 7.31.

Similar experiments were carried out using sodium, lithium, and potassium metal in liquid ammonia with varying degrees of success (10–40% yields of **21**).

Rolipram [(−)-13]. To 20.0 mg (0.068 mmol) of pyrrolidinone **21** in 3.75 mL of THF and 1.25 mL of methanol was added 13.0 mg (0.21 mmol) of sodium cyanoborohydride (Aldrich) followed by a crystal of bromocresol green indicator. Methanolic HCl (2 M) was added dropwise until a pale yellow color persisted for >15 min. The solution was allowed to stir at ambient temperature for an additional 2.5 h, quenched with 1 M HCl, and extracted with four portions of ethyl acetate. The organic layers were dried over $MgSO_4$ and concentrated in vacuo to 31.3 mg of a yellow oil which was passed through a silica gel plug with 4:1 ether/triethylamine, providing 15.8 mg of a colorless solid which appeared to be ca. 95% pure by ^{1}H NMR. Radial chromatography (90:5:5 dichloromethane/triethylamine/acetone; 1 mm) provided 13.8 mg (73%) of Rolipram (**13**) as an off white solid: mp 126–128 °C (lit.[11] mp 132 °C), mixed mp 130–132 °C; ^{1}H NMR ($CDCl_3$) δ 6.82–6.74 (m, 3 H), 5.94 (br s, 1 H), 4.76–4.72 (m, 1 H), 3.81 (s, 3 H), 3.74 (app t, *J* = 8.2 Hz, 1 H), 3.61 (app p, *J* = 8.4 Hz, 1 H), 3.36 (dd, *J* = 7.2 Hz, *J* = 9.1 Hz, 1 H), 2.70 (dd, *J* = 8.8 Hz, *J* = 17.0 Hz, 1 H), 2.46 (dd, *J* = 8.8 Hz, *J* = 16.9 Hz, 1 H), 2.02–1.75 (m, 6 H), 1.63–1.57 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.8, 149.2, 147.9, 134.5, 118.8, 113.8, 112.2, 80.6, 56.1, 49.8, 39.9, 38.1, 32.8, 24.0; IR (film) 3211, 3051, 2956, 1686, 1517, 1264, 1137, 1030, 808, 736 cm^{-1}; $[\alpha]_D$ = −19.5° (*c* 1.15, MeOH). An authentic sample showed identical spectral characteristics, although specific rotations did not match; $[\alpha]_D$ = −31° (see Figure 2).

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