Enantiopure 4- and 5-Aminopiperidin-2-ones: Regiocontrolled Synthesis and Conformational Characterization as Bioactive β-Turn Mimetics

Klaus Weber, Ursula Ohnmacht, and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstraβe 19, D-91052 Erlangen, Germany

Gmeiner@pharmazie.uni-erlangen.de

Received April 12, 2000

Starting from aspartic acid, we synthesized lactam-bridged β- and γ-amino acid equivalents. Using the 1,4-bis-electrophile **1b** as a central intermediate, the 4- and 5-aminopiperidin-2-ones **4** and **8**, respectively, were approached by regioselective functionalization and subsequent lactamization. Diastereoselective C-alkylation was performed after N-protection of the lactam functionality when exclusive trans configuration resulting in the formation of **5a**−**f** was observed in the 4-amino series. On the other hand, cis selectivity was typical for the alkylations of the 5-amino lactams **5a**,**b**. To investigate the ability of the lactam building blocks to induce reverse-turn structures by intramolecular hydrogen bonding, the model peptidomimetics **12** and **14** representing Homo−Freidinger lactams of type II and III were prepared from **4a** and **8a**, respectively. Conformational analyses in dilute solution (1 mM) by IR and NMR spectroscopy at room temperature clearly indicated that the 4-aminopiperidin-2-one derivative **12** predominantly adopts a reverse-turn structure stabilized by a CO−HN hydrogen bond in an 11-membered ring. VT NMR experiments showed a substantial temperature dependency of the terminal NH when $\Delta\delta_{NH}/\Delta T = -6.5$ indicated that the amount of intramolecular hydrogen bonding is higher at low temperature. An application in the field of medicinal chemistry was demonstrated. Thus, starting from the Homo−Freidinger lactam **11c** and the enantiomer *ent*-**11c**, we synthesized the peptidomimetics **15c** and **16c** and investigated them as lactam-bridged analogues of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG). Both test compounds turned out to enhance significantly the agonist binding of dopamine D2 receptors, when the isomer **15c** revealed a potency comparable to the genuine ligand PLG.

Introduction

One of the most challenging aspects of modern medicinal chemistry is the design of highly potent, target-selective, and metabolically stable peptidomimetics.[1] An important step in the development of drug candidates of this type is the employment of molecular scaffolds, inducing conformational restraints.[2] Within this field, reverse-turn templates are of special interest because a large number of small peptides having regulatory roles in organisms adopt β- or γ-turn conformations.[3]

In conjunction with a program to design β-analogues[4] of the dopamine D2 receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG),[5] we investigated the synthesis of lactam-bridged amino acid derivatives by regioselective functionalization of aspartic acid and asparagine.[6,7] Instead of using γ-amino-substituted lactams of type I (Freidinger lactams),[8] which have proven useful for the design of a variety of medicinally relevant enzyme inhibitors,[9] we attempted to approach analogous β- and γ-amino acid-derived congeners of type II and III, respectively, which we call Homo−Freidinger lactams (Scheme 1).

We report here an ex-chiral pool approach to β-amino acids[10,11] and β- and γ-amino-substituted piperidin-2-ones, including C-alkylation products. Furthermore, the incorporation of the conformationally restricted building blocks into tripeptide mimics and their conformational properties, especially the ability to adopt β-turn-related structures, are described. Application of the strategy led to the PLG mimetics **15c** and **16c**, which induced an increase in the affinity of dopamine D2 receptors.

(1) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244.

(2) Beck-Sickinger, A. G. In *Methods in Molecular Biology, Neuropeptide Protocols*; Irvine, G. B., Williams, C. H., Eds.; Humana Press: Totowa, NJ, 1997; p 61. Tamura, K.; Agrios, K. A.; Vander Velde, D.; Aubé, J.; Borchardt, R. T. *Bioorg. Med. Chem.* **1997**, *5*, 1859.

(3) For examples, see: Vacca, J. P.; Condra, J. H. *Drug Discovery Today* **1997**, *2*, 261. Blommaert, A. G. S.; Dhôtel, H.; Ducos, B.; Durieux, C.; Goudreau, N.; Bado, A.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 647. Hruby, V. J. *Drug Discovery Today* **1997**, *2*, 165.

(4) Thomas, C.; Ohnmacht, U.; Niger, M.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2885.

(5) Chiu, S.; Paulose, C. S.; Mishra, R. K. *Science* **1981**, *214*, 1261. Johnson, R. L.; Rajakumar, G.; Mishra, R. K. *J. Med. Chem.* **1986**, *29*, 2100.

(6) For preliminary communication, see: Weber, K.; Gmeiner, P. *Synlett* **1998**, 885.

(7) Michel, D.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 365. Lehmann, T.; Michel, D.; Glänzel, M.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 1389.

(8) Freidinger, R. M.; Schwenk Perlow, D.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104. Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631. Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348.

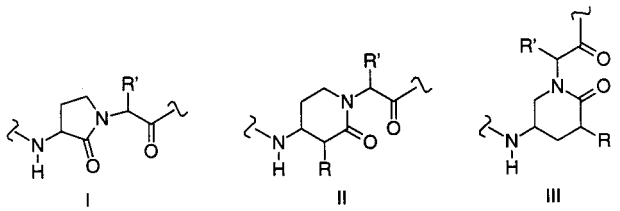
(9) Wolfe, M. S.; Dutta, D.; Aubé, J. *J. Org. Chem.* **1997**, *62*, 654 and references therein.

(10) For review, see: Juaristi, E., Ed. *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, 1997.

(11) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717. Weber, K.; Kuklinkski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647.

10.1021/jo000555c CCC: $19.00
Published on Web 10/03/2000

Scheme 1



I II III

Results and Discussion

As a straightforward strategy for the synthesis of both 4- and 5-aminopiperidinones, representing lactam-bridged β- and γ-amino acids, respectively, we chose a regioselective functionalization of the 1,4-bis-electrophile **1b**, which is readily available from natural aspartic acid via the aminobutanediol **1a** (Scheme 2).[12] According to previous experiments, attempts to isolate and store the dimesylate **1b** are generally not successful because migration of the dibenzylamino function followed by formation of enantiomerically pure *N*,*N*-dibenzyl-3-mesyloxypyrrolidinium occurs.[13,14] Thus, the bis-electrophile **1b** should be employed as a freshly prepared solution in THF. For the transformation to the target compounds, we envisioned subsequent incorporation of amine and carboxylate equivalents followed by cyclization. Because of earlier observations on displacement reactions with mono-O-protected derivatives, we anticipated a significantly higher kinetic reactivity of position 1, which is activated by an anchimeric participation of the dibenzylamino group.[12] In practice, treatment of the dimesylate **1b** with LiCN at room temperature resulted in exclusive formation of the β-amino nitrile **2**. Conversion of the mono-electrophile **2** into the β,δ-diamino nitrile **3a** was best accomplished when liquid ammonia was used as a nucleophile, affording the cyclization precursor in 82% yield based on **1a**. Besides the function as an intermediate for the synthesis of Homo−Freidinger lactams, the mesyloxynitrile **3a** can also serve as a building block for the preparation of β-amino acids when C,C-bond formation was facilitated by organocuprates.[15,16] Thus, reaction of **3a** with Me_2CuLi and Bu_2CuLi gave the β-amino nitriles **3b** and **3c**, which were converted into the N-protected β-amino acids **3d** and **3e** by acidic hydrolysis. On the other hand, treatment of the diamino nitrile **3a** with HCl in aqueous MeOH resulted in lactam formation. Thus, the 4-aminopiperidinone **4a** could be produced efficiently in high overall yield (58% based on Asp).

As a complement of this route, we attempted to access 5-aminopiperidinones[17] by changing the order of displacement reactions. In this case, the bis-electrophile **1b** has to be reacted first with an NH_2 equivalent in position 1 in the presence of the leaving group in position 4. To prevent pyrrolidine formation by intramolecular alkylation, it was necessary to employ a protected N-nucleophile. Thus, we reacted **1b** with 1 equiv of phthalimide-K to afford the monosubstitution product **6a**. Because phthalimide-K reacted slower than LiCN and yielded only 40% product, we increased the nucleophile concentration. The best yield (61%, besides 16% of easily separable diimide **6b**) was observed when 4 equiv was used. Upon treatment of the sulfonate **6b** with LiCN, formation of the displacement product **6c** was observed. Subsequent hydrazinolysis yielded the diamino nitrile **7** as a cyclization precursor. Finally, ring closure was achieved under acidic conditions, resulting in formation of the *N*,*N*-dibenzyl-protected 5-aminopiperidin-2-one **8a**.

Whereas the 4-amino regioisomer **4a** represents a lactam-bridged β-alanine unit, the building block **8a** can be regarded as a γ-aminobutyric acid (GABA) analogue.[18] We were intrigued by the question of whether deprotonation of the lactam α positions and subsequent trapping with suitable electrophiles gave us the opportunity to introduce residues representing amino acid side chains.

The C-alkylations should be performed after N-protection of the lactam functionality. Thus, we converted the lactams **4a** and **8a** into the mixed imides **4b** and **8b**, respectively, by treatment with Boc_2O in the presence of Et_3N/DMAP.[19] Alternatively, benzyl substituents were attached by NaH-induced N-deprotonation and subsequent reaction with benzyl bromide. Starting from the orthogonally protected 4-aminolactam **4b**, our alkylation studies were performed in THF, employing LDA as a base and methyl iodide as an electrophile. C-Alkylation in high yield and complete diastereoselection was observed when 2 equiv of base and 2.5 equiv of the electrophile turned out to represent the optimal stoichiometry. Under these conditions, the trans diastereomer **5a** could be isolated in 75% yield. Both diastereomeric purity and relative configuration were determined by ^{1}H NMR spectroscopic investigation when no signal of any impurity of the crude product exceeded the intensity of the ^{13}C satellites of the *N*-benzyl resonances (signal-to-noise ratio > 4:1), indicating a diastereoselectivity higher than 99%. The trans configuration including an equatorial orientation of both substituents was elucidated unambiguously by diagnostic coupling constants and NOEs.[20] Obviously, the *si* face of an anionic reaction intermediate is effectively shielded by the sterically demanding dibenzylamino substituent, causing an exclusive attack of the electrophile from the opposite side (*re*). Similar results were obtained when employing benzyl bromide as an electrophile. Thus, the lactam-bridged β-homophenylalanine derivative **5b** could be diastereoselectively synthesized from **4b** in 85% yield. Because fluoro-substituted amino acid analogues become more and more important in bioorganic and medicinal chemistry,[21] we elaborated an electrophilic fluorination

(12) Gmeiner, P.; Kärtner, A.; Junge, D. *Tetrahedron Lett.* **1993**, *34*, 4325. Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. Gmeiner, P.; Kärtner, A. *Synthesis* **1995**, 83.

(13) Gmeiner, P.; Orecher, F.; Thomas, C.; Weber, K. *Tetrahedron Lett.* **1995**, *36*, 381.

(14) Thomas, C.; Orecher, F.; Gmeiner, P. *Synthesis* **1998**, 1491.

(15) Posner, G. H. In *Organic Reactions*; Baldwin, J. E., Bittmann, R., Dauben, W. G., Heck, R. F., Kende, A. S., Leimgruber, W., Marshall, J. A., McKusick, B. C., Meinwald, J., Trost, B. M., Weinstein, B., Eds.; John Wiley & Sons: New York, 1975; Vol. 22, p 253.

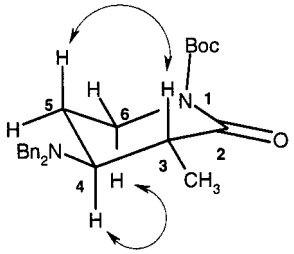
(16) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigière, C.; Viallefont, P. *Tetrahedon Lett.* **1984**, *25*, 2759.

(17) For a previous synthesis of (*S*)-5-aminopiperidin-2-one, see: Panday, S. K.; Langlois, N. *Tetrahedron Lett.* **1995**, *36*, 8205.

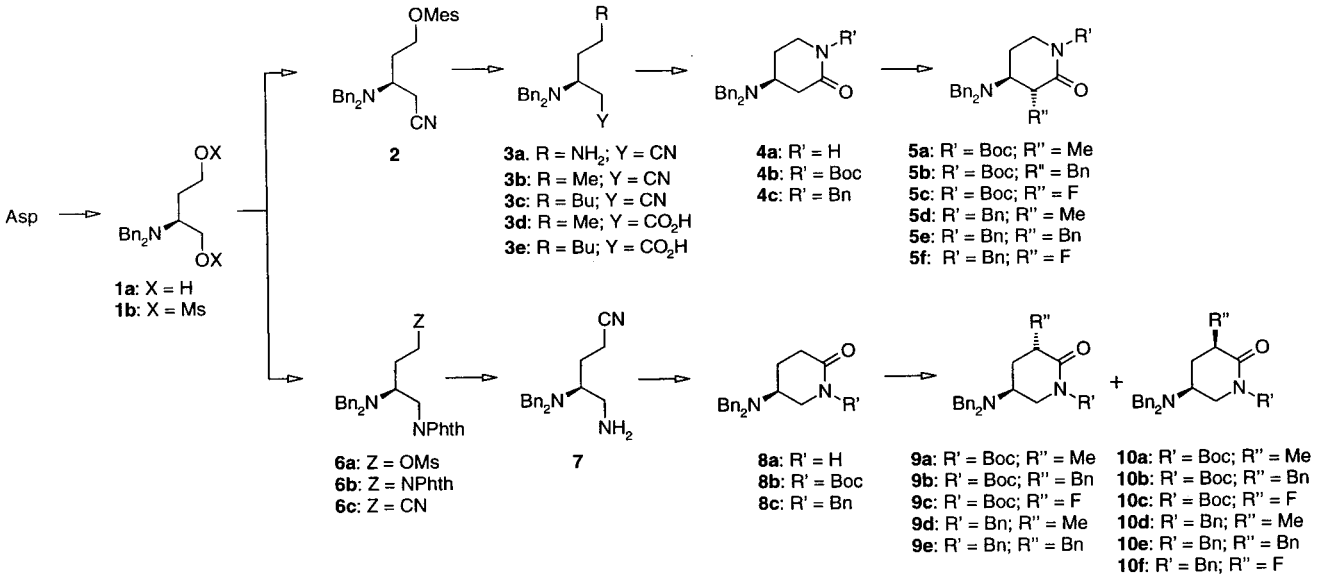
(18) Krogsgaard-Larsen, P. *J. Med. Chem.* **1981**, *24*, 1377.

(19) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(20) Diagnostic NOEs for **5a**:



Scheme 2



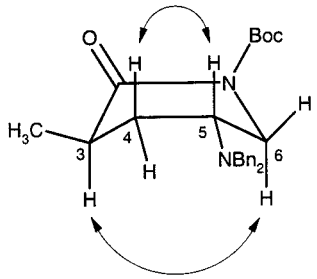
of the building block **4b** with NFSI (*N*-fluorobenzene sulfonimide).[22] Again, we observed a trans-selective substitution, resulting in the formation of the α-fluoro lactam **5c**. In connection with structural variations of benzamide-typed antipsychotics,[23] *N*-benzylpiperidinone-derived chiral building blocks are of special interest for our SAR studies. Therefore, we envisioned to extend the alkylation reactions described above for a stereoselective synthesis of *N*-benzyllactams. In fact, the formal exchange of Boc by benzyl did not change the reactivity of the systems toward C-alkylations when deprotonation of **4c** and subsequent treatment with methyl iodide, benzyl bromide, and NFSI gave the trans isomers **5d**, **5e**, and **5f**, respectively. The products were formed in high yield (38−72%) and highly diastereoselectively. Application of the protocol elaborated for the synthesis of the 5-aminopiperidinone surrogates turned out to be more difficult. Starting from the *N*-Boc-protected lactam **8b**, the attempted methylation and benzylation initially failed. Employing NFSI as an electrophile, we observed the formation of a mono-C-alkylation product in 26% yield. Careful NMR analysis indicated diastereomeric purity and cis configuration. The stereoselective production of **10c** was surprising to us because we assume a chairlike transition state with an equatorially dispositioned dibenzylamine substituent state, which should favor an axial attack. This would preferably lead to the trans isomer **9c**. However, the CH-acidic properties of the α-fluoro imide structure are expected to facilitate equilibration during the reaction. Thus, the formation of the bis-equatorially substituted isomer **10c** will be due to thermodynamic control. When elaborating suitable reaction conditions for the methylation and benzylation reactions of the Boc-protected 5-aminopiperidinone **5b**, we found that addition of 4 equiv of the cosolvents HMPA facilitated the methylation, giving access to the chromatographically separable diastereomers **9a** and **10a** in a 3:4 ratio (yield 66%). The relative stereochemistry could be clearly analyzed by diagnostic coupling patterns of the ^{1}H NMR spectra. It is interesting to note that both diastereomers revealed different conformational properties. In agreement with all of the lactams described above, the cis isomer **10a** predominantly exists in a half-chair conformation. On the other hand, substantial NOEs between the axially oriented protons in the positions 3 and 6 as well as 4 and 5 clearly indicate a boatlike structure for the trans isomer **9a**, making it possible that both residues are positioned equatorially.[24] In the presence of HMPA, benzylation and fluorination of **8b** was also accomplished, furnishing 1:9 and 1:20 mixtures of the diastereomers **9b**/**10b** and **9c**/**10c**,[25] respectively. According to diagnostic ^{1}H NMR coupling constants, both diastereomers showed half-chair conformations. The deprotonation of the *N*-benzyl lactam **8c**, followed by treatment with the electrophiles methyl iodide, benzyl bromide, and NFSI gave smooth and effective conversions, resulting in the formation of target compounds **9d**/**10d**, **9e**/**10e**, and **10f**, respectively. In accordance with the observations made for the Boc-protected 5-amino lactams, the methylation proceeded cis selective when a 3:10 ratio of the diastereomers **9d** and **10d** was determined. A 3:10 cis selectivity was also noticed for the

(21) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1990. *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. Imperiali, B. *Adv. Biotechnol. Processes* **1988**, *10*, 97. Filler, R., Kobayashi, Y., Eds. *Biomedical Aspects of Fluorine Chemistry*; Kodanasha Ltd., Elsevier Biomedical Press: Tokyo, 1982. Chirakal, R.; Garnett, E. S.; Schrobilgen, G. J.; Nahmias, C.; Firnau, G. *Chem. Br.* **1991**, *27*, 47.

(22) Differding, E.; Duthaler, R. O.; Krieger, A.; Rüegg, G. M.; Schmit, C. *Synlett* **1991**, 395.

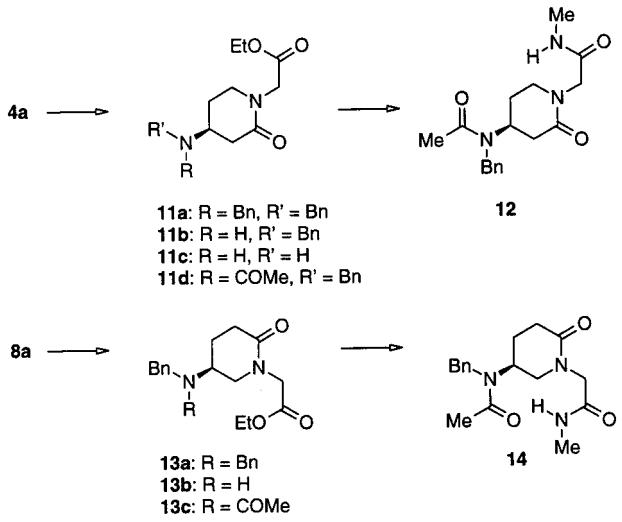
(23) For review, see: Högberg, T. *Drugs Future* **1991**, *16*, 333. For a very recent example, see: Thomas, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 841.

(24) Diagnostic NOEs for **9a**:

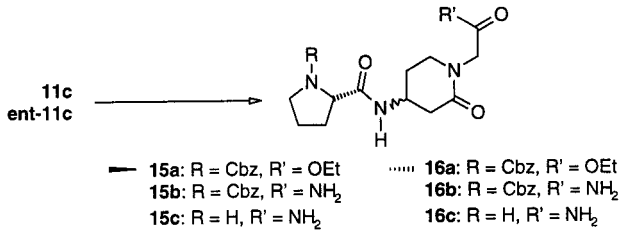


(25) The minor diastereomer **9c** was not isolated but detected unambiguously in the ^{1}H NMR spectrum of crude **10c** (diagnostic signal: δ 5.02 (J = 47.9, 6.8, 6.8, 1H, $3H_{eq}$)).

Scheme 3



Scheme 4



benzylation reaction, whereas the fluorination of **8c** gave the cis diastereomer **10f** exclusively.

To investigate the ability of the 4- and 5-amino lactams to induce folded conformations, the synthesis of the model tripeptide mimetics **12** and **14** was intended (Scheme 3). Thus, deprotonation of the lactam **4a** by KH and subsequent N-alkylation gave the protected dipeptide mimetic **11a**. Subsequently, controlled N-debenzylation was elaborated. Utilizing $Pd(OH)_2/C$ as a catalyst, we observed complete hydrogenolysis after 15 h to give the primary amine **11c**. Terminating the reaction after 40 min and repeating the procedure four times after the respective product separations gave access to the mono-debenzylation product **11b**. Alternatively, treatment of the tertiary amine **11b** with CAN[26] gave a more convenient and selective approach to **11b**. The synthesis of the potential reverse-turn mimetic **12** was completed by N-acylation, yielding **11d**, followed by aminolysis with $MeNH_2$. Using the same reaction sequence, the 5-aminopiperidone derivative **14** was prepared from the building block **8a** via the intermediates **13a** and **13c**.

As an application in the field of dopamine receptor modulating reagents, we tried to incorporate the Homo−Freidinger lactam **11c** and the optical antipode *ent*-**11c**, readily available from (*R*)-aspartic acid, into the conformatively rigidized PLG mimetics **15c** and **16c**, respectively (Scheme 4). In practice, DCC/HOBt coupling of **11c** and *ent*-**11c** with Cbz−Pro afforded the protected tripeptide mimetics **15a** and **16a**, respectively. Subsequent treatment with liquid ammonia resulted in the formation of the carboxamides **15b** and **16b**, which were deprotected by catalytic hydrogenation to give the PLG mimetics **15c** and **16c**, respectively.

(26) Hungerhoff, B.; Samanta, S. S.; Roels, J.; Metz, P. *Synlett* **2000**, 77.

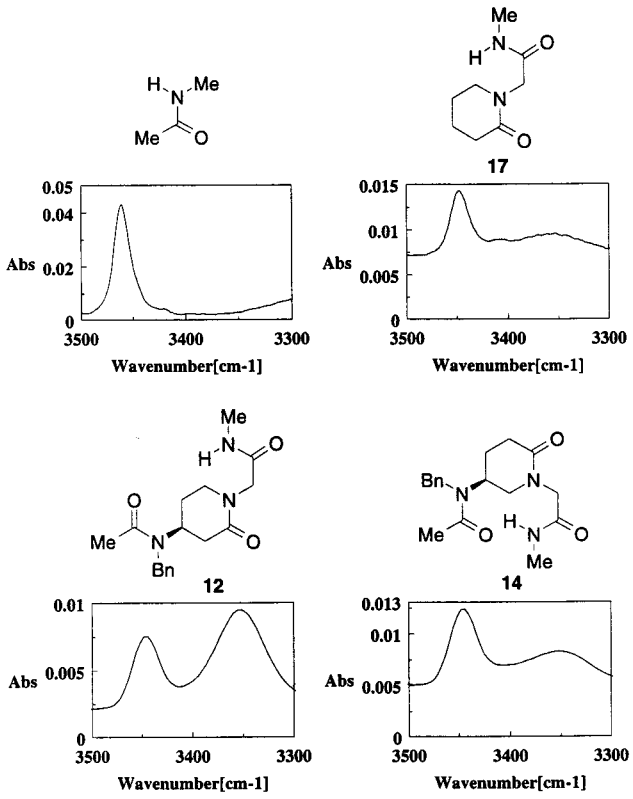


Figure 1. NH stretch FT-IR data for 1 mM samples in CH_2Cl_2 at room temperature after subtraction of the spectrum of pure CH_2Cl_2.

We were intrigued by the question of whether the Homo−Freidinger lactams II and III representing lactam-bridged β- and γ-amino acid equivalents in peptidomimetics are able to induce stable reverse turns. Thus, we observed the conformational behavior of the model compounds **12** and **14** in dilute solution by IR (1 mM, CH_2Cl_2) and ^1H NMR spectroscopy (1 mM, $CDCl_3$). Figure 1 shows the NH stretch regions of the IR spectra, recorded at room temperature, of **12** and **14** compared to *N*-methylacetamide and *N*-methyl-2-(2-oxopiperidin-1-yl)acetamide (**17**). In accordance with the literature,[27] *N*-methylacetamide displays a solvent-exposed NH band at 3460 cm^{-1}. Besides the extensive non-hydrogen-bonded amide absorption at 3450 cm^{-1}, the oxopiperidinylacetamide **17** shows a small amount of intramolecular hydrogen bonding, indicated by a broad absorption at 3350 cm^{-1}. Thus, formation of a seven-membered-ring hydrogen bond is not favored. On the other hand, the major NH stretch band of the peptidomimetic **12** at 3350 cm^{-1} indicates strong internal hydrogen bonding. The combination of the data led us to conclude that this is the result of an 11-membered-ring interaction. Obviously, the molecular scaffold **12** shows a substantial tendency for reverse-turn formation. The amide **12** also displays a minor absorption maximum at 3450 cm^{-1}, which may be assigned to a fully solvated NH. IR spectral data of the amide **14** representing the Homo−Freidinger lactam III display little intramolecular hydrogen bonding (major band at 3450 cm^{-1} and minor absorption at 3350 cm^{-1}).

(27) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228. Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719. Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555.

Besides the IR-based analysis, ^{1}H NMR investigations of intermolecular hydrogen-bonding interactions of **12** including VT measurements were performed. The NMR work was done in $CDCl_3$ because protic dipolar solvents such as D_2O lead to a H/D exchange of the diagnostic amide signals. D_2O as an alternative solvent would be more similar to biological liquids. However, we are interested in model studies giving reference to putatively bio-active conformations. When exerting its function, a peptidomimetic is bound to a membrane receptor or an enzyme. Then it is generally nonsolvated. In contrast to the IR data, only one NH resonance (δ 6.6) was observed by NMR because equilibrium among hydrogen-bonded and non-hydrogen-bonded states is usually rapid on the NMR time scale. Thus, the value represents a mixture of both populations. By comparison, measurement of *N*-methylacetamide under identical conditions displayed a δ_{NH} at 5.45 ppm. VT NMR measurements showed a significant chemical shift change for the NH proton with temperature. Juxtaposition of the chemical shifts employing 10 °C steps between 230 and 320 K gave $\Delta\delta_{NH}/\Delta T = -6.5$, indicating that the amount of intramolecular hydrogen bonding is substantially higher at low temperature.

After peak assignment utilizing H,H-COSY and C,H-COSY experiments, careful analysis of the ^{1}H NMR spectrum of the peptidomimetic **12** and comparison to that of the regioisomer **14** and the synthetic precursors **11d** and **13c**, respectively, supported the assumption of a folded conformation for **12**. According to coupling patterns, the piperidinone ring of **12** predominantly exists in a twisted conformation with a perpendicularly orientated amine substituent (narrow signals for 3-H and 4-H). This is in contrast to the ^{1}H NMR data of the non-hydrogen-bonded Homo−Freidinger lactams **11d**, **13c**, and **14** when ^3J values for antiperiplanar-positioned protons (10.6−11.4 Hz) indicated half-chair conformations with equatorially positioned substituents. Obviously, this conformational change is caused by the tendency of the molecule to form an internal hydrogen bond, which is possible only when the aminoacyl group is directed pseudoaxially. Systematic conformational analysis based on force-field calculations showed that the NH hydrogen donor and the CO hydrogen acceptor cannot come closer than 4.6 Å when the aminoacyl group is orientated equatorially. However, energetically favorable conformations allowing H bonding could be found for the twisted system. Geometry optimization gave a minimal energy conformation with an NH−OC distance of 2.06 Å (Figure 2).

The PLG analogues **15c** and **16c** were tested for their ability to increase the binding of the dopamine receptor agonist [^{3}H]pramipexole to dopamine D2 receptors prepared from bovine striatal membranes.[28] The results were expressed as percentages in specific binding compared to control membranes. Figure 3 shows the effects of PLG, which is known as a genuine dopamine receptor modulator probably exerting the effect in a type II β-bend conformation, and the lactam-bridged analogues **15c** and **16c**. Significant enhancement of [^{3}H]pramipexole binding

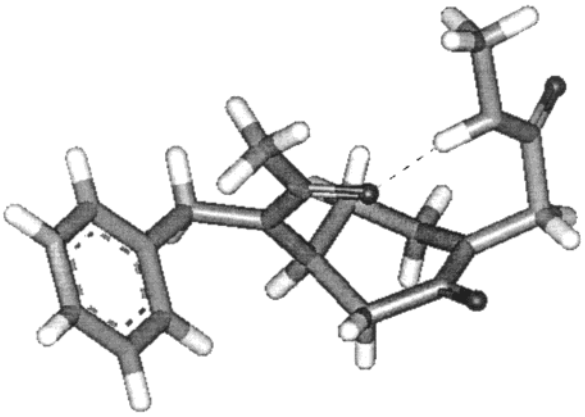


Figure 2. Minimal energy conformation of **12** obtained by molecular mechanics calculations.

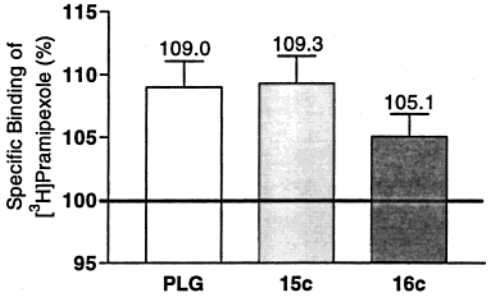


Figure 3. Stimulation of [^{3}H]pramipexole binding to striatal membranes by PLG, **15c**, and **16c** in concentrations of 10^{-9} M. Results are means ± SEM of three to five experiments each carried out in triplicate; the data are significantly different from the control value ($p < 0.05$).

was observed for both test compounds when the diastereomer **15c** revealed an activity comparable to PLG. Because dopamine receptor modulating agents are of potential interest for the treatment of neurologic and psychiatric disorders, further efforts in this field are in progress.

Experimental Section

General. Solvents and reagents were purified and dried by standard procedures. Unless otherwise noted, reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Flash chromatography was carried out with 230−400 mesh silica gel. If not otherwise stated, MS were run by EI ionization (70 eV) with a solid inlet, and HRMS were obtained by employing peak matching $M/\Delta M = 10\,000$. ^{1}H NMR spectra were recorded on 250 MHz, 360 MHz, and 400 MHz spectrometers, if not otherwise stated in $CDCl_3$ relative to TMS (*J* values are in hertz); ^{13}C NMR spectra were recorded at 63 MHz in $CDCl_3$. Elemental analyses were performed by Beetz Microanalysis Laboratory and by the Institute of Organic Chemistry (Analytical Departments) of the Friedrich-Alexander University Erlangen−Nürnberg.

(3*S*)-Methanesulfonic Acid 4-Cyano-3-(*N*,*N*-dibenzylamino)butyl Ester (2). To a solution of **1a**[14] (5.76 g, 20.2 mmol) and Et_3N (6.13 g, 60.6 mmol) in THF (100 mL) was added methanesulfonyl chloride (4.74 g, 41.4 mmol) at −23 °C. After 30 min of stirring at room temperature, the mixture was added to a precooled solution of LiCN (48 mL, 0.5 M in DMF) at −30 °C. After 3 h at room temperature, saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue (crude **2**) could be purified by flash

(28) Ohnmacht, U.; Tränkle, C.; Mohr, K.; Gmeiner, P. *Pharmazie* **1999**, *54*, 294.

(29) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 256. Subasinghe, N. L.; Bontems, R. J.; McIntee, E.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 2356. Reed, L. L.; Johnson, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 7523.

chromatography (petroleum ether−EtOAc, 1:1) to give **2** (5.57 g, 74%) as a colorless oil. *ent*-**2** was prepared under the same reaction conditions, starting from *ent*-**1a**. **2**: TLC R_f 0.38 (petroleum ether−EtOAc, 1:1); $[\alpha]^{23}_D$ −49.9° (c = 1.2, $CHCl_3$); IR 3030, 2940, 2250, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.93 (dddd, J = 14.6, 8.0, 5.9, 5.2, 1H), 2.16 (dddd, J = 14.6, 9.2, 5.7, 5.6, 1H), 2.46 (dd, J = 16.8, 6.7, 1H), 2.60 (dd, J = 16.8, 6.3, 1H), 2.83 (s, 3H), 3.24 (dddd, J = 9.2, 6.7, 6.3, 5.2, 1H), 3.51 (d, J = 13.7, 2H), 3.80 (d, J = 13.7, 2H), 4.25 (ddd, J = 10.0, 8.0, 5.6, 1H), 4.34 (ddd, J = 10.0, 5.9, 5.7, 1H), 7.20−7.42 (m, 10H); CIMS 373 (M + 1). Anal. Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found: C, 64.39; H, 6.51; N, 7.60.

(3*S*)-5-Amino-3-(*N*,*N*-dibenzylamino)pentanenitrile (3a). To a solution of crude **2** in MeOH (200 mL) was added liquid NH_3 (50 mL) at −30 °C. After 4 days of stirring at room temperature, saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether−acetone, 1:4) to give pure **3a** (4.86 g, 82%) as a colorless oil. *ent*-**3a** was prepared under the same reaction conditions, starting from *ent*-**2**. **3a**: TLC R_f 0.10 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{22}_D$ −31.3° (c = 0.9, $CHCl_3$). *ent*-**3a**: $[\alpha]^{20}_D$ +32.1° (c = 1.0, $CHCl_3$); IR 3370, 3060, 2930, 2240, 1600, 1450 cm^{-1}; ^1H NMR (250 MHz) δ 1.46−1.63 (m, 1H), 1.83−2.01 (m, 1H), 2.41 (dd, J = 16.8, 6.8, 1H), 2.58 (dd, J = 16.8, 6.3, 1H), 2.74−2.81 (m, 2H), 3.07−3.20 (m, 1H), 3.47 (d, J = 13.6, 2H), 3.77 (d, J = 13.6, 2H), 7.24−7.38 (m, 10H); CIMS 294 (M + 1).

(*S*)-3-(*N*,*N*-Dibenzylamino)hexanenitrile (3b). To a stirred suspension of CuI (1.66 g, 8.69 mmol) in Et_2O was added MeLi (9.9 mL, 1.6 M in Et_2O) at −50 °C. After 30 min, **3a** (0.29 g, 0.79 mmol) dissolved in Et_2O (10 mL) was added dropwise, and the mixture was allowed to warm to −20 °C over 3.5 h. Then the mixture was added to saturated aqueous $NaHCO_3$ and Et_2O. The organic layer was dried, evaporated, and purified by flash chromatography (petroleum ether−EtOAc, 9:1) to give pure **3b** (0.108 g, 47%) as a colorless oil: TLC R_f 0.18 (petroleum ether−EtOAc, 9:1); $[\alpha]^{23}_D$ −15.7° (c = 0.6, $CHCl_3$); IR 3030, 2960, 2230, 1450 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (t, J = 7.3, 3H), 1.22−1.34 (m, 1H), 1.39−1.51 (m, 2H), 1.70−1.81 (m, 1H), 2.37 (dd, J = 16.9, 6.6, 1H), 2.51-(dd, J = 16.9, 6.6, 1H), 2.85−3.04 (m, 1H), 3.54 (d, J = 13.2, 2H), 3.71 (d, J = 13.9, 2H), 7.20−7.40 (m, 10H); CIMS 293 (M + 1). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.28; H, 8.15; N, 9.47.

(*S*)-3-(*N*,*N*-Dibenzylamino)nonanenitrile (3c). CuI (1.40 g, 7.38 mmol) and *n*-BuLi (8.4 mL, 1.6 M in hexane) in Et_2O (40 mL) as well as **2** (0.25 g, 0.67 mmol) in Et_2O (10 mL) were reacted and worked up as described above for **3b** to give **3c** (0.11 g, 48%) as a colorless oil: TLC R_f 0.21 (petroleum ether−EtOAc, 95:5); $[\alpha]^{23}_D$ −12.0° (c = 0.9, $CHCl_3$); IR 3030, 2920, 2240, 1600, 1450 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (t, J = 7.1, 3H), 1.20−1.29 (m, 7H), 1.35−1.46 (m, 2H), 1.70−1.81 (m, 1H), 2.38 (dd, J = 16.8, 6.2, 1H), 2.51 (dd, J = 16.8, 6.9, 1H), 2.96−3.03 (m, 1H), 3.53 (d, J = 13.8, 2H), 3.70 (d, J = 13.8, 2H), 7.21−7.39 (m, 10H); EIMS 334 (M^+). Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.18; H, 8.99; N, 8.35.

(*S*)-3-(*N*,*N*-Dibenzylamino)hexanoic Acid (3d). A solution of **3b** (81 mg, 0.28 mmol) in concentrated aqueous HCl (3 mL) was stirred at 80 °C for 2 h. Then the mixture was concentrated, basified with 2 N aqueous NaOH, adjusted to pH 6 by addition of 10% aqueous citric acid, and then extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2−MeOH, 9:1) to give **3d** (68.6 mg, 79%) as a colorless solid: TLC R_f 0.50 (CH_2Cl_2−MeOH, 9:1); $[\alpha]^{23}_D$ +54.3° (c = 1.4, $CHCl_3$); IR 3030, 2960, 1720, 1600, 1460 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (t, J = 7.3, 3H), 1.14−1.38 (m, 2H), 1.39−1.46 (m, 1H), 1.80−1.88 (m, 1H), 2.39−2.54 (m, 2H), 3.06−3.14 (m, 1H), 3.43 (d, J = 13.2, 2H), 4.00 (d, J = 12.5, 2H), 7.26−7.38 (m, 10H); CIMS 312 (M + 1). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.59; H, 8.30; N, 4.84.

(*S*)-3-(*N*,*N*-Dibenzylamino)nonanoic Acid (3e). A solution of **3c** (57.5 mg, 0.17 mmol) in concentrated aqueous HCl (5 mL) was reacted and worked up as described for **3d** to give pure **3e** (36.5 mg, 61%) as a colorless oil: TLC R_f 0.48 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{23}_D$ +53.3° (c = 0.5, $CHCl_3$); IR 3030, 2930, 1710, 1600, 1450 cm^{-1}; ^1H NMR (400 MHz) δ 0.90 (t, J = 7.0, 3H), 1.28−1.41 (m, 9H), 1.79−1.89 (m, 1H), 2.33−2.57 (m, 2H), 2.98−3.12 (m, 1H), 3.40 (d, J = 13.1, 2H), 3.99 (d, J = 13.1), 7.24−7.40 (m, 10H); MS 171 (M − 182). Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.85; H, 8.80; N, 3.29.

(4*S*)-4-(*N*,*N*-Dibenzylamino)piperidin-2-one (4a). A solution of **3a** (6.96 g, 23.7 mmol) in MeOH−H_2O (200 mL, 99:1) was saturated with HCl gas and, subsequently, stirred for 12 h at 60 °C. Then the mixture was adjusted to pH 8 by addition of aqueous 2 N NaOH and $NaHCO_3$. After addition of Et_2O, the organic layer was dried and evaporated, and the residue was purified by flash chromatography (MeOH−CH_2Cl_2−*N*-ethyldimethylamine, 10:90:1) to give pure **4a** (4.90 g, 70%) as a colorless solid. *ent*-**4a** was prepared under the same reaction conditions, starting from *ent*-**3a**. **4a**: TLC R_f 0.24 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{23}_D$ −73.4° (c = 1.0, $CHCl_3$). *ent*-**4a**: $[\alpha]^{25}_D$ +73.0° (c = 1.0, $CHCl_3$); mp 83−85 °C; IR 3200, 3020, 2920, 1650, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.75 (dddd, J = 12.4, 12.3, 12.2, 5.5, 1H), 2.00−2.09 (m, 1H), 2.46 (dd, J = 17.3, 11.5, 1H), 2.59 (ddd, J = 17.3, 5.5, 2.0, 1H), 3.01 (ddd, J = 12.0, 5.5, 3.2, 1H), 3.12 (ddd, J = 12.0, 12.2, 4.0, 1H), 3.28−3.35 (m, 1H), 3.63 (d, J = 14.2, 2H), 3.67 (d, J = 14.2, 2H), 5.88 (s, 1H), 7.19−7.39 (m, 10H); CIMS 295 (M + 1). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.54; N, 9.52. Found: C, 77.56; H, 7.65; N, 9.36.

(4*S*)-4-(*N*,*N*-Dibenzylamino)-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (4b). To a solution of **4a** (0.37 g, 1.25 mmol) in CH_2Cl_2 (20 mL) were added 4-dimethylaminopyridine (0.15 g, 1.25 mmol), NEt_3 (174 μL, 1.25 mmol), and di-*tert*-butyl dicarbonate (0.55 g, 2.5 mmol). After 15 h of stirring at room temperature, the mixture was concentrated, and the residue was purified by MPLC (petroleum ether−EtOAc, 7:3) to give pure **4b** (0.35 g, 71%) as slightly yellowish crystals. *ent*-**4b** was prepared under the same reaction conditions, starting from *ent*-**4a**. **4b**: TLC R_f 0.27 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −45.4° (c = 1.0, $CHCl_3$). *ent*-**4b**: $[\alpha]^{20}_D$ +45.5° (c = 1.0, $CHCl_3$); mp 118−119 °C; IR 2980, 2930, 1770, 1720 cm^{-1}; ^1H NMR (360 MHz) δ 1.5 (s, 9H), 1.79 (dddd, J = 15.8, 11.1, 10.7, 4.8, 1H), 2.05−2.14 (m, 1H), 2.63 (dd, J = 16.4, 9.8, 1H), 2.70 (ddd, J = 16.4, 6.3, 1.3, 1H), 3.09−3.19 (m, 1H), 3.35 (ddd, J = 13.0, 10.7, 4.3, 1H), 3.60 (d, J = 13.8, 2H), 3.65 (d, J = 13.8, 2H), 3.85 (ddd, J = 13.0, 4.8, 4.3, 1H), 7.20−7.42 (m, 10H); CIMS 395 (M + 1). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.03; H, 7.73; N, 6.99.

(4*S*)-1-Benzyl-4-(*N*,*N*-dibenzylamino)piperidin-2-one (4c). To a solution of **4a** (0.66 g, 2.24 mmol) in THF (20 mL) was added NaH (0.18 g, 4.48 mmol, 60% suspension in paraffin). The mixture was stirred for 30 min at 0 °C and for an additional 30 min at room temperature. After addition of benzyl bromide (665 μL, 5.6 mmol), the mixture was stirred for 15 h at room temperature. Then saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by MPLC (petroleum ether−EtOAc, 6:4) to give pure **4c** (0.61 g, 71%) as colorless crystals. *ent*-**4c** was prepared under the same reaction conditions, starting from *ent*-**4a**. **4c**: TLC R_f 0.33 (petroleum ether−EtOAc, 6:4); $[\alpha]^{20}_D$ −56.5° (c = 1.1, $CHCl_3$). *ent*-**4c**: $[\alpha]^{20}_D$ +56.6° (c = 1.0, $CHCl_3$); mp 129−130 °C; IR 3060, 2930, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.74 (dddd, J = 12.3, 12.3, 12.1, 5.6, 1H), 2.0−2.1 (m, 1H), 2.57 (dd, J = 17.1, 11.3, 1H), 2.73 (ddd, J = 17.14, 5.5, 2.1, 1H), 3.00−3.10 (m, 1H), 3.05, (ddd, J = 12.1, 12.1, 4.6, 1H), 3.21 (ddd, J = 12.1, 5.6, 2.5, 1H), 3.61 (d, J = 14.1, 2H), 3.67 (d, J = 14.1, 2H), 4.28 (d, J = 14.6, 1H), 4.78 (d, J = 14.6, 1H), 7.17−7.37 (m, 15H); EIMS 384 (M^+). Anal. Calcd for $C_{26}H_{28}N_2O$ (+0.5 H_2O): C, 79.97; H, 7.40; N, 7.17. Found: C, 79.68; H, 7.25; N, 7.04.

(3*R*,4*S*)-4-(*N*,*N*-Dibenzylamino)-3-methyl-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (5a). To a solution

of **4b** (108 mg, 0.27 mmol) in THF (20 mL) was added LDA (3.1 mL, 0.175 M in THF) at −78 °C. After 1 h, methyl iodide (42 μL, 0.68 mmol) was added and stirring was continued for another 1 h at −78 °C. Then the mixture was allowed to warm up to room temperature. After 12 h, saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by MPLC (petroleum ether−EtOAc, 8:2) to give pure **5a** (83 mg, 75%) as slightly yellowish crystals. *ent*-**5a** was prepared under the same reaction conditions, starting from *ent*-**4b**. **4b**: TLC R_f 0.27 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ +37.1° (c = 5.5, $CHCl_3$). *ent*-**5a**: $[\alpha]^{20}_D$ −36.9° (c = 1.0, $CHCl_3$); mp 111 °C; IR 2980, 2930, 1770, 1710 cm^{-1}; ^1H NMR (360 MHz) δ 1.31 (d, J = 6.5, 3H), 1.50 (s, 9H), 1.82 (dddd, J = 14.3, 9.6, 9.5, 4.8, 1H), 2.08 (m, 1H), 2.59 (m, 1H), 2.65 (m, 1H), 3.38 (d, J = 13.8, 2H), 3.53 (ddd, J = 13.0, 9.6, 4.7, 1H), 3.72 (ddd, J = 13.0, 5.3, 4.8), 3.83 (d, J = 13.8, 2H), 7.24−7.38 (m, 10H); CIMS 409 (M + 1). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.66; H, 7.99; N, 6.80.

(3*R*,4*S*)-3-Benzyl-4-(*N*,*N*-dibenzylamino)-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (5b). A solution of **4b** (100 mg, 0.25 mmol) in THF (20 mL), LDA (2.85 mL, 0.175 M in THF), and benzyl bromide (75 μL, 0.63 mmol) were reacted and worked up as described for **5a** to give pure **5b** (103 mg, 85%) as slightly yellowish crystals. *ent*-**5b** was prepared under the same reaction conditions, starting from *ent*-**4b**. **5b**: TLC R_f 0.43 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −41.5° (c = 1.0, $CHCl_3$). *ent*-**5b**: $[\alpha]^{20}_D$ +42.0° (c = 1.0, $CHCl_3$); mp 46−47 °C; IR 3060, 3030, 2980, 2930, 1770, 1710 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 1.46 (s, 9H), 1.63−1.75 (m, 1H), 2.06−2.14 (m, 1H), 2.70 (ddd, J = 13.1, 10.0, 3.0, 1H), 2.84 (dd, J = 13.1, 4.5, 1H), 2.88−2.98 (m, 2H), 3.15 (dd, J = 13.1, 4.5, 1H), 3.42 (d, J = 13.5, 2H), 3.72−3.79 (m, 1H), 3.80 (d, J = 13.5, 2H), 6.53−6.58 (m, 2H), 6.98−7.09 (m, 3H), 7.20−7.40 (m, 10H); ^{13}C NMR (61 MHz) δ 21.6, 28.0, 35.6, 42.9, 50.5, 53.9, 55.0, 82.7, 127.2, 127.9, 128.4, 128.9, 129.7, 138.6, 139, 151.8, 173.3; CIMS 485 (M + 1). HRMS calcd for $C_{31}H_{36}N_2O_3$ (M^+): 484.2726. Found: 484.2725.

(3*R*,4*S*)-4-(*N*,*N*-Dibenzylamino)-3-fluoro-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (5c). A solution of **4b** (50 mg, 0.13 mmol) in THF (20 mL), LDA (1.48 mL, 0.175 M in THF), and NFSI (104 mg, 0.63 mmol) in THF (5 mL) were reacted and worked up as described for **5a** to give pure **5c** (42 mg, 78%) as colorless crystals: TLC R_f 0.19 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ +4.0° (c = 1.0, $CHCl_3$); mp 145 °C; IR 3030, 2980, 2930, 1780, 1730 cm^{-1}; ^1H NMR (360 MHz) δ 1.49 (s, 9H), 1.89 (dddd, J = 14.5, 9.9, 9.5, 5.1, 1H), 2.04−2.16 (m, 1H), 3.3 (dddd, J = 11.9, 10.2, 9.9, 6.0, 1H), 3.52 (ddd, J = 13.3, 9.5, 4.3, 1H), 3.61 (ddd, J = 13.3, 5.3, 5.1, 1H), 3.76 (d, J = 13.7, 2H), 3.82 (d, J = 13.7, 2H), 5.11 (dd, J = 48.7, 10.2, 1H), 7.19−7.40 (m, 10H); CIMS 413 (M + 1). Anal. Calcd for $C_{24}H_{29}FN_2O_3$: C, 69.88; H, 7.09; N, 6.79. Found: C, 69.88; H, 7.20; N, 6.53.

(3*R*,4*S*)-1-Benzyl-4-(*N*,*N*-dibenzylamino)-3-methylpiperidin-2-one (5d). A solution of **4c** (1.35 g, 3.52 mmol) in THF (50 mL), LDA (20.1 mL, 0.175 M in THF), and methyl iodide (546 μL, 8.8 mmol) were reacted and worked up as described for **5a** to give pure **5d** (738 mg, 53%) as colorless crystals. *ent*-**5d** was prepared under the same reaction conditions, starting from *ent*-**4c**. **5d**: TLC R_f 0.16 (petroleum ether−EtOAc, 8:2); $[\alpha]^{25}_D$ +30.0° (c = 1.0, $CHCl_3$). *ent*-**5d**: $[\alpha]^{25}_D$ −30.5° (c = 1.0, $CHCl_3$); mp 107−108 °C; IR 3030, 2930, 16408, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.36 (d, J = 6.5, 3H), 1.64 (dddd, J = 12.3, 12.1, 11.6, 5.2, 1H, $5H_{ax}$), 2.06−2.15 (m, 1H), 2.54−2.63 (m, 1H), 2.65 (ddd, J = 11.6, 11.1, 3.0, 1H), 3.02 (ddd, J = 12.1, 12.1, 4.1, 1H), 3.24 (ddd, J = 12.1, 5.2, 2.7, 1H), 3.36 (d, J = 13.5, 2H), 3.85 (d, J = 13.5, 2H), 4.25 (d, J = 14.6, 1H), 4.78 (d, J = 14.6, 1H), 7.16−7.40 (m, 15H); EIMS 398 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.30. Found: C, 81.40; H, 7.66; N, 7.04.

(3*R*,4*S*)-1,3-Dibenzyl-4-(*N*,*N*-dibenzylamino)piperidin-2-one (5e). A solution of **4c** (51 mg, 0.13 mmol) in THF (10 mL), LDA (1.14 mL, 0.175 M in THF), and benzyl bromide (39 μL, 0.33 mmol) were reacted and worked up as described for **5a** to give pure **5e** (44.5 mg, 72%) as a colorless oil: TLC R_f 0.34 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ +35.6° (c = 1.0, $CHCl_3$); IR 3060, 3030, 2930, 1630, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.59 (dddd, J = 12.1, 12.1, 12.1, 4.2, 1H), 2.00−2.05 (m, 1H), 2.56 (ddd, J = 12.1, 12.0, 3.2, 1H), 2.90−3.01 (m, 4H), 3.32 (dd, J = 12.7, 4.3, 1H), 3.39 (d, J = 13.5, 2H), 3.84 (d, J = 13.5, 2H), 4.37 (d, J = 14.7, 1H), 4.56 (d, J = 14.7, 1H), 6.57−6.62 (m, 2H), 6.93−7.00 (m, 2H), 7.18−7.38 (m, 10H); EIMS 474 (M^+). Anal. Calcd for $C_{33}H_{34}N_2O$: C, 83.51; H, 7.22; N, 5.90. Found: C, 83.49; H, 7.13; N, 5.92.

(3*R*,4*S*)-1-Benzyl-4-(*N*,*N*-dibenzylamino)-3-fluoropiperidin-2-one (5f). A solution of **4c** (47 mg, 0.12 mmol) in THF (10 mL), LDA (1 mL, 0.175 M in THF), and NFSI (94.6 mg, 0.30 mmol) in THF (5 mL) were reacted and worked up as described for **5a** to give pure **5f** (47 mg, 38%) as a colorless oil: TLC R_f 0.19 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −6.4° (c = 1.0, $CHCl_3$); IR 3030, 2930, 1660, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.81 (dddd, J = 12.8, 12.1, 12.1, 5.8, 1H), 1.95−2.04 (m, 1H), 3.05 (ddd, J = 12.1, 12.0, 4.5, 1H), 3.12 (ddd, J = 12.00, 5.8, 3.0, 1H), 3.25 (dddd, J = 12.1, 12.1, 10.3, 3.9, 1H), 3.73 (d, J = 13.8, 2H), 3.83 (d, J = 13.8, 2H), 4.34 (d, J = 14.5, 1H), 4.68 (d, J = 14.5, 1H), 5.09 (dd, J = 48.6, 10.3, 1H), 7.15−7.45 (m, 15H); EIMS 384 (M^+). HRMS calcd for $C_{26}H_{27}FN_2O$: 402.2108. Found: 402.2122.

(3*S*)-Methanesulfonic Acid 4-Phthalimido-3-(*N*,*N*-dibenzylamino)butyl Ester (6a) and (2*S*)-2-(*N*,*N*-Dibenzylamino)-1,4-diphthalimidobutane. To a solution of **1a**[14] (11.04 g, 38.7 mmol) and Et_3N (11.75 g, 116.1 mmol) was added methansulfonyl chloride (9.09 g, 79.3 mmol) at −23 °C. After 30 min of stirring at room temperature, the mixture was added to a precooled solution of phthalimide-K (7.17 g, 154.8 mmol in 200 mL of THF) at −30 °C. After an additional 90 min at room temperature, saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether−EtOAc, 1:1) to give **6a** (11.7 g, 61%) as a colorless solid besides **6b** (3.4 g, 16%). *ent*-**6a** was prepared under the same reaction conditions, starting from *ent*-**1a**. **6a**: TLC R_f 0.19 (petroleum ether−EtOAc, 7:3); $[\alpha]^{25}_D$ −12.7° (c = 1.0, $CHCl_3$). *ent*-**6a**: $[\alpha]^{20}_D$ +12.4° (c = 1.0, $CHCl_3$); mp 114 °C; IR 3200, 3060, 3030, 1770, 1750, 1710 cm^{-1}; ^1H NMR (360 MHz) δ 1.76 (dddd, J = 14.4, 6.5, 6.3, 6.3, 1H), 2.17 (dddd, J = 14.4, 6.8, 6.6, 6.5, 1H), 2.78 (s, 3H), 3.13 (dddd, J = 6.8, 6.8, 6.7, 6.5, 1H), 3.55 (dd, J = 13.6, 6.8, 1H), 3.61 (d, J = 13.4, 2H), 3.75 (d, J = 13.4, 2H), 4.09 (dd, J = 13.6, 6.7, 1H), 4.21 (ddd, J = 9.8, 6.6, 6.3, 1H), 4.31 (ddd, J = 9.8, 6.5, 6.3, 1H), 7.31−7.13 (m, 10H), 7.73−7.81 (m, 2H), 7.78−7.90 (m, 2H); EIMS 423 (M^+). **6b**: ^1H NMR (360 MHz) δ 1.61−1.72 (m, 1H), 2.17 (dddd, J = 14.0, 9.5, 9.5, 5.0, 1H), 3.04 (m, 1H), 3.43 (ddd, J = 13.8, 11.4, 4.7, 1H), 3.64 (dd, J = 14.0, 7.0, 1H), 3.70 (s, 4H), 4.02 (ddd, J = 13.8, 10.7, 5.0), 4.08 (dd, J = 14.0, 6.4, 1H), 7.12−7.30 (m, 10H), 7.70−7.75 (m, 4H), 7.80−7.85 (m, 4H); EIMS 543 (M^+).

(4*S*)-4-(*N*,*N*-Dibenzylamino)-5-phthalimidopentanenitrile (6c). To a solution of LiCN (46.2 mL, 0.5 M in DMF) was added **6a** (3.8 g, 7.7 mmol). After 3 days of stirring at room temperature, saturated aqueous $NaHCO_3$ and Et_2O were added. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was purified by MPLC (petroleum ether−EtOAc, 7:3) to give **6c** (2.68 g, 82%) as colorless crystals. *ent*-**6c** was prepared under the same reaction conditions, starting from *ent*-**6a**. **6c**: TLC R_f 0.28 (petroleum ether−EtOAc, 7:3); $[\alpha]^{23}_D$ −35.4° (c = 1.0, $CHCl_3$). *ent*-**6c**: $[\alpha]^{20}_D$ +36.6° (c = 1.0, $CHCl_3$); mp 126−128 °C; IR 3200, 3060, 2940, 1770, 1750, 1710 cm^{-1}; ^1H NMR (360 MHz) δ 1.69 (dddd, J = 14.0, 9.1, 6.2, 4.8, 1H), 1.98 (dddd, J = 14.0, 9.4, 9.4, 4.8, 1H), 2.08 (ddd, J = 16.5, 9.4, 6.2, 1H), 2.52 (ddd, J = 16.5, 9.1, 4.8, 1H), 2.94 (dddd, J = 9.4, 8.2, 4.9, 4.8, 1H), 3.61 (dd, J = 13.5, 8.2, 1H), 3.68 (d, J = 13.3, 2H), 3.78 (d, J = 13.3, 2H), 4.08 (dd, J = 13.5, 4.9, 1H), 7.18−7.53 (m, 10H), 7.71−7.78 (m, 2H), 7.82−7.89 (m, 2H); EIMS 423 (M^+). Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.22; H, 5.71; N, 9.53.

(4*S*)-5-Amino-4-(*N*,*N*-dibenzylamino)pentanenitrile (7). To a solution of **6c** (3.49 g, 8.24 mmol) in MeOH (100 mL) was added hydrazinehydrate (5.2 g, 80 proz., 82.4 mmol). The

solution was refluxed for 14 h. After evaporation, saturated aqueous $NaHCO_3$ and Et_2O were added to the residue. The organic layer was dried and evaporated to leave crude **7**. For analytical data, purification was performed by flash chromatography (petroleum ether−acetone, 1:4). *ent*-**7** was prepared under the same reaction conditions, starting from *ent*-**6c**. **7**: TLC R_f 0.27 (petroleum ether−acetone, 2:8); $[\alpha]^{20}_D$ +7.5° (*c* = 1.0, MeOH). *ent*-**7**: $[\alpha]^{20}_D$ −7.7° (*c* = 1.0, $CHCl_3$); IR 3370, 3030, 2930, 2250, 1600, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.74 (dddd, *J* = 14.1, 8.5, 6.5, 6.3, 1H), 1.84−1.96 (m, 1H), 2.24 (ddd, *J* = 16.9, 8.5, 6.5, 1H), 2.44 (ddd, *J* = 16.9, 8.6, 6.3, 1H), 2.52−2.64 (m, 2H), 2.91−3.08 (m, 1H), 3.62 (d, *J* = 13.5, 2H), 3.65 (d, *J* = 13.5, 1H), 7.22−7.35 (m, 10H); EIMS 293 (M^+).

(5*S*)-5-(*N*,*N*-Dibenzylamino)piperidin-2-one (8a). Crude **7**, which was prepared as described above, was dissolved in MeOH−H_2O (200 mL, 99:1). After saturation of the solution with HCl gas, the mixture was refluxed for 12 h. Then pH 8 was adjusted by addition of aqueous 2 N NaOH and $NaHCO_3$. After an additional 2 h of stirring, Et_2O was added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by MPLC (petroleum ether−acetone, 2:8) to give pure **8a** (2.01 g, 83%) as colorless crystals. *ent*-**8a** was prepared under the same reaction conditions, starting from *ent*-**7**. **8a**: TLC R_f 0.33 (petroleum ether−acetone, 2:8); $[\alpha]^{20}_D$ −8.3° (*c* = 1.0, $CHCl_3$). *ent*-**8a**: $[\alpha]^{25}_D$ +8.7° (*c* = 1.0, $CHCl_3$); mp 60 °C; IR 3210, 3030, 2940, 1670, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.83 (dddd, *J* = 12.2, 12.2, 12.1, 5.3, 1H), 2.00−2.10 (m, 1H), 2.25 (ddd, *J* = 17.7, 12.1, 6.0, 1H), 2.49 (ddd, *J* = 17.7, 5.3, 2.5, 1H), 3.00−3.10 (m, 1H), 3.26−3.76 (m, 2H), 3.62 (d, *J* = 14.0, 2H), 3.72 (d, *J* = 14.0, 2H), 6.17 (s, 1H), 7.19−7.39 (m, 10H); EIMS 294 (M^+). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.05; H, 7.64; N, 9.59.

(5*S*)-5-(*N*,*N*-Dibenzylamino)-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (8b). To a solution of **8a** (3.18 g, 10.8 mmol) in CH_2Cl_2 (100 mL) were added 4-dimethylaminopyridine (2.64 g, 21.6 mmol), NEt_3 (2.3 mL, 16.2 mmol), and di-*tert*-butyl dicarbonate (7.07 g, 32.4 mmol). After 4 h of refluxing, the mixture was concentrated, and the residue was purified by MPLC (petroleum ether−EtOAc, 6:4) to give pure **8b** (2.83 g, 66%) as slightly yellowish crystals: TLC R_f 0.26 (petroleum ether−EtOAc, 7:3); $[\alpha]^{20}_D$ −47.0° (*c* = 1.0, $CHCl_3$); mp 71−73 °C; IR 3030, 2980, 2930, 1770, 1720 cm^{-1}; ^1H NMR (360 MHz) δ.51 (s, 9H), 1.85 (dddd, *J* = 12.8, 11.0, 9.9, 5.5, 1H), 2.05 (dddd, *J* = 12.8, 6.8, 6.2, 4.7, 1H), 2.33 (ddd, *J* = 16.8, 11.0, 6.2, 1H), 2.58 (ddd, *J* = 16.8, 5.5, 4.7, 1H), 3.12 (dddd, *J* = 9.9, 6.8, 6.6, 6.6, 1H), 3.64 (d, *J* = 14.0, 2H), 3.69 (d, *J* = 14.0, 2H), 3.74 (d, *J* = 6.6, 2H), 7.20−7.37 (m, 10H); CIMS 395 (M + 1). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.50; H, 7.80; N, 6.81.

(5*S*)-1-Benzyl-5-(*N*,*N*-dibenzylamino)piperidin-2-one (8c). A solution of **8a** (0.27 g, 0.92 mmol) in THF (20 mL) was reacted with NaH (73.6 mg, 1.84 mmol, 60 proz. suspension in paraffin) and benzyl bromide (393 μL, 2.3 mmol) and worked up as described for **4c** to give **8c** (0.34 g, 97%) as a colorless oil. *ent*-**8c** was prepared under the same reaction conditions, starting from *ent*-**8a**. **8c**: TLC R_f 0.16 (petroleum ether−EtOAc, 6:4); $[\alpha]^{20}_D$ −43.0° (*c* = 1.0, $CHCl_3$). *ent*-**8c**: $[\alpha]^{20}_D$ +42.5° (*c* = 1.0, $CHCl_3$); IR 3030, 2930, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.84 (dddd, *J* = 12.2, 11.9, 11.8, 5.5, 1H), 1.99−2.07 (m, 1H), 2.34 (ddd, *J* = 17.6, 11.9, 6.2, 1H), 2.62 (ddd, *J* = 17.6, 5.5, 3.0, 1H), 3.03 (dddd, *J* = 11.8, 8.2, 7.2, 4.0, 1H), 3.21 (dd, *J* = 12.0, 8.2, 1H), 3.24 (dd, *J* = 12.0, 7.2, 1H), 3.58 (d, *J* = 13.8, 2H), 3.64 (d, *J* = 13.8, 2H), 4.40 (d, *J* = 14.7, 1H), 4.59 (d, *J* = 14.7, 1H), 7.15−7.40 (m, 15H); EIMS 384 (M^+). Anal. Calcd for $C_{26}H_{28}N_2O$: C, 77.58; H, 7.51; N, 6.91. Found: C, 77.84; H, 7.12; N, 6.91.

(3*S*,5*S*)-5-(*N*,*N*-Dibenzylamino)-3-methyl-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (9a) and (3*R*,5*S*)-5-(*N*,*N*-Dibenzylamino)-3-methyl-2-oxopiperidine-1-carboxylic *tert*-Butyl Ester (10a). A solution of **8b** (57 mg, 0.14 mmol) in THF (15 mL), HMPA (98 μL, 0.56 mmol), LDA (1.6 mL, 0.175 M in THF), and methyl iodide (22 μL, 0.35 mmol) were reacted and worked up as described for **5a** to give **9a** (16 mg, 28%) and **10a** (22 mg, 38%) as colorless oils. **9a**: TLC R_f 0.24 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ +26.4° (*c* = 0.5, $CHCl_3$); IR 3030, 2980, 2930, 1770, 1720, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.16 (d, *J* = 6.9, 3H), 1.49 (s, 9H), 1.66 (ddd, *J* = 14.0, 10.3, 8.7, 1H), 2.09 (ddd, *J* = 14.0, 6.9, 6.8, 1H), 2.64 (dqd, *J* = 10.3, 6.9, 6.9, 1H), 3.16 (dddd, *J* = 11.1, 8.7, 6.8, 5.0, 1H), 3.42 (dd, *J* = 12.9, 11.1, 1H), 3.66 (d, *J* = 13.9, 2H), 3.70 (d, *J* = 13.9, 2H), 4.23 (dd, *J* = 12.9, 5.0, 1H), 7.21−7.39 (m, 10H); EIMS 408 (M^+). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.48; H, 7.88; N, 6.77. **10a**: TLC R_f 0.29 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −41.2° (*c* = 0.5, $CHCl_3$); IR 3030, 2980, 2930, 1770, 1710, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.20 (d, *J* = 6.6, 3H), 1.52 (s, 9H), 1.62 (ddd, *J* = 13.0, 12.6, 10.3, 1H), 2.12 (ddd, *J* = 13.0, 6.4, 6.2, 1H), 2.31 (dqd, *J* = 12.6, 6.6, 6.4, 1H), 3.23 (dddd, *J* = 10.3, 6.2, 6.1, 5.8, 1H), 3.50 (dd, *J* = 13.7, 6.1, 1H), 3.56 (d, *J* = 13.9, 2H), 3.70 (d, *J* = 13.9, 2H), 4.10 (dd, *J* = 13.7, 5.8, 1H), 7.22−7.35 (m, 10H); EIMS 408 (M^+). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.54; H, 7.89; N, 6.84.

(3*S*,5*S*)-3-Benzyl-5-(*N*,*N*-dibenzylamino)-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (9b) and (3*R*,5*S*)-3-Benzyl-5-(*N*,*N*-dibenzylamino)-2-oxopiperidine-1-carboxylic *tert*-Butyl Ester (10b). A solution of **8b** (106 mg, 0.27 mmol) in THF (15 mL), HMPA (189 μL, 1.08 mmol), LDA (3.1 mL, 0.175 M in THF), and benzyl bromide (81 μL, 0.68 mmol) were reacted and worked up as described for **5a** to give **9b** (5.3 mg, 4%) and **10b** (46 mg, 35%) as colorless oils. **9b**: TLC R_f 0.28 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ +56.8° (*c* = 0.4, $CHCl_3$); IR 3060, 3030, 2850, 1770, 1720, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.52 (s, 9H), 1.62 (ddd, *J* = 14.6, 9.1, 6.7, 1H), 1.92 (ddd, *J* = 14.6, 8.4, 7.2, 1H), 2.49 (dd, *J* = 14.0, 9.9, 1H), 2.80 (dddd, *J* = 9.9, 8.4, 6.7, 4.3, 1H), 3.18 (dddd, *J* = 9.1, 9.0, 7.2, 5.3, 1H), 3.29 (dd, *J* = 14.0, 4.3, 1H), 3.43 (dd, *J* = 12.9, 9.0, 1H), 3.49 (d, *J* = 14.1, 2H), 3.61 (d, *J* = 14.1, 2H), 4.12 (dd, *J* = 12.9, 5.3, 1H), 7.08−7.37 (m, 15H); EIMS 484 (M^+). HRMS calcd for $C_{31}H_{36}N_2O_3$: 484.2726. Found: 484.2725. **10b**: TLC R_f 0.31 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −67.1° (*c* = 1.0, $CHCl_3$); IR 3060, 3030, 1770, 1710, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.49 (ddd, *J* = 13.7, 12.0, 9.4, 1H), 1.54 (s, 9H), 2.02 (ddd, *J* = 13.7, 6.2, 5.5, 1H), 2.45 (dddd, *J* = 12.0, 8.9, 5.5, 4.3, 1H), 2.59 (dd, *J* = 13.9, 8.9, 1H), 3.10 (dddd, *J* = 10.5, 6.2, 5.9, 5.9, 1H), 3.40 (dd, *J* = 13.9, 4.3, 1H), 3.47 (dd, *J* = 13.7, 5.9, 1H), 3.52 (d, *J* = 14.1, 2H), 3.66 (d, *J* = 14.1, 2H), 4.04 (dd, *J* = 13.7, 5.9, 1H), 7.14−7.32 (m, 15H); EIMS 484 (M^+). HRMS calcd for $C_{31}H_{36}N_2O_3$: 484.2726. Found: 484.2729.

(3*R*,5*S*)-5-(*N*,*N*-Dibenzylamino)-3-fluoro-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (10c). A solution of **8b** (75 mg, 0.13 mmol) in THF (20 mL), LDA (2.2 mL, 0.175 M in THF), and NFSI (150 mg, 0.48 mmol) were reacted and worked up as described for **5a** to give pure **10c** (20 mg, 26%) as a colorless oil. In the presence of HMPA (4 equiv), a 96:4 diastereomeric mixture of **10c** and **9c** was obtained in 22% yield. **10c**: TLC R_f 0.26 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −6.4° (*c* = 0.5, $CHCl_3$); IR 3030, 2980, 2930, 1780, 1730 cm^{-1}; ^1H NMR (360 MHz) δ 1.52 (s, 9H), 2.13 (dddd, *J* = 12.8, 12.6, 10.9, 10.7, 1H), 2.55 (dddd, *J* = 12.6, 10.4, 6.0, 5.8, 1H), 3.2 (dddd, *J* = 10.7, 8.0, 5.8, 5.5, 1H), 3.64 (d, *J* = 14.1, 2H), 3.67 (dd, *J* = 13.5, 5.5, 1H), 3.68 (d, *J* = 14.1, 2H), 3.88 (dd, *J* = 13.5, 8.0, 1H), 4.79 (ddd, *J* = 47.7, 10.9, 6.0, 1H), 7.19−7.40 (m, 10H); CIMS 413 (M + 1). Anal. Calcd for $C_{24}H_{29}FN_2O_3$: C, 69.88; H, 7.09; N, 6.79. Found: C, 69.97; H, 7.03; N, 6.51.

(3*S*,5*S*)-1-Benzyl-5-(*N*,*N*-dibenzylamino)-3-methylpiperidin-2-one (9d) and (3*R*,5*S*)-1-Benzyl-5-(*N*,*N*-dibenzylamino)-3-methylpiperidin-2-one (10d). A solution of **8c** (173 mg, 0.45 mmol) in THF (20 mL), HMPA (314 μL, 1.8 mmol), LDA (3 mL, 0.3 M in THF), and methyl iodide (70 μL, 1.13 mmol) were reacted and worked up as described for **5a** to give pure **9d** (34 mg, 19%) and **10d** (88 mg, 49%) as colorless oils. *ent*-**9d** and *ent*-**10d** were prepared under the same reaction conditions, starting from *ent*-**8c**. **9d**: TLC R_f 0.20 (petroleum ether−EtOAc, 6:4); $[\alpha]^{20}_D$ −10.2° (*c* = 0.9, $CHCl_3$). *ent*-**9d**: $[\alpha]^{25}_D$ +9.7° (*c* = 1.0, $CHCl_3$); IR 3060, 2930, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.20 (d, *J* = 6.9, 3H), 1.70−1.79 (m, 1H), 2.05 (ddd, *J* = 13.4, 9.6, 6.6, 1H), 2.72 (qdd, *J* = 6.9, 6.6, 6.4, 1H), 3.12 (dddd, *J* = 9.9, 9.6, 5.3, 4.8, 1H), 3.17 (dd, *J* = 12.0, 5.3, 1H), 3.25 (dd, *J* = 12.0, 9.9, 1H), 3.55 (d, *J* =

14.1, 2H), 3.64 (d, J = 14.1, 2H), 4.31 (d, J = 14.7, 1H), 4.56 (d, J = 14.7, 1H), 7.11−7.37 (m, 15H); EIMS 398 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.34; H, 7.56; N, 7.04. **10d**: TLC R_f 0.33 (petroleum ether−EtOAc, 6:4); $[\alpha]^{20}_D$ −25.4° (c = 1.0, $CHCl_3$). *ent*-**10d**: $[\alpha]^{25}_D$ +25.5° (c = 1.0, $CHCl_3$); IR 3060, 2930, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.28 (d, J = 6.7, 3H), 1.60 (ddd, J = 12.4, 12.3, 12.0, 1H), 2.15−2.30 (m, 1H), 2.31 (dqd, J = 12.4, 6.7, 6.2, 1H), 3.08 (dddd, J = 12.0, 8.7, 7.0, 3.5, 1H), 3.22 (dd, J = 12, 8.7, 1H), 3.27 (ddd, J = 12.0, 7.0, 1.1, 1H), 3.56 (d, J = 13.8, 2H), 3.60 (d, J = 13.8, 2H), 4.44 (d, J = 14.6, 1H), 4.62 (d, J = 14.6, 1H), 7.16−7.40 (m, 15H); EIMS 398 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.39; H, 7.52; N, 7.10.

(3*R*,5*S*)-1,3-Dibenzyl-5-(*N*,*N*-dibenzylamino)-3-methylpiperidin-2-one (10e). A solution of **8c** (51 mg, 0.13 mmol) in THF (20 mL), HMPA (91 μL, 0.52 mmol), LDA (1.51 mL, 0.175 M in THF), and benzyl bromide (40 μL, 0.33 mmol) were reacted and worked up as described for **5a** to give pure **10e** (33 mg, 54%) as a colorless solid. ^1H NMR spectroscopy of the crude product mixture indicated a mixture of the diastereomeres **9e** and **10e** in a 1:14 ratio. **10e**: TLC R_f 0.18 (petroleum ether−EtOAc, 8:2); $[\alpha]^{20}_D$ −28.9° (c = 1.0, $CHCl_3$); IR 3060, 3030, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.52 (ddd, J = 12.3, 12.3, 12.3, 1H), 1.88−1.97 (m, 1H), 2.52 (dddd, J = 12.3, 9.1, 5.4, 3.7, 1H), 2.79 (dd, J = 13.7, 9.1, 1H), 2.99 (dddd, J = 12.3, 9.6, 6.0, 3.3, 1H), 3.15 (dd, J = 11.7, 9.6, 1H), 3.22 (ddd, J = 11.7, 6.0, 1.6, 1H), 3.41 (dd, J = 13.7, 3.7, 1H), 3.41 (s, 4H), 4.53 (d, J = 14.9, 1H), 4.58 (d, J = 14.9, 1H), 7.12−7.38 (m, 20H); EIMS 474 (M^+). HRMS calcd for $C_{33}H_{34}N_2O$: 474.2671. Found: 474.2683.

(3*R*,5*S*)-1-Benzyl-5-(*N*,*N*-dibenzylamino)-3-fluoropiperidin-2-one (10f). A solution of **8c** (74 mg, 0.19 mmol) in THF (15 mL), HMPA (132 μL, 0.76 mmol), LDA (2.2 mL, 0.175 M in THF), and NFSI (151 mg, 0.48 mmol) in THF (2 mL) were reacted and worked up as described for **5a** to give pure **10f** (25 mg, 32%) as a colorless oil. **10f**: TLC R_f 0.34 (petroleum ether−EtOAc, 6:4); $[\alpha]^{20}_D$ +9.5° (c = 1.0, $CHCl_3$); IR 3060, 3030, 2920, 1670, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 2.09 (dddd, J = 12.4, 12.2, 12.1, 11.4, 1H), 2.51−2.61 (m, 1H), 3.06−3.17 (m, 1H), 3.20 (ddd, J = 11.7, 5.5, 1.4, 1H), 3.27 (dd, J = 11.7, 10.5, 1H), 3.56 (d, J = 14.0, 2H), 3.62 (d, J = 14.0, 2H), 4.50 (d, J = 14.6, 1H), 4.57 (d, J = 14.6, 1H), 4.80 (ddd, J = 47.5, 11.4, 6.1, 1H), 7.25−7.40 (m, 15H); EIMS 402 (M^+). HRMS calcd for $C_{26}H_{27}FN_2O$: 402.2107. Found: 402.2106.

(4*S*)-4-(*N*,*N*-Dibenzylamino-2-oxopiperidin-1-yl)acetic Acid Ethyl Ester (11a). To a solution of **4a** (600 mg, 2.05 mmol) in THF (20 mL) was added KH (470 mg, 35% solution in paraffin) at 0 °C. After 30 min of stirring, ethyl bromoacetate (450 μL, 4.1 mmol) was added and stirring was continued for another 4 h at 4 °C and 19 h at room temperature. Then EtOAc and a saturated aqueous NaCl solution were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether−EtOAc, 2:8) to give pure **11a** (750 mg, 96%) as a colorless oil. *ent*-**11a** was prepared under the same reaction conditions, starting from *ent*-**4a**. **11a**: TLC R_f 0.48 (petroleum ether−EtOAc, 2:8); $[\alpha]^{24}_D$ −43.5° (c = 1.0, $CHCl_3$). *ent*-**11a**: $[\alpha]^{25}_D$ +41.0° (c = 1.0, $CHCl_3$); IR 3020, 2920, 1740, 1650, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.23 (t, J = 7.1, 3H), 1.89 (dddd, J = 12.3, 12.3, 9.9, 7.5, 1H), 2.02−2.14 (m, 1H), 2.53 (dd, J = 17.1, 11.3, 1H), 2.68 (ddd, J = 17.1, 5.5, 2.1, 1H), 3.07−3.15 (m, 1H), 3.23−3.33 (m, 2H), 3.63 (d, J = 14.2, 2H), 3.67 (d, J = 14.2, 2H), 4.00 (d, J = 17.1, 1H), 4.10 (d, J = 17.1, 1H), 4.15 (q, J = 7.1, 2H), 7.16−7.41 (m, 10H); EIMS 380 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_3$ (+0.6 H_2O): C, 70.60; H, 7.52; N, 7.16. Found: C, 70.40; H, 7.27; N, 7.05.

(4*S*)-4-(*N*-Benzylamino-2-oxopiperidin-1-yl)acetic Acid Ethyl Ester (11b). A: A mixture of **11a** (218 mg, 0.45 mmol) and $Pd(OH)_2/C$ (20 mg) in MeOH (10 mL) was stirred under a balloon of H_2 for 40 min. The mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified by flash chromatography (MeOH−CH_2Cl_2, 5:95) to give **11b** and recovered **11a**. After repeating the procedure with the recovered **11a** nine times, 108 mg (83%) of **11b** was left as a colorless oil. B: To a solution of **11a** (125 mg, 0.33 mmol) in acetonitrile (4 mL) was added CAN (383.8 mg, 0.7 mmol) in H_2O (1 mL) at 0 °C. After 30 min of stirring at 0 °C, saturated aqueous $NaSO_3$ and Et_2O were added. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (MeOH−CH_2Cl_2, 5:95) to give pure **11b** (57 mg, 60%) as a colorless oil: TLC R_f 0.43 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{20}_D$ −25.1° (c = 1.0, $CHCl_3$); IR 3300, 2930, 2870, 1750, 1640, 1450 cm^{-1}; ^1H NMR (360 MHz) δ 1.26 (t, J = 7.1, 3H), 1.79 (dddd, J = 13.5, 8.8, 8.8, 5.4, 1H), 2.02−2.12 (m, 1H), 2.32 (dd, J = 17.1, 8.4, 1H), 2.72 (ddd, J = 17.1, 5.1, 1.6, 1H), 3.11 (dddd, J = 8.6, 8.4, 5.1, 3.3, 1H), 3.35 (ddd, J = 11.6, 8.8, 4.9, 1H), 3.43 (ddd, J = 11.6, 5.7, 5.4, 1H), 3.81 (d, J = 13.5, 1H), 3.85 (d, J = 13.5, 1H), 4.00 (d, J = 17.4, 1H), 4.18 (q, J = 7.1, 2H), 4.20 (d, J = 17.4, 1H), 7.25−7.35 (m, 5H); EIMS 290 (M^+). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.12; H, 7.57; N, 9.66.

(4*S*)-(4-Amino-2-oxopiperidin-1-yl)acetic Acid Ethyl Ester (11c). A mixture of **11a** (218 mg, 1.40 mmol) and $Pd(OH)_2/C$ (107 mg) in MeOH (10 mL) was stirred under a balloon of H_2 for 15 h at room temperature. The mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified by flash chromatography (MeOH−CH_2Cl_2−*N*-ethyldimethylamine, 20:80:1) to give pure **11c** (269 mg, 70%) as a colorless oil. *ent*-**11c** was prepared under the same reaction conditions, starting from *ent*-**11a**. **11c**: TLC R_f 0.1−0.3 (CH_2Cl_2−MeOH, 9:1); $[\alpha]^{20}_D$ −33.3° (c = 1.0, MeOH). *ent*-**11c**: $[\alpha]^{20}_D$ +33.1° (c = 1.0, MeOH); IR 3430, 2980, 1740, 1630 cm^{-1}; ^1H NMR (360 MHz) δ 1.08 (t, J = 7.2, 3H), 2.51 (dddd, J = 13.0, 11.5, 10.7, 5.9, 1H), 2.66−2.73 (m, 1H), 3.26 (dd, J = 17.0, 11.0, 1H), 3.35 (ddd, J = 17.0, 5.6, 1.5, 1H), 3.52 (dddd, J = 11.5, 11.0, 5.5, 3.8, 1H), 3.55−3.64 (m, 2H), 4.08 (d, J = 17.6, 1H), 4.09 (q, J = 7.2, 2H), 4.48 (d, J = 17.6, 1H); EIMS 200 (M^+).

(4*S*)-[4-(*N*,*N*-Acetylbenzylamino)-2-oxopiperidin-1-yl]-acetic Acid Ethyl Ester (11d). To a solution of **11c** (57 mg, 0.2 mmol) in pyridine (2 mL) was added acidic anhydride (1 mL). After 15 h of stirring at room temperature, CH_2Cl_2 and H_2O were added. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2−MeOH, 95:5) to give pure **11d** (64 mg, 96%) as a colorless oil: TLC R_f 0.15 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{20}_D$ −15.3° (c = 1.0, $CHCl_3$); IR 2980, 2940, 1750, 1640 cm^{-1}; ^1H NMR (360 MHz) δ 1.26 (t, J = 7.2, 3H), 1.88−1.97 (m, 1H), 2.06 (dddd, J = 11.9, 11.7, 11.4, 5.3, 1H), 2.11 (s, 3H), 2.55 (dd, J = 17.2, 10.9, 1H), 2.63 (ddd, J = 17.2, 6.3, 1.5, 1H), 3.27 (ddd, J = 11.7, 5.3, 2.8, 1H), 3.43 (ddd, J = 11.7, 11.7, 4.3, 1H), 4.02 (d, J = 17.0, 1H), 4.12 (d, J = 17.0, 1H), 4.18 (q, J = 7.2, 2H), 4.55 (s, 2H), 4.81 (dddd, J = 11.4, 10.9, 6.3, 3.7, 1H), 7.13−7.40 (m, 5H); EIMS 332 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.01; H, 7.26; N, 8.32.

(4*S*)-[4-(*N*,*N*-Acetylbenzylamino)-2-oxopiperidin-1-yl]-*N*-methylacetamide (12). A solution of **11c** (12 mg, 0.04 mmol) in ethanolic methylamine solution (5 mL, 8.03 M in EtOH) was stirred for 15 h at room temperature. After evaporation, the residue was purified by flash chromatography (CH_2Cl_2−MeOH, 95:5) to give pure **12** (11.4 mg, 100%) as a colorless oil: TLC R_f 0.11 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{20}_D$ −29.7° (c = 1.0, $CHCl_3$); IR 3310, 2930, 1630 cm^{-1}; ^1H NMR (360 MHz) δ 1.88−1.96 (m, 1H), 2.00−2.10 (m, 1H), 2.13 (s, 3H), 2.62 (d, J = 7.9, 2H), 2.77 (d, J = 4.8, 3H), 3.37−4.43 (m, 2H), 3.72 (d, J = 15.2, 1H), 4.12 (d, J = 15.2, 1H), 4.47−4.51 (m, 1H), 4.49 (d, J = 17.8, 1H), 4.56 (d, J = 17.8, 1H), 6.60 (s, 1H), 7.17−7.41 (m, 5H); ^{13}C NMR (63 MHz) δ 22.6, 26.1, 27.3, 35.8, 47.1, 49.6, 50.2, 51.5, 125.8, 127.8, 129.1, 136.9, 169.0, 169.4, 171.7; EIMS 317 (M^+). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 63.78; H, 7.25; N, 13.20.

(5*S*)-5-(*N*,*N*-Dibenzylamino-2-oxopiperidin-1-yl)acetic Acid Ethyl Ester (13a). To a solution of **8a** (580 mg, 1.97 mmol) in THF (20 mL) was added KH (157.6 mg, 60% solution in paraffin, 3.94 mmol) at 0 °C. After 30 min of stirring, ethyl bromoacetate (547 μL, 4.93 mmol) was added, and stirring was continued for an additional 4 h at 4 °C and 19 h at room

temperature. Then EtOAc (10 mL) and a saturated aqueous NaCl solution (10 mL) were added. After extraction with EtOAc, the organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (petroleum ether−EtOAc, 1:4) to give pure **13a** (273 mg, 36.4%) as a yellow oil, in addition to recovered **8a** (352 mg, 1.19 mmol): TLC R_f 0.39 (petroleum ether−EtOAc, 2:8); $[\alpha]^{20}_D$ −26.0° (c = 1.0, $CHCl_3$); IR 3030, 1750, 1650 cm^{-1}; ^1H NMR (360 MHz) δ 1.23 (t, J = 7.2, 3H), 1.91 (dddd, J = 12.2, 12.0, 11.7, 5.1, 1H), 2.05−2.12 (m, 1H), 2.29 (ddd, J = 17.5, 12.0, 5.7, 1H), 2.59 (ddd, J = 17.5, 5.1, 3.1, 1H), 3.15 (dddd, J = 11.7, 10.3, 5.7, 3.9, 1H), 3.31 (ddd, J = 11.3, 5.7, 1.3, 1H), 3.45 (dd, J = 11.3, 10.3, 1H), 3.61 (d, J = 14.0, 2H), 3.76 (d, J = 14.0, 2H), 3.86 (d, J = 17.3, 1H), 4.11 (d, J = 17.1, 1H), 4.16 (q, J = 7.2, 2H), 7.18−7.39 (m, 10H); EIMS 380 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_3$ (+0.6 H_2O): C, 70.60; H, 7.52; N, 7.16. Found: C, 70.27; H, 7.93; N, 7.24.

(5*S*)-5-(*N*-Benzylamino-2-oxopiperidin-1-yl)acetic Acid Ethyl Ester (13b). A mixture of **13a** (270 mg, 0.72 mmol) and $Pd(OH)_2$/C (25 mg) in MeOH (10 mL) was reacted and worked up as described for **11b** to give **13b** (175 mg, 84%) as a colorless oil: TLC R_f 0.39 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{20}_D$ −28.0° (c = 0.5, $CHCl_3$); IR 3310, 2930, 1740, 1640 cm^{-1}; ^1H NMR (360 MHz) δ 1.27 (t, J = 7.2, 3H), 1.81 (dddd, J = 13.1, 8.7, 8.2, 6.1, 1H), 2.05 (ddddd, J = 13.1, 6.4, 6.2, 3.5, 0.6, 1H), 2.41 (ddd, J = 17.8, 8.7, 6.4, 1H), 2.59 (ddd, J = 17.8, 6.2, 6.1, 1H), 3.14 (dddd, J = 8.2, 7.5, 4.1, 3.5, 1H), 3.23 (dd, J = 11.4, 7.5, 1H), 3.50 (ddd, J = 11.4, 4.1, 0.6, 1H), 3.82 (d, J = 13.1, 1H), 3.87 (d, J = 13.1, 1H), 4.07 (s, 2H), 4.19 (q, J = 7.2, 2H), 7.22−7.38 (m, 5H); EIMS 290 (M^+). HRMS calcd for $C_{22}H_{16}N_2O_3$: 290.1630. Found: 290.1627.

(5*S*)-[5-(*N*,*N*-Acetylbenzylamino)-2-oxopiperidin-1-yl]-acetic Acid Ethyl Ester (13c). A mixture of **13b** (73 mg, 0.25 mmol) in pyridine (2 mL) and acidic anhydride (1 mL) was reacted and worked up as described for **11c**. After flash chromatography (petroleum ether−acetone, 1:1), pure **13c** (67 mg, 81%) was obtained: TLC R_f 0.31 (petroleum ether−acetone, 1:1); $[\alpha]^{20}_D$ −37.9° (c = 1.0, $CHCl_3$); IR 3030, 2980, 1750, 1650 cm^{-1}; ^1H NMR (360 MHz) δ 1.25 (t, J = 7.1, 3H), 1.82−1.95 (m, 1H), 2.04 (dddd, J = 12.0, 11.7, 11.6, 6.0, 1H), 2.10 (s, 3H), 2.44 (ddd, J = 17.6, 11.7, 6.2, 1H), 2.53 (ddd, J = 17.6, 6.0, 2.9, 1H), 3.33 (ddd, J = 10.8, 5.6, 0.9, 1H), 3.43 (dd, J = 10.8, 10.5, 1H), 3.72 (d, J = 17.4, 1H), 3.90 (d, J = 17.4, 1H), 4.16 (q, J = 7.1, 2H), 4.54 (d, J = 17.8, 1H), 4.59 (d, J = 17.8, 1H), 4.88 (dddd, J = 11.6, 10.5, 5.6, 4.8, 1H), 7.13−7.40 (m, 5H); EIMS 332 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_4$ (+0.75 H_2O): C, 62.50; H, 7.43; N, 8.10. Found: C, 62.68; H, 7.44; N, 8.03.

(5*S*)-[5-(*N*,*N*-Acetylbenzylamino)-2-oxopiperidin-1-yl]-*N*-methylacetamide (14). A solution of **13c** (47 mg, 0.14 mmol) in ethanolic methylamine solution (5 mL, 8.03 M in EtOH) was reacted and worked up as described for **12** to give pure **14** (44 mg, 99%) as a colorless oil: TLC R_f 0.11 (CH_2Cl_2−MeOH, 95:5); $[\alpha]^{20}_D$ −31.9° (c = 1.0, $CHCl_3$); IR 3310, 2940, 1640 cm^{-1}; ^1H NMR (360 MHz) δ 1.78−1.95 (m, 1H), 2.05 (dddd, J = 12.2, 12.0, 11.8, 6.0, 1H), 2.10 (s, 3H), 2.43 (ddd, J = 17.7, 11.8, 6.1, 1H), 2.53 (ddd, J = 17.7, 6.0, 3.1, 1H), 2.77 (d, J = 5.0, 3H), 3.42 (dd, J = 11.4, 6.6, 1H), 3.47 (ddd, J = 11.4, 10.6, 1H), 3.79 (d, J = 15.3, 1H), 3.99 (d, J = 15.3, 1H), 4.52 (d, J = 17.9, 1H), 4.58 (d, J = 17.9, 1H), 4.76 (dddd, J = 12.0, 10.6, 6.6, 4.0, 1H), 6.45 (s, 1H), 7.12−7.43 (m, 5H); EIMS 317 (M^+). HRMS calcd for $C_{17}H_{23}N_3O_3$: 317.1739. Found: 317.1739.

(2*S*,4*S*)-4-[[[1-Benzyloxycarbonylpyrrolidine-2-carbonyl]amino]piperidin-1-yl]acetic Acid Ethyl Ester (15a). To a solution of Cbz-L-proline (183 mg, 0.73 mmol) in THF (5 mL) at −7 °C were added HOBt (99 mg, 0.73 mmol), DCC (159 mg, 0.77 mmol), and **11c** (147 mg, 0.73 mmol) dissolved in THF (10 mL). The reaction mixture was stirred for 3 h at 0 °C and 19 h at room temperature. The mixture was filtrated and diluted with EtOAc (10 mL). The solution was washed consecutively with brine, 0.5 N $KHSO_4$, brine, 5% $NaHCO_3$, and then brine; dried ($MgSO_4$); and evaporated. The residue was purified by flash chromatography ($CHCl_3$−MeOH, 95:5) to give pure **15a** (193 mg, 61%) as a colorless oil: TLC R_f 0.30 ($CHCl_3$−MeOH, 95:5); $[\alpha]^{20}_D$ −24.7° (c = 1.0, $CHCl_3$); IR 3300, 3070, 2940, 1750, 1700, 1650, 1640 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.20 (t, J = 7.1, 3H), 1.59 (dddd, J = 12.9, 9.1, 9.1, 6.5, 1H), 1.69−1.97 (m, 4H), 2.03−2.18 (m, 1H), 2.23 (dd, J = 16.7, 9.1, 1H), 2.44 (dd, J = 16.7, 5.0, 1H), 3.17−3.25 (m, 1H), 3.28−3.51 (m, 3H), 3.88−4.00 (m, 1H), 3.90/3.95 (d, J = 17.2/17.0, 1H), 4.07−4.18 (m, 1H), 4.10 (q, J = 7.1, 2H), 4.12/4.14 (d, J = 17.2/17.0, 1H), 4.96/5.04 (d, J = 13.0/12.8, 1H), 5.08/5.09 (d, J = 13.0/12.8, 1H), 7.26−7.42 (m, 5H), 8.00/8.06 (d, J = 7.4/7.1, 1H); EIMS 431 (M^+).

(2*S*,4*S*)-4-[[[1-Benzyloxycarbonyl-2-pyrrolidinyl]carbonyl]amino](2-oxopiperidin-1-yl)acetamide (15b). To a solution of MeOH (10 mL) saturated with NH_3 at −30 °C was added **15a** (153 mg, 0.35 mmol). The mixture was stirred for 10 h at room temperature. After evaporation, the residue was purified by flash chromatography (CH_2Cl_2−MeOH, 9:1) to give pure **15b** (120 mg, 85%) as a colorless oil: TLC R_f 0.32 (CH_2Cl_2−MeOH, 9:1); $[\alpha]^{20}_D$ −34.5° (c = 1.0, $CHCl_3$); IR 3300, 3070, 2950, 1700, 1680, 1630 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.53−1.53 (m, 5H), 2.03−2.15 (m, 1H, $5H_b$), 2.18 (dd, J = 16.4, 8.3, 1H), 2.41 (dd, J = 16.4, 5.0, 1H), 3.14 (ddd, J = 17.7, 11.9, 6.0, 1H), 3.24−3.51 (m, 3H), 3.73/3.74 (d, J = 16.3/16.3, 1H), 3.87/3.90 (d, J = 16.3/16.3, 1H), 3.94−4.07 (m, 1H), 4.09−4.18 (m, 1H), 4.95/5.03 (d, J = 12.8/12.8, 1H), 5.08/5.09 (d, J = 12.8/12.8, 1H), 7.06 (s, 1H), 7.25−7.40 (m, 6H), 8.02/8.04 (d, J = 7.5/7.5, 1H); EIMS 402 (M^+). Anal. Calcd for $C_{20}H_{26}N_4O_5$ (+0.5 H_2O): C, 58.38; H, 6.61; N, 13.62. Found: C, 58.71; H, 6.66; N, 13.53.

(2*S*,4*S*)-4-[(2-Pyrrolidinylcarbonyl)amino](2-oxopiperidin-1-yl)acetamide (15c). A solution of **15b** (177 mg, 0.44 mmol) and NEt_3 (61 μL, 0.44 mmol) in MeOH (10 mL) was hydrogenated (15 h, 50 bar H_2) at room temperature using Pd/C (44 mg) as a catalyst. The mixture was filtered through Celite and evaporated to give **15c** (118 mg, 100%) as a colorless solid: TLC R_f 0.29 (CH_2Cl_2−MeOH, 8:2); $[\alpha]^{21}_D$ −26.7° (c = 1.0, MeOH); IR 3310, 3200, 2980, 1680, 1640 cm^{-1}; ^1H NMR (C_5D_5N, 360 MHz) δ 1.53 (dddd, J = 12.8, 12.8, 12.8, 6.5, 1H), 1.64 (dddd, J = 12.8, 7.0, 7.0, 7.0, 1H), 1.88−2.10 (m, 5H), 2.63 (dd, J = 17.2, 8.3, 1H), 2.83−2.96 (m, 2H), 3.32−3.55 (m, 3H), 4.22/4.30 (d, J = 16.2/16.2, 1H), 4.54/4.57 (d, J = 16.2/16.2, 1H), 4.45−4.55 (m, 1H), 8.06 (s, 1H), 8.25 (s, 1H), 8.39 (d, J = 7.5, 1H); EIMS 268 (M^+). HRMS calcd for $C_{12}H_{20}N_4O_3$: 268.1535. Found: 268.1534.

(2*S*,4*R*)-4-[[[1-Benzyloxycarbonylpyrrolidine-2-carbonyl]amino]piperidin-1-yl]acetic Acid Ethyl Ester (16a). To a solution of Cbz-L-proline (365.5 mg, 1.43 mmol) in THF (5 mL) at −7 °C were added HOBt (193 mg, 1.43 mmol), DCC (310 mg, 1.50 mmol), and *ent*-**11c** (286 mg, 1.43 mmol) dissolved in THF (10 mL). The reaction mixture was reacted and worked up as described for **15a** to give pure **16a** (187 mg, 30%) as a colorless oil: TLC R_f 0.40 (hexane−acetone, 1:4); $[\alpha]^{20}_D$ −71.0° (c = 1.0, $CHCl_3$); IR 3300, 3070, 2980, 1740, 1700, 1650, 1640 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.20 (t, J = 7.1, 3H), 1.61−1.97 (m, 5H), 2.08−2.19 (m, 1H), 2.22 (dd, J = 17.4, 9.1, 1H), 2.40 (dd, J = 17.4, 5.5, 1H), 3.24−3.93 (m, 4H), 3.89−4.03 (m, 1H), 3.94/3.96 (d, J = 17.1/17.0, 1H), 4.10 (q, J = 7.1, 2H), 4.12 (d, J = 17.0, 1H), 4.12−4.20 (m, 1H), 4.96/5.04 (d, J = 13.0/13.1, 1H), 5.08/5.09 (d, J = 13.0/13.1, 1H), 7.22−7.40 (m, 5H), 8.00/8.05 (d, J = 7.5/7.5, 1H); EIMS 431 (M^+).

(2*S*,4*R*)-4-[[[1-Benzyloxycarbonyl-2-pyrrolidinyl]carbonyl]amino](2-oxopiperidin-1-yl)acetamide (16b). To a solution of MeOH (10 mL) saturated with NH_3 at −30 °C was added **16a** (260 mg, 0.60 mmol). The mixture was stirred for 10 h at room temperature. After evaporation, the residue was purified by crystalisation (MeOH−Et_2O) to give pure **16b** (193.5 mg, 80%) as a colorless crystals: TLC R_f 0.28 (CH_2Cl_2−MeOH, 9:1); $[\alpha]^{20}_D$ −29.4° (c = 0.67, $CHCl_3$−MeOH, 1:2); mp 218−219 °C; IR 3320, 2960, 1704, 1680, 1630 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.63−1.93 (m, 5H), 2.04−2.15 (m, 1H), 2.19 (dd, J = 17.3, 8.3, 1H), 2.41 (dd, J = 17.3, 5.7, 1H), 3.15−3.52 (m, 4H), 3.75/3.90 (d, J = 16.3/16.3, 1H), 3.90/3.91 (d, J = 16.3/16.3, 1H), 3.97−4.06 (m, 1H), 4.08−4.19 (m, 1H), 4.96/5.04 (d, J = 12.8/12.8, 1H), 5.07/5.09 (d, J = 12.8/12.8, 1H), 7.05 (s, 1H), 7.26−7.39 (m, 6H), 8.02/8.06 (d, J = 7.5/7.5, 1H);

EIMS 402 (M^+). Anal. Calcd for $C_{20}H_{26}N_4O_5(+0.5\ H_2O)$: C, 58.38; H, 6.61; N, 13.62. Found: C, 58.39; H, 6.62; N, 13.32.

(2*S*,4*R*)-4-[(2-Pyrrolidinylcarbonyl)amino](2-oxopiperidin-1-yl)acetamide (16c). A mixture of **16b** (54.5 mg, 0.14 mmol), NEt_3 (20 μl, 0.14 mmol), and Pd/C (11 mg) as a catalyst in MeOH (10 mL) was reacted and worked up as described for **15c** to give pure **16c** (36.5 mg, 100%) as a colorless solid: TLC R_f 0.30 (CH_2Cl_2−MeOH, 8:2); $[\alpha]^{21}_D$ −24.2° (c = 1.0, MeOH); IR 3310, 3200, 2980, 1680, 1640 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.55−1.84 (m, 5H), 1.84−2.05 (m, 3H), 3.19−4.00 (m, 4H), 3.79−3.93 (m, 1H), 3.82/3.85 (d, J = 16.1/16.1, 1H), 3.87/3.89 (d, J = 16.1/16.1, 1H), 3.96−4.10 (m, 1H), 7.05 (s, 1H), 7.34 (s, 1H), 7.87/7.98 (d, J = 7.6, 1H); EIMS 268 (M^+).

NMR Experiments. The variable-temperature NMR experiments were performed with a 1 nM solution of the amide **12** (analytical-grade purity) in degassed $CDCl_3$ of highest quality. NOEs were ascertained by nuclear Overhauser difference spectroscopy, using multiple selective irradiation. For presaturation, each signal was irradiated for 4 s altogether, with the decoupler attenuated to 78 dB. The samples were degassed by five freeze−pump−thaw cycles and sealed under Ar. H,H-COSY and H,C-COSY (HMBQ) were performed in phase-sensitive mode, using company-provided standard pulse sequences. 1K data points were used in F_2, zero-filled to 1K (H,H-COSY) and 512 (HMBQ) in F_1. Adopted Gaussian windows were applied in both dimensions.

Computational Studies. The Tripos force field choosing Gasteiger−Marsili charges, included in the program package Sybyl 6.5.1, was employed. Starting from two conformations of **12** including equatorially and axially dispositioned amino substituents, respectively, we performed a systematic conformational search. The conformational space was investigated by systematically varying the torsional angles of the CN bond in position 4 of the piperidinone as well as the exocyclic NCH_2 and CH_2CO single bonds in 60° steps. Employing a conjugate gradient-type algorithm, we performed geometry optimization on the basis of the starting conformations.

Dopamine Receptor Binding. Bovine striatal membranes were homogenized in 20 vol % sucrose (0.32 M).[28] The suspension was centrifuged at 1000*g* for 15 min. Subsequently, the supernatant was then centrifuged for 1 h at 100000*g*. The resultant pellet was resuspended in Tris−EDTA buffer (50 mM Tris, 1 mM EDTA, pH 7.4) and stored at −80 °C in small aliquots. On the day of use, the membrane preparations were thawed; diluted with Tris−EDTA buffer containing 5 mM $MgCl_2$, 0.1 mM dithiothreitol, 100 μg/mL bacitracin, and 5 μg/mL soybean trypsin inhibitor as an incubation buffer; and used for binding assays.

For the binding assays, ∼300 μg membrane proteins and 0.5 nM [^{3}H]pramipexole were incubated without (control) or with the modulating agents PLG, **15c** or **16c**, employed as 10^{-9} M solutions in an incubation buffer, for 2 h at 23 °C. Nonspecific binding was determined in the presence of 1 μM (+)-butaclamol. Incubation was terminated by rapid filtration. The filters were rinsed with ice-cold Tris−EDTA buffer (3 × 5 mL), and the radioactivity was determined in a scintillation counter (LS 6500). The results were expressed as percent of specific binding compared to control membranes (100%). The statistical significance of the data was performed using a t test. Values of $p < 0.05$ were considered to be significantly different from those of the control.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie. Dr. R. Waibel is acknowledged for NMR and HRMS measurements.

JO000555C