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Chirospecific Synthesis of Spirocyclic β-Lactams and Their Characterization as Potent Type II β-Turn Inducing Peptide Mimetics

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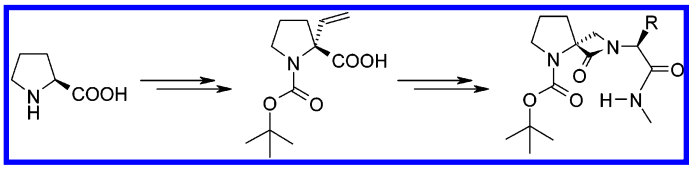

Starting from natural proline, a practical chirospecific synthesis of spirocyclic β-lactams of type **2** is described when a methylene moiety showing minimal steric demand is employed as a constraint element for adjusting the dihedral angle Ψ(i + 1). Employing the concept of self-reproduction of chirality, C-formylation of the oxazolidinone **5** afforded the key intermediate **7** taking advantage of an intermediate protection of the bridging element as a vinyl moiety. NMR- and IR-based conformational studies clearly indicated that spiro-β-lactams of type **2** can serve as efficient β-turn nucleators.

Introduction

Proline-derived spirocyclic γ-lactams of type **1** have been shown to exhibit valuable conformational properties enabling for their utilization as reverse turn nucleators with a spirocyclic moiety occupying the i + 1 position.[1−3] Upon introduction into naturally occurring peptides as substitutes for Pro-X patterns, bioactive peptide mimetics were obtained, benefiting from decreased numbers of degrees of freedom caused by an ethylene bridge as a constraining element.[4−7] Displaying dihedral angles Φ(Pro) and Ψ(Pro) of −51° and 129°, respectively, the spirocyclic scaffold proved capable of inducing type II β-turns, which are close to the ideal angles of −60° and 120°.[8−10] Monocyclic Freidinger-type β-lactams rigidizing Ψ(i + 1) to 123° also displayed a significant capability of inducing type II β-turns when the ethylene bridge is contracted to a one-atom constraint element.[11,12] Interestingly, contraction of the lactam ring size enables for a more ideal calibration of the geometrical properties required for the adoption of a canonical type II β-turn leading to a coplanar spatial arrangement of N(i + 1), Cα(i + 1), N(i + 2), and Cα(i + 2) and, thus, to promising antiparallel pleated β-sheet nucleators. The combination of both the spirocyclic structure and further conformational constraints by a four-membered lactam has been described when the synthetic methodology, however, required both the separation of isomeric mixtures and sterically demanding substituents at the constraining bridge which might lead to clashes when bound to a biological target.[13,14] In this article, we present an enantiospecific synthesis and conformational studies of methylene-bridged peptidomimetics of type **2**.

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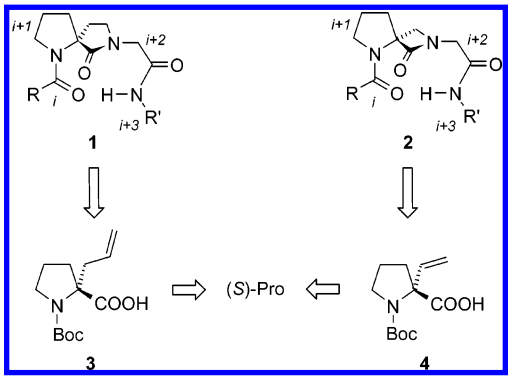
CHART 1



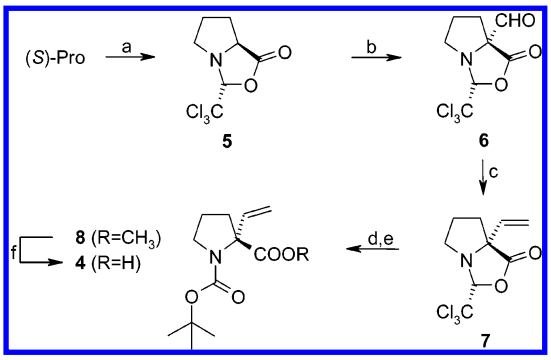
Results and Discussion

With the aim to calculate the structural consequences of the formal ring contraction, we employed density functional calculations on a high level of theory (B3LYP/6-311G*) minimizing the energy of the model peptides **1** and **2** (Chart 1). In fact, comparison of the $\Psi(i + 1)$ angles showed a decrease from 132.4° to 124.2° upon reduction of the ring size, the latter more ideally mimicking the geometrical properties of an ideal type II β-turn. While the $C{=}O^{i}\cdots HN^{i+3}$ distance was not significantly affected by ring size variation (2.1 Å for **1**, 2.0 Å for **2**), differing β-pseudodihedral angles between $C(i)$, $C^{\alpha}(i + 1)$, $C^{\alpha}(i + 2)$, and $N(i + 3)$ of 23.1° and 13.2° for for **1** and **2**, respectively, showed a higher potency for the adoption of a canonical β-turn for the [3.4]-spiro-β-lactam **2** when compared to the homologous spirolactam **1**.

Taking advantage of Seebach et al.'s self-reproduction of chirality methodology[15] that we have employed for the synthesis of α-allylproline (**3**) derived β-turn mimetics,[7] our plan of synthesis was based on the protected α-vinylproline **4** as the key intermediate when peptide coupling, reductive cleavage of the C,C-double bond, and ring closure were envisaged to provide target compounds of type **1**. Since a C-allyl substituent proved to be an excellent precursor for an ethylene bridge, we expected a vinyl system to be suitable for masking a methylene unit as a constraint element.

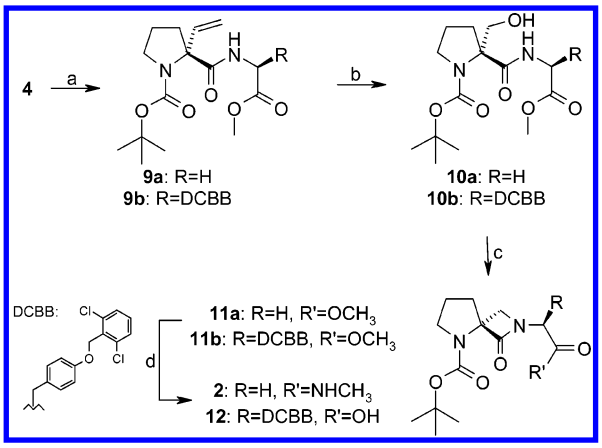
For the preparation of hitherto unknown enantiopure α-vinylproline derivatives,[16] (*S*)-proline was reacted with anhydrous trichloroacetic aldehyde to afford the chiral building block **5** (Scheme 1).[17] Our initial investigations to introduce a vinyl substituent by deprotonation, subsequent hydroxyethylation with acetic aldehyde, activation of the alcohol function, and β-elimination failed since the final step could not be accomplished. Thus, C-formylation and subsequent methenylation should be elaborated as a straightforward alternative. In detail, treatment of the proline derivative **5** with LDA, followed by addition of methyl formate, furnished a 65% yield of the carbaldehyde **6** in diastereomerically pure form. When elaborating suitable reaction conditions for a Wittig olefination of **6**, we observed a *retro-Claisen* reaction resulting in deformylation which we could avoid by employing Li-free conditions. Thus, pretreatment of methyl triphenylphosphonium bromide with KO^{t}Bu at elevated temperature and subsequent olefination at room temperature

SCHEME 1[a]



[a] (a) Cl_3CCHO, CH_3CN, rt, 2.5 h (87%). (b) 1. LDA, THF, −78 °C, 2. $HCOOCH_3$, −40 °C (65%). (c) 1. Methyltriphenylphosphonium bromide, KO^{t}Bu, toluene, 80 °C, 2 h, 2. **6**, rt, 1 h (74%). (d) AcCl, MeOH, 0 °C to rt, 7 d. (e) DIPEA, Boc_2O, CH_2Cl_2, rt, 2.5 d (73%). (f) NaOH, MeOH, H_2O, 50 °C, 1 h (78%).

SCHEME 2[a]



[a] (a) For **9a**: HATU, DIPEA, NMP, GlyOMe·HCl, rt, 30 min (64%); for **9b**: HATU, DIPEA, NMP, *O*-(2,6-dichlorobenzyl)tyrosine methyl ester hydrochloride, rt, 25 min (92%). (b) 1. O_3, CH_2Cl_2, −78 °C, 2. Na[B-H(OAc)$_3$], rt, 6−24 h (77−86%). (c) DEAD, PPh_3, THF, rt, 2.5−5 h (63−65%). (d) For **2**: CH_3NH_2, EtOH, 0 °C, 40 min (97%); for **12**: LiOH, THF, H_2O, 0 °C, 1 h (82%).

gave access to the bicyclic α-vinylproline derivative **7**, which was transformed into (*R*)-α-vinylproline methyl ester under acidic conditions and, subsequently, N-protected by carbamoylation. Finally, basic hydrolysis of the methyl ester **8** led to enantiomerically pure (*R*)-*N*-Boc-α-vinylproline (**4**).

For the synthesis of the spirocyclic model system **2**, the sterically demanding amino acid **4** was activated by HATU[19] and coupled with glycine methyl ester hydrochloride, giving rise to the protected peptide derivative **9a** (Scheme 2). Ozonolysis of the vinyl group and subsequent reduction with an excess of Na[BH(OAc)$_3$] yielded the hydroxymethyl-substituted derivative **10a** in 86% yield. Formation of the β-lactam was accomplished by intramolecular Mitsunobu reaction with DEAD and PPh_3,[20,21] furnishing the molecular scaffold **11a**. Finally, the molecular probe **2** was prepared by aminolysis of **11a**. To

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TABLE 1. Spectroscopic Data of Model Peptides 1 and 2 (2 mM, $CHCl_3$)

model peptide	1	2
IR absorption band	3337 cm^{-1}	3338 cm^{-1}
^1H NMR: δ(NH)	7.81 ppm	8.23 ppm
^1H NMR: $\Delta\delta/\Delta T$(NH)	−5.6 ppb/K	−4.6 ppb/K

demonstrate versatility of the synthesis toward the nature of the amino acid in position $i + 2$, a lactam-bridged Pro-Tyr scaffold was prepared when the central building block **2** was activated and reacted with *O*-(2,6)-dichlorobenzyl-protected tyrosine methyl ester hydrochloride[18] to give the coupling product **9b** in 92% yield. Employing identical reaction conditions, the protected methyl ester **11b** was obtained via the intermediate **10b**. To investigate the configurational stability of the Tyr C^α moiety, LiOH-promoted hydrolysis was performed,[22] indicating partial epimerization (9% detected by HPLC-MS) of the Pro-Tyr surrogate **12**. As a reference compound for conformational investigations, the [4.4]-spirocyclic model peptide **1** was synthesized by aminolysis of the corresponding methyl ester,[8] which we prepared according to a previous protocol.[7,23]

To investigate the conformational properties of our β-turn model system **2** in comparison to the [4.4]-spirocyclic template **1** being described as a highly potent type II β-turn mimetic,[1] IR and NMR studies including variable temperature (VT) experiments were performed in 2 mM solution thus excluding intermolecular interactions.[24,25] For a type II β-turn, a stable hydrogen bond between the Boc C═O group and the NH will be expected, which was clearly indicated by the extensive absorption bands at 3337 (for **1**) and 3338 cm^{-1} (for **2**). On the other hand, N−H stretching absorptions in the range of 3450 cm^{-1} being diagnostic for non-hydrogen-bonded states could not be detected. In contrast to the IR data, NMR-derived δ-(NH) values significantly differed when NH of the β-lactam **2** resonated even more downfield (8.23 ppm) than that of the γ-lactam **1** (7.81 ppm). Temperature-dependent chemical shift changes of ^1H NMR signals as a measure for the stability of secondary structures corroborated the assumption that the spirocyclic β-lactam **2** might form a more stable intramolecular H-bond when $\Delta\delta/\Delta T$ values of −5.6 (for **1**) and −4.6 ppb/K (for **2**) were observed (Table 1).

In conclusion, we could establish a versatile synthetic approach toward enantiomerically pure [3.4]-spiro-β-lactam containing type II β-turn mimetics. Applying the same synthetic protocol, a [3.4]-spirocyclic Pro-Tyr mimicking template could be synthesized, serving as an example for virtually any Pro-X dipeptide. Choosing appropriate protecting groups may enable for the introduction of these templates into SPPS, giving rise to larger peptides bearing the [3.4]-spirocyclic constraint. Boc strategy usually requires cleavage by HF or other strongly acidic conditions potentially harmful to the integrity of the β-lactam substructure. However, this issue might be circumvented by introduction of different protecting groups compatible with the milder conditions of Fmoc SPPS protocols. According to our computational studies, restriction of the Ψ(Pro) dihedral angle to values more ideally mimicking the geometrical requirements for an ideal type II β-turn found in the homologous [4.4]-spirocycles favors reverse turn formation.

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Experimental Section

Methods and Materials. Chemicals and solvents were purchased in the highest purity available. All reactions were carried out under nitrogen atmosphere except ozonolysis, aminolysis, and ester hydrolysis. Column chromatography was performed using 60-μm silica gel. For TLC silica gel, 60 F254 plates were used (UV, I_2, or ninhydrin detection). Melting temperatures were uncorrected. NMR chemical shifts were noted in ppm relative to TMS. IR spectroscopy was carried out on a FT/IR spectrometer. HPLC-MS and ESI-MS analyses were carried out on an analytic HPLC system with a VWL detector, coupled to a mass spectrometer with electron spray ionization.

(2*R*,5*S*)-2-Trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octane-4-one (5). (*S*)-Proline (35.0 g, 0.304 mol) was suspended in acetonitrile (150 mL). Anhydrous trichloroacetic aldehyde (74.0 mL, 0.758 mol) was added slowly while being stirred vigorously. After 2.5 h, the clear solution was concentrated to dryness. The residue was redissolved in CH_2Cl_2 (150 mL) and filtered, and the solvent was removed. Repetition of this cycle, followed by thorough drying in vacuo, yielded 65.0 g (87%) of **5**. Analytical data were in agreement with the literature.

(2*R*,5*R*)-4-Oxo-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]-octane-5-carbaldehyde (6). At −78 °C, LDA solution (0.8 M, 153 mL, 122 mmol), freshly prepared from diisopropylamine (18.1 mL, 128 mmol) and *n*-butyllithium solution (2.5 M in hexanes, 51.2 mL, 128 mmol) in THF (90.7 mL), was added to a solution of **5** (20.0 g, 81.8 mmol) in THF (100 mL). After 30 min methyl formate (20.2 mL, 328 mmol) was added over 5 min. The mixture was stirred at −78 °C for 10 min, and then it was allowed to warm to −40 °C over 45 min. After 10 min at this temperature aqueous citric acid (10%, 150 mL) was added, and the mixture was extracted with ether (2 × 150 mL). The combined organic layers were washed with brine (200 mL), dried with magnesium sulfate, and evaporated, and the residue was purified by column chromatography (hexanes/ethyl acetate 6:1 increasing to 3:1), furnishing 14.4 g (65%) of **6** as colorless crystals. mp 89 °C; R_f 0.40 (hexanes/ethyl acetate 1:1); $[\alpha]^{25}_D$ 29.5° (*c* 2.0, $CHCl_3$); IR (neat) 2978, 1811, 1732 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.80−1.91 (m, 1H), 1.92−2.03 (m, 1H), 2.29 (ddd, 1H, J = 13.4, 6.7, 6.7 Hz), 2.40 (ddd, 1H, J = 13.4, 7.8, 6.7 Hz), 3.33 (ddd, 1H, J = 11.5, 6.1, 5.6 Hz), 3.54 (ddd, 1H, J = 11.5, 7.8, 6.4 Hz), 5.19 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 25.5, 33.8, 58.9, 78.2, 99.9, 102.4, 169.3, 193.5; EIMS 244, 242, 246 (M − CO; M^+ not observed). Anal. Calcd for $C_8H_8Cl_3NO_3$: C, 35.26; H, 2.96; N, 5.14. Found: C, 35.13; H, 2.72; N, 5.15.

(2*R*,5*R*)-2-Trichloromethyl-5-vinyl-1-aza-3-oxabicyclo[3.3.0]-octane-4-one (7). Methyl triphenylphosphonium bromide (7.86 g, 22.0 mmol) and potassium *tert*-butoxide (2.47 g, 22.0 mmol) were suspended in toluene (400 mL) and stirred vigorously for 2 h at 80 °C. After cooling to room temperature, a solution of **6** (5.00 g, 18.3 mmol) in toluene (50 mL) was added and stirring was continued for 1 h. Ether (400 mL) was added, and the precipitate formed was removed by fitration and washed with ether (2×100 mL). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate 95:5 increasing to 9:1), yielding 3.67 g (74%) of **7** as a colorless oil. R_f 0.27 (hexanes/ethyl acetate 4:1); $[\alpha]^{22}_D$ 47.2° (*c* 0.25, $CHCl_3$); IR (neat) 2952, 1805, 1641 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.79−1.89 (m, 1H), 1.89−1.99 (m, 1H), 2.03 (ddd, 1H, J = 12.4, 6.2, 6.2 Hz), 2.19 (ddd, 1H, J = 12.4, 7.3, 7.3 Hz,), 3.20 (ddd, 1H, J

= 11.0, 6.5, 6.5 Hz), 3.47 (ddd, 1H, *J* = 11.0, 6.4, 6.4 Hz), 5.08 (s, 1H), 5.23 (dd, 1H, *J* = 10.3, 1.1 Hz), 5.52 (dd, 1H, *J* = 17.0, 1.1 Hz), 6.02 (dd, 1H, *J* = 17.0, 10.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.1, 38.5, 58.5, 73.7, 100.8, 102.8, 116.3, 136.0, 174.3; EIMS 242 (M − CH=CH_2), 152 (M − CCl_3; M^+ not observed). Anal. Calcd for $C_9H_{10}Cl_3NO_2$: C, 39.96; H, 3.73; N, 5.18. Found: C, 40.05; H, 3.82; N, 5.07.

(*R*)-*N*-*tert*-Butoxycarbonyl-2-vinylproline Methyl Ester (8). Acetyl chloride (3.95 mL, 55.6 mmol) was added dropwise to methanol (15 mL) while stirring in an ice bath. After 5 min, a solution of **7** (1.51 g, 5.58 mmol) in methanol (5 mL) was added. The ice bath was removed, and the mixture was stirred at room temperature. After 7 days, the solvent was removed in vacuo, and the residue was redissolved in methanol, concentrated, and dried thoroughly. After addition of CH_2Cl_2 (15 mL) and DIPEA (1.91 mL, 11.2 mmol), a solution of Boc_2O (3.65 g, 16.7 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred at room temperature for 2.5 days. The solvent was evaporated, and the residue was purified twice by column chromatography (hexanes/ethyl acetate 9:1 and hexanes/2-propanol 97:3), furnishing 1.04 g (73%) of **8** as a colorless oil. R_f 0.15 (hexanes/ethyl acetate 4:1); $[\alpha]^{22}_D$ 62.4° (*c* 0.5, $CHCl_3$); IR (neat) 2978, 1746, 1702, 1643 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.35 (s, 6H), 1.45 (s, 3H), 1.76−1.94 (m, 2H), 1.96−2.05 (m), 2.17 and 2.21 (2 × dd, 1H, *J* = 11.6, 10.6, 7.2 and 12.2, 10.6, 6.9 Hz), 3.52−3.59 (m, 1H), 3.61−3.68 (m, 1H), 3.73 and 3.74 (2 × s, 3H), 5.04 and 5.05 (2 × dd, 1H, *J* = 17.1, 1.0 and 17.1, 0.9 Hz), 5.15 and 5.17 (2 × dd, 1H, *J* = 10.6, 1.0 and 10.5, 0.9 Hz), 6.32 and 6.33 (2 × dd, 1H, *J* = 17.1, 10.6 and 17.1, 10.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers were observed) δ 21.9, 28.2 and 28.4, 38.0 and 39.2, 47.9 and 48.0, 52.2 and 52.4, 69.3 and 69.5, 79.8 and 80.0, 113.0 and 113.1, 136.5 and 137.2, 153.5, 173.7; EIMS 196 (M − $COOCH_3$; M^+ not observed). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.98; H, 8.25; N, 5.43.

(*R*)-*N*-*tert*-Butoxycarbonyl-2-vinylproline (4). To a solution of **8** (864 mg, 3.38 mmol) in methanol (15 mL) was added aqueous NaOH (2 N, 15 mL), and the mixture was stirred at 50 °C for 1 h. After cooling to room temperature, water (15 mL) was added, and the methanol was removed under reduced pressure. The solution was washed with ether (2 × 15 mL), then aqueous citric acid (20%, 45 mL) was added, and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were washed with water, dried with magnesium sulfate, and concentrated, yielding 634 mg (78%) of **4** as colorless crystals. mp 134 °C; R_f 0.49 (CH_2Cl_2/methanol 9:1); $[\alpha]^{23}_D$ −60.3° (*c* 0.4, $CHCl_3$); IR (neat) 2970, 1731, 1701, 1638 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$; rotamers were observed) δ 1.37 (s, 4.1H), 1.41 (s, 4.9H), 1.81−1.94 (m, 2.55H), 2.06 (ddd, 0.45H, *J* = 12.1, 6.3, 3.3 Hz), 2.30 (dd, 0.45H, *J* = 12.1, 11.0. 6.8 Hz), 2.59−2.64 (m, 0.55H), 3.50−3.53 (m, 1.1H), 3.60 (ddd, 0.45H, *J* = 10.1, 9.8, 6.8 Hz), 3.66 (ddd, 0.45H, *J* = 10.1, 7.7, 3.0 Hz), 5.07 (d, 0.45H, *J* = 17.0 Hz), 5.16 and 5.17 (2 × d, 1H, *J* = 17.6 and 10.6 Hz), 5.25 (d, 0.55H, *J* = 10.6 Hz), 6.07 (dd, 0.55H, *J* = 17.6, 10.6 Hz), 6.29 (dd, 0.45H, *J* = 17.0, 10.6 Hz), 11.07 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$; rotamers were observed) δ 21.9 and 22.8, 28.1 and 28.4, 37.8 and 39.4, 47.8 and 48.7, 69.3 and 71.3, 80.6 and 81.9, 113.3 and 115.1, 136.6, 153.5 and 156.2, 174.4 and 179.0; EIMS 241 (M^+). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.87; H, 7.87; N, 5.80.

(*R*)-*N*-(*N*-*tert*-Butoxycarbonyl-2-vinylprolin-1-yl)glycine Methyl Ester (9a). To a solution of **4** (200 mg, 0.829 mmol) and HATU (347 mg, 0.912 mmol) in NMP (2 mL) was added DIPEA (355 μL, 2.07 mmol). After stirring the mixture at room temperature for 5 min, we added a suspension of glycine methyl ester hydrochloride (208 mg, 1.66 mmol) and DIPEA (284 μL, 1.66 mmol) in NMP (2 mL) and continued stirring for 30 min. After addition of aqueous citric acid (20%, 5 mL), the mixture was extracted with ether (3 × 5 mL), and the combined organic layers were washed with saturated Na_2CO_3 solution (5 mL), brine (5 mL), and water (5 mL), dried with magnesium sulfate, and evaporated. The residue was purified by column chromatography (hexanes/ethyl acetate 1:1), furnishing 166 mg (64%) of **9a** as colorless crystals. mp 65 °C; R_f 0.16 (hexanes/ethyl acetate 1:1); $[\alpha]^{20}_D$ −44.2° (*c* 0.5, $CHCl_3$); IR (neat) 3362, 2978, 1756, 1695, 1681 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, 330 K) δ 1.43 (s, 9H), 1.75−1.91 (m, 2H), 1.92−2.00 (m, 1H), 2.42−2.58 (m, 1H), 3.51−3.59 (m, 2H), 3.73 (s, 3H), 3.99 (dd, 1H, *J* = 18.6, 5.3 Hz), 4.05 (dd, 1H, *J* = 18.6, 5.3 Hz), 5.16 (bd, 1H, *J* = 17.6 Hz), 5.22 (dd, 1H, *J* = 10.8, 0.6 Hz), 6.29 (dd, 1H, *J* = 17.6, 10.8 Hz), 7.44 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers and broadened signals were observed) δ 22.1 and 23.0, 28.5, 37.6 and 39.6, 41.7, 48.7, 52.3, 71.0 and 71.3, 80.7, 114.5 and 115.2, 138.2, 154.0 and 155.0, 170.3, 173.0; EIMS 312 (M^+). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.74; H, 7.62; N, 8.98.

(2*S*,2′*R*)-*N*-(*N*-*tert*-Butoxycarbonyl-2-vinylprolin-1-yl)-*O*-(2,6-dichlorobenzyl)tyrosine Methyl Ester (9b). 9b was prepared from **4** (200 mg, 0.892 mmol), HATU (378 mg, 0.995 mmol), DIPEA (567 μL, 3.32 mmol) in NMP (4 mL), and *O*-(2,6-dichlorobenzyl)-tyrosine methyl ester hydrochloride (597 mg, 2.07 mmol) in NMP (3 mL) as described for **9a** (preactivation time: 15 min, reaction time: 25 min, washing with saturated $NaHCO_3$, brine, and water). Column chromatography (hexanes/ethyl acetate 2:1) yielded 440 mg (92%) of **9b** as a colorless resin. R_f 0.37 (hexanes/ethyl acetate 1:1); $[\alpha]^{24}_D$ −27.5° (*c* 1.0, $CHCl_3$); IR (neat) 3420, 2977, 1746, 1698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 320 K; broadened signals were observed) δ 1.41 (bs, 9H), 1.63−2.63 (m, 4H), 2.97 (dd, 1H, *J* = 13.8, 7.2 Hz), 3.14 (dd, 1H, *J* = 13.8, 5.6 Hz), 3.35−3.63 (m, 1H), 3.71 (s, 3H), 4.80 (ddd, 1H, *J* = 7.4, 7.2, 5.6 Hz), 4.97−5.32 and 5.24 (m and s, 4H), 6.11−6.34 (m, 1H), 6.53 (bs, 0.5H), 6.91−6.97 (m, 2H), 7.05−7.10 (m, 2H), 7.21−7.24 (m, 1H), 7.34−7.36 (m, 2H), 7.68 (bs, 0.5H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers were observed) δ 22.0 and 23.1, 28.3 and 28.5, 37.4, 39.8, 48.5 and 48.7, 52.3, 53.5 and 53.8, 65.4, 71.0 and 71.4, 80.5 and 81.0, 113.9, 115.0 and 115.3, 128.6, 129.3, 130.4, 130.6, 132.3, 137.2, 138.3, 153.9 and 155.0, 172.0, 172.3 and 172.6; EIMS 576 (M^+). Anal. Calcd for $C_{29}H_{34}Cl_2N_2O_6$: C, 60.31; H, 5.93; N, 4.85. Found: C, 60.43; H, 5.87; N, 4.88.

(*R*)-*N*-(*N*-*tert*-Butoxycarbonyl-2-hydroxymethylprolin-1-yl)-glycine Methyl Ester (10a). An ozone-enriched stream of oxygen was bubbled through a −78 °C cold solution of **9a** (128 mg, 0.409 mmol) in CH_2Cl_2 (5 mL) until it turned light blue. Excess ozone was removed by flushing the solution with oxygen and nitrogen, whereupon Na[$BH(OAc)_3$] (434 mg, 2.05 mmol) was added. The mixture was allowed to warm to room temperature while being stirred vigorously. After 6 h, the reaction was stopped by addition of aqueous NaOH (2 N, 0.5 mL), followed by drying with magnesium sulfate and evaporation of the solvent. Column chromatography (hexanes/ethyl acetate 1:1) of the residue furnished 112 mg (86%) of **10a** as a colorless resin. R_f 0.16 (100% ethyl acetate); $[\alpha]^{20}_D$ −39.0° (*c* 0.5, $CHCl_3$); IR (neat) 3342, 2976, 1755, 1696, 1669 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, 330 K) δ 1.44 and 1.46 (bs and s, 10H), 1.77−1.94 (m, 2H), 2.01−2.19 (m, 1H), 2.30 (ddd, 1H, *J* = 12.4, 6.1, 6.1 Hz), 3.47 (ddd, 1H, *J* = 10.7, 7.6, 7.6 Hz), 3.63 (ddd, 1H, *J* = 10.7, 6.2, 6.2 Hz), 3.71−3.81 and 3.75 (m and s, 4H), 4.00 (dd, 1H, *J* = 18.2, 4.9 Hz), 4.09 and 4.09−4.14 (dd and m, 2H, *J* = 18.2, 5.4 Hz), 6.92 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$; rotamers were observed) δ 22.1, 28.2 and 28.3, 35.4, 40.8 and 41.4, 48.1 and 49.3, 52.6 and 52.7, 64.3 and 66.5, 67.6 and 71.4, 81.1 and 81.4, 153.5 and 156.2, 170.0 and 170.5, 173.1 and 176.3; EIMS 316 (M^+). Anal. Calcd for $C_{14}H_{24}N_2O_6 \times 0.3H_2O$: C, 52.26; H, 7.71; N, 8.71. Found: C, 52.27; H, 7.71; N, 8.35.

(2*S*,2′*R*)-*N*-(*N*-*tert*-Butoxycarbonyl-2-hydroxymethylprolin-1-yl)-*O*-(2,6-dichlorobenzyl)tyrosine Methyl Ester (10b). 10b was prepared from **9b** (384 mg, 0.665 mmol) in CH_2Cl_2 (10 mL) and Na[$BH(OAc)_3$] (705 mg, 3.32 mmol) as described for **10a** (reaction time: 24 h; after 5.5 h, a second portion of Na[$BH(OAc)_3$] (282 mg, 1.33 mmol) was added; the reaction was stopped by addition

of aqueous NaOH (0.67 N, 3 mL); the crude product was obtained by repeated extraction with CH_2Cl_2). Twofold column chromatography (hexanes/ethyl acetate 1:1) furnished 297 mg (77%) of **10b** as colorless crystals. mp 143 °C; R_f 0.41 (100% ethyl acetate); $[\alpha]^{23}_D$ −15.8° (*c* 0.5, $CHCl_3$); IR (KBr) 3342, 3259, 2981, 1744, 1697, 1654 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 320 K; broadened signals were observed) δ 1.21−1.50 and 1.43 (m and s, 10H), 1.61−1.71 (m, 1H), 1.73−1.80 (m, 1H), 1.85−2.38 (m, 2H), 3.03 (dd, 1H, *J* = 13.9, 6.1 Hz), 3.15 (dd, 1H, *J* = 13.9, 6.0 Hz), 3.37−3.44 (m, 1H), 3.49−3.53 (m, 1H), 3.61−3.91 and 3.72 (m and s, 4H), 3.97−4.29 (m, 1H), 4.82 (ddd, 1H, *J* = 6.2, 6.1, 6.0 Hz), 5.25 (s, 2H), 6.16−7.13 (m, 5H), 7.21−7.24 (m, 1H), 7.34−7.37 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$; broadened signals were observed) δ 22.3, 28.4, 35.5, 37.3, 49.1, 52.5, 53.5, 65.4, 66.4, 71.2, 81.3, 115.2, 128.6, 128.8, 130.5, 130.6, 132.3, 137.11, 156.0, 158.2, 171.9, 172.9; EIMS 580, 582 (M^+). Anal. Calcd for $C_{28}H_{34}Cl_2N_2O_7$: C, 57.84; H, 5.89; N, 4.82. Found: C, 57.82; H, 5.81; N, 4.86.

(*R*)-2-(5-*tert*-Butoxycarbonyl-1-oxo-2,5-diazaspiro[3.4]oct-2-yl)acetic Acid Methyl Ester (11a). To a stirred solution of **10a** (77.1 mg, 0.244 mmol) and triphenylphosphine (95.9 mg, 0.366 mmol) in THF (5 mL) was added DEAD solution (40% in toluene, 106 μL, 0.366 mmol) at room temperature. After being stirred for 2 h, additional DEAD solution (21.1 μL, 48.7 μmol) was added, and stirring was continued for 30 min, whereupon the solvent was removed under reduced pressure. The residue was purified by 2-fold column chromatography (hexanes/ethyl acetate 1:1), furnishing 47.0 mg (65%) of **11a** as a colorless oil. R_f 0.35 (100% ethyl acetate); $[\alpha]^{19}_D$ −4.2° (*c* 0.5, $CHCl_3$); IR (neat) 2975, 1769, 1750, 1698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$; rotamers were observed) δ 1.44 and 1.45 (2 × s, 9H), 1.77−1.88 (m, 1H), 1.92−2.01 (m, 1H), 2.19−2.27 (m, 1H), 2.34−2.45 (m, 1H), 3.39−3.56, 3.45 and 3.48 (m, d and d, 3H, *J* = 4.4 and 4.4 Hz), 3.66 and 3.66 (2 × d, 1.2 H, *J* = 17.9 and 4.4 Hz), 3.72, 3.74 and 3.75 (d, s and s, 3.4 H, *J* = 18.2 Hz), 3.86 (d, 0.4 H, *J* = 4.4 Hz), 4.40 (d, 0.6H, *J* = 17.9 Hz), 4.49 (d, 0.4H, *J* = 18.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers were observed) δ 22.8 and 23.3, 28.3 and 28.5, 34.0 and 35.1, 42.6 and 43.0, 47.9 and 48.1, 52.2 and 52.3, 54.4 and 56.0, 73.6 and 73.8, 80.2 and 80.8, 153.4, 168.6 and 169.0, 170.4 and 170.5; EIMS 283 (M − CH_3; M^+ not observed). Anal. Calcd for $C_{14}H_{22}N_2O_5 \times 0.2H_2O$: C, 55.69; H, 7.48; N, 9.28. Found: C, 55.88; H, 7.53; N, 9.19.

(2*S*,4′*R*)-3-(4-[2,6-Dichlorobenzyloxy]phenyl)-2-(5-*tert*-butoxycarbonyl-1-oxo-2,5-diazaspiro[3.4]oct-2-yl)propionic Acid Methyl Ester (11b). 11b was prepared from **10b** (69.4 mg, 0.119 mmol), triphenylphosphine (47.0 mg, 0.179 mmol) in THF (2 mL), and DEAD solution (40% in toluene, 73.0 + 16 μL, 0.167 + 0.0358 mmol) as described for **11a** (after second DEAD addition stirring was continued for 3 h). Column chromatography (CH_2Cl_2/methanol 97:3) yielded 42.5 mg (63%) of **11b** as a colorless resin. R_f 0.18 (hexanes/ethyl acetate 1:1); $[\alpha]^{23}_D$ 19.2° (*c* 0.25, $CHCl_3$); IR (neat) 2973, 1766, 1742, 1697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$; rotamers were observed) δ 1.36 (s, 4.5H), 1.46 (s, 4.5H), 1.74−1.83 (m, 1H), 1.90−1.97 (m, 1H), 2.07−2.11 (m, 0.5H), 2.15−2.19 (m, 0.5H), 2.27−2.34 (m, 1H), 3.06, 3.08 and 3.12 (dd, dd and dd, 1.5H, *J* = 14.0, 7.4 and 13.0, 7.3 and 13.0, 7.7 Hz), 3.23 (dd, 0.5H, *J* = 14.0, 6.2 Hz), 3.33 (d, 0.5H, *J* = 4.5 Hz), 3.37−3.44 and 3.38 (m and d, 2H, *J* = 4.3 Hz), 3.48−3.53 (m, 0,5H), 3.62 (d, 0.5H, *J* = 4.3 Hz), 3.65 and 3.68 (2 × s, 3H), 3.83 (d, 0.5H, *J* = 4.5 Hz), 4.67 (dd, 0.5H, *J* = 7.7, 7.3 Hz), 4.75 (dd, 0.5H, *J* = 7.4, 6.2 Hz), 5.25 (s, 2H), 6.93−6.97 (m, 2H), 7.12−7.14 (m, 1H), 7.22−7.26 (m, 2H), 7.35−7.38 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers were observed) δ 22.7 and 23.4, 28.3 and 28.6, 33.9 and 35.6, 35.5, 48.0, 52.2 and 52.4, 53.1 and 53.6, 55.0 and 55.5, 65.4, 72.1 and 72.6, 80.0 and 81.1, 115.2 and 115.4, 128.6, 128.8 and 129.3, 130.3 and 130.6, 130.5, 132.2 and 132.4, 137.1, 153.2 and 153.6, 158.0 and 158.3, 170.2 and 170.6, 171.0; EIMS 461, 463 (M − Boc; M^+ not observed). Anal. Calcd for $C_{28}H_{32}Cl_2N_2O_6$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.52; H, 5.66; N, 5.08.

(*R*)-2-(5-*tert*-Butoxycarbonyl-1-oxo-2,5-diazaspiro[3.4]oct-2-yl)-*N*-methylacetamide (2). 11a (16.0 mg, 0.0536 mmol) was dissolved in methylamine solution (8 M in ethanol, 2 mL) while cooling with an ice bath. The mixture was stirred at this temperature for 40 min, whereupon the solvent was removed at low temperature under reduced pressure. The residue was purified by column chromatography (100% ethyl acetate), furnishing 15.4 mg (97%) of **2** as a colorless oil. R_f 0.22 (CH_2Cl_2/methanol 95:5); $[\alpha]^{23}_D$ 72.8° (*c* 0.25, $CHCl_3$); IR (neat) 3483 (w), 3338 (s), 2976, 1767, 1680 cm^{-1}; IR ($CHCl_3$, 2 mM) 3338 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.81−1.89 (m, 1H), 1.96−2.01 (m, 1H), 2.16 (ddd, 1H, *J* = 12.9, 6.7, 4.4 Hz), 2.36 (ddd, 1H, *J* = 12.9, 10.2, 6.8 Hz), 2.82 (d, 3H, *J* = 4.9 Hz), 3.25 (d, 1H, *J* = 4.9 Hz), 3.44 und 3.41−3.49 (d and m, 3H, *J* = 17.8 Hz), 3.82 (d, 1H, *J* = 4.9 Hz), 4.45 (d, 1H, *J* = 17.8 Hz), 8.24 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.3, 26.0, 28.4, 33.2, 45.2, 47.9, 54.4, 74.1, 81.3, 153.9, 168.0, 169.1; EIMS 298 (M + 1), 297 (M^+). Anal. Calcd for $C_{14}H_{23}N_3O_4 \times 0.5H_2O$: C, 54.89; H, 7.90; N, 13.72; Found: C, 54.70; H, 7.45; N, 13.56.

(2*S*,4′*R*)-2-(5-*tert*-Butoxycarbonyl-1-oxo-2,5-diazaspiro[3.4]-oct-2-yl)-3-[4-(2,6-dichlorbenzyloxy)phenyl]propionic Acid (12). A solution of **11b** (92.0 mg, 0.163 mmol) in THF (7 mL) was cooled in an ice bath. Aqueous LiOH (0.5 N, 7 mL) was added slowly, and the mixture was stirred at this temperature for 1 h. After addition of aqueous citric acid (20%, 14 mL), THF was removed under reduced pressure, and the remaining solution was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL) and water (15 mL), dried with magnesium sulfate, concentrated, and purified by column chromatography (CH_2Cl_2/methanol/formic acid 95:4:1), furnishing 73.2 mg (82%) of **12** as a colorless solid. HPLC-MS analysis indicated the presence of 9% of the epimeric compound. mp 77−83 °C; R_f 0.22 (CH_2Cl_2/methanol/formic acid 95:4:1); IR (neat) 2974, 2929, 1764 (sh), 1746, 1698 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6; rotamers were observed) δ 1.29 (s, 4.05H), 1.47 (s, 4.95H), 1.80−1.92 (m, 2H), 2.10−2.20 (m, 1.45H), 2.73−2.88 (m, 0.55H), 3.12 (dd, 0.45H, *J* = 13.8, 7.9 Hz), 3.18 and 3.18−3.20 (dd and m, 1.55H, *J* = 13.8, 6.6 Hz), 3.27 (d, 0.55H, *J* = 4.6 Hz), 3.29−3.42 (m, 1.55H), 3.45 and 3.44−3.48 (d and m, 0.9H *J* = 4.6 Hz), 3.64 (d, 0.45H, *J* = 4.6 Hz), 3.82 (d, 0.55H, *J* = 4.6 Hz), 4.53 (dd, 0.55H, *J* = 7.2, 7.2 Hz), 4.57 (dd, 0.45H, *J* = 7.9, 6.6 Hz), 5.31 (s, 2H), 6.98−7.05 (m, 2H), 7.28−7.36 (m, 2H), 7.44−7.47 (m, 1H), 7.51−7.53 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$; rotamers were observed) δ 23.5, 28.5, 32.6, 35.2, 48.0 and 55.5, 60.9, 65.6, 72.9, 82.0, 115.4, 128.7, 129.7, 130.3, 130.6, 130.7, 132.3 and 137.1, 154.1 and 158.1, 169.2 and 170.7; ESI-MS 549 (M + 1). Anal. Calcd for $C_{27}H_{30}Cl_2N_2O_6$: C, 59.02; H, 5.50; N, 5.10. Found: C, 59.13; H, 5.39; N, 5.11.

(*R*)-2-(1-*tert*-Butoxycarbonyl-6-oxo-1,7-diazaspiro[4.4]non-7-yl)acetic Acid *N*-Methyl Amide (1). 1 was prepared from (*R*)-2-(1-*tert*-butoxycarbonyl-6-oxo-1,7-diazaspiro[4.4]non-7-yl)acetic acid methyl ester (26.8 mg, 0.0858 mmol) and methylamine solution (8 M in ethanol, 2 mL) as described for **3** (2.75 h at 0 °C, then 15 h at room temperature). Column chromatography (hexanes/ethyl acetate 1:2 increasing to 0:1) yielded 21.0 mg (79%) of **1** as yellowish crystals. mp 121 °C; R_f 0.46 (CH_2Cl_2/methanol 9:1); $[\alpha]^{23}_D$ 69.6° (*c* 0.5, $CHCl_3$) IR (neat) 3338, 2975, 2929, 1697, 1673

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cm^{-1}; IR (2 mM, $CHCl_3$) 3337 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.80−1.93 (m, 2H), 2.02−2.11 and 2.07 (m and ddd, 2H, J = 13.4, 9.2, 3.8 Hz), 2.20−2.31 (m, 1H), 2.47 (ddd, 1H, J = 13.4, 9.8, 6.0 Hz), 2.80 (d, 3H, J = 4.6 Hz), 3.29 (ddd, 1H, J = 9.5, 9.2, 6.0 Hz), 3.38 (d, 1H, J = 17.0 Hz), 3.48−3.52 (m, 2H), 3.57 (ddd, 1H, J = 9.8, 9.5, 3.8 Hz), 4.57 (d, 1H, J = 17.0 Hz), 7.82 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.0, 26.2, 28.6, 31.5, 38.2, 44.7, 47.5, 47.8, 66.5, 80.7, 154.5, 168.3, 174.5; EIMS 311 (M^+). Anal. Calcd for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.91; H, 8.11; N, 13.49.

Computational Studies. The structure of **2** was derived from X-ray data of a suitable precursor, which was further used as a template to build **1**. Both structures were submitted to a series of DFT calculations using Gaussian98.[26] A B3LYP density functional with a 3-21G basis set was used to produce a reasonable geometry in appropriate time. Then the basis set was increased in two subsequent steps to the double-valence d-polarized level 6-31G(d) and the triple-valence d,p-polarized level 6-311G(d,p) to enhance the quality of the structure.

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