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Synthesis of Fmoc-Protected trans-4-Methylproline

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Fmoc-protected trans-4-methylproline was synthesized starting from D-serine. The chiral scaffold of serine in the form of olefinated Garner’s aldehyde was used to control the diastereoselective formation of the new stereocenter on the hydrogenation of allylic alcohol. The diastereoselectivity (syn/anti ratio) of the process was 86:14, attained with Raney nickel. Hydrogen migration seems not to be the sole factor lowering the diastereoselectivity, as nickel is known not to promote double-bond migration. Instead, the moderate stereocontrol is attributed to the mobility of the side chain of 4, which allows the attack of hydrogen on both faces of the olefin (open transition state). A series of transformations led to ring precursor, which after recrystallization afforded the trans diastereoisomer in dr = 95:5. Protected trans-4-methylproline was obtained from 8 in a straightforward fashion.

Introduction and Background

Substituted prolines are interesting targets as they are considered to be constrained analogues of natural amino acids.¹ Thus, their incorporation into bioactive peptides renders conformationally constrained peptides. Such so-called peptidomimetics (or peptide mimics) are useful tools for the development of superior pharmaceutical agents and for establishing structure–bioactivity relationships, which could aid in the understanding of biological processes.¹

While efficient asymmetric syntheses of 3- and 5-substituted prolines have been achieved,² only a few approaches have been reported for 4-substituted prolines.¹ Thus, in 1989, Koskinen and Rapoport³ described the synthesis of various cis- and trans-4-alkyl- and -phenylprolines by conversion of 4-substituted glutamic acid esters to the corresponding 5-hydroxypentanoic acids, followed by separation of diastereoisomers and intramolecular nitrogen alkylation. 4-Phenylproline has also been synthesized from 4-hydroxyproline⁴ by tosyl formation and further substitution of that group with lithium diphenylcuprate.⁵ Although the reaction proceeds with retention of configuration at the carbon bearing the tosylxy group, participation of the 

α-carbon, leading to 2:1 or 2:3 mixtures of diastereomers. Better results in terms of diastereomeric ratios were attained via Friedel–Craft reaction of benzene with different trans-4-hydroxyproline derivatives (pure cis- and trans-4-phenylproline were obtained)³ and from 4-ketoprolines (cis-4-phenylproline was obtained pure and the trans diastereomer as a 9:1 mixture).¹ Thottathil and co-workers⁶ reported the synthesis of trans-4-cyclohexylproline from pyroglutamic acid, in good yield and complete diastereoselectivity. Recently, Sasaki and co-workers⁷ described the synthesis of a proline structure with two discernible hydroxy functionalities, which according to the authors, could provide a range of 4-substituted proline derivatives. Proline is known to have profound conformational effects in the tertiary structures of peptides and proteins.⁸ In connection with our studies on the structure and biosynthesis of collagen,⁴ we needed an efficient synthesis of trans-4-methylproline,² suitable for incorporation in automated peptide synthesis. The free amino acid was isolated from apples by Hulme and Arthington in 1954,⁵ and its first synthesis was reported in 1962 by Gray and Bowden.⁵ Those authors hydrogenated the naturally occurring 4-methylproline with Adam’s catalyst, obtaining cis-4-methylproline as the major diastereoisomer. Later on, Lavergne and co-workers⁹ obtained a 1:1

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mixture of cis- and trans-4-methylproline by cyclization of \( \delta \)-chlorinated compounds obtained by irradiating N-chloro-L-amino acids. In 1988, Belokon and co-workers described the synthesis of a 2:1 cis/trans-4-methylproline mixture, via condensation of glycine with activated olefins.

In view of the mentioned results, we were challenged to develop a new synthetic strategy for trans-4-methylproline. In this paper, we describe the synthesis of Fmoc-protected trans-4-methylproline. We believe that this route also constitutes a general synthetic pathway to 4-substituted prolines.

On the basis of retrosynthetic analysis, the 4-substituted proline structure can be reached from serine-derived \( \alpha \)-enolates, as outlined in Scheme 1.

Some of our preliminary results on the hydrogenation of \( E \)-enolates derived from fully protected serinal促使 us to further studies on the selectivity of the process, and to develop a synthetic route to 4-alkylprolines.

Results and Discussion

The synthetic pathway proposed for Fmoc-protected trans-4-methylproline is based on a diastereoselective approach, starting from the Garner’s aldehyde (1, Scheme 2).

A Wittig reaction between phosphorane 2 and the Garner’s aldehyde (1) provided \( \alpha,\beta \)-unsaturated ester 3 in 72% yield, with the \( E/Z \) ratio \( \geq 96:4 \) (the \( Z \)-enolate was not observed by \( \text{H} \) NMR, as we have already described. The enantiomeric excess of 3 was determined following the method described by Mann and co-workers. Thus, the hemiaminal moiety of 3 was hydrolyzed (p-TsOH in MeOH, rt, 2 h), and the resulting alcohol group was treated with Mosher’s reagent. Analysis of the resulting Mosher ester by HPLC (Chiralcel OD column, Hex/IPA 95:5, 1 mL/min, 254 nm; \( t_{R,\text{Z}} = 16.8 \) min, \( t_{R,\text{H}} = 19.0 \) min) and \( \text{H} \) NMR gave 96% ee for 3, revealing that minimal racemization had occurred. This result is in agreement with that of Mann and co-workers, who reported 98% ee for a compound similar to 3 (containing a hydrogen atom instead of the 2-methyl group).

Previous studies carried out in our laboratory on the reduction of the double bond of 3 using different heterogeneous catalysts gave as the best result a 5:1 \( \text{syn/anti} \) diastereomeric ratio for the corresponding saturated ester (using \( \text{Pt/C} \) in Hex). The moderate diastereoselectivity was rationalized on the basis of a hydrogen migration, which results in the isomerization of the double bond. With the aim to improve those results, we next attempted the hydrogenation of allylic alcohol 4, obtained in 88% yield by reduction of the ester functionality of 3 with DIBAL-H in toluene. We hoped that the hydroxyl moiety could interact strongly with the catalyst, providing a more rigid transition state that could favor the diastereofacial discrimination. Initially, hydrogenation of 4 was carried out on 10% \( \text{Pt/C} \). Slightly surprisingly, the deoxygenated compound (5a) was formed as the major product of the hydrogenation reaction (80% yield), even in hexane. In light of the literature, the acidic character of charcoal seems to be responsible for the large extent of the deoxygenation process. To avoid the cleave of the allylic C–O bond, neutral catalysts in basic media were tested. The results obtained are summarized in Table 1.

The deoxygenated product (5a) was not detected in any experiment, which confirmed that its formation is an acid-catalyzed process. Clean formation of saturated alcohol 5b occurred with moderate selectivity. Palladium was discarded as it is the most active deoxygenating catalyst. Platinum oxide was used instead. Although it is known that platinum promotes less hydrogen migration than palladium, only a 75:25 \( \text{syn/anti} \) ratio was afforded with platinum oxide (Table 1, entry 1). The use of iridium was attempted, as according to Rylander, iridium is the metal with the greatest ability to deliver hydrogen in a cis manner, which is essential to attain selectivity. Iridium on charcoal in ethyl acetate turned out to be inactive even to promote deoxygenation of allylic alcohol 4. In view of those results, we decided to turn to Raney Nickel, catalyst that does not promote isomerization (Table 1, entries 4–11). As the diastereoselectivity increased only to a maximum of 86:14 \( \text{syn/anti} \), other factors in addition to double bond migration are envisaged to work against the diastereoselectivity of the process. Namely, the conformational mobility of allylic alcohol 4 must allow the complexation of the metal on the two faces of the double bond, lowering the diastereofacial selectivity.

Replacement of the hydroxy functionality of compound 5b (86:14 \( \text{syn/anti} \)) by chloride (\( \text{PPh}_3, K_2\text{CO}_3, \text{CCl}_4 \) in MeCN) had as a drawback the difficult separation of the phosphorus-containing compounds from the target molecule, which resulted in a lower yield of chloride 6a. Moreover, cleavage of the hemiaminal protecting group leading to 7a occurred to a large extent during flash chromatography, even using pretreated moisture-free silica gel. On the other hand, exchange of the alcohol group by bromide was a much easier reaction to work up and rendered compound 6b in high yield (90%). Hydrolysis of the hemiaminal moiety of 6b was achieved with 80% \( \text{AcOH} \) at 50 °C (91%). Benzoylation of the alcohol group of 7a and 7b (\( \text{PhCOCl, Py, 95\%} \)) rendered ring precursors 8a and 8b, respectively, as white solids. Recrystallization of 8a (dr = 86:14) from hexane/ether 4:1 provided diasteromer (2R,4S)-8 in dr = 95:5. The diastereomeric purity of compound 8b was also increased by recrystallization (the conditions were not optimized). Cylization of (2R,4S)-8 (dr = 95:5) was carried out in tetrahydrofuran, using KHMDMS as the base. The yield

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of the cyclization process is not affected by the temperature or the nature of the halogen (for 8a: 70% yield after 15 min at 40 °C and 72% yield at 0 °C; for 8b: 69% yield after 15 min at 0 °C). This fact can be expected taking into account the fast reaction rate. The reaction yield decreases as a result of the competing basic hydrolysis (aminolysis) of the Boc and benzoyl groups promoted by the base (KHMDS). The resulting amino alcohol is very soluble in water and is lost during work up. This problem is overcome when protected prolinol 9 is not isolated (vide infra).

Various attempts to deprotect the benzoyl group of 9 under basic conditions (NaOH) led to mixtures of compounds in which cleavage of the Boc group was observed. The problem was solved by hydrolyzing both the Boc and the benzoyl groups under acidic conditions (1 N HCl, 100 °C). The resulting amino alcohol is very soluble in water and is lost during work up. This problem is overcome when protected prolinol 9 is not isolated (vide infra).

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Table 1. Hydrogenation of Allylic Alcohol 4

<table>
<thead>
<tr>
<th>entry</th>
<th>metal catalyst (substrate/catalyst)</th>
<th>solvent</th>
<th>additive</th>
<th>syn/anti ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtO (4:1)</td>
<td>EtOH</td>
<td>NaNO 2</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>PtO (4:1)</td>
<td>Hex</td>
<td>Et 3N</td>
<td>70:30</td>
</tr>
<tr>
<td>3</td>
<td>PtO (8:1)</td>
<td>Hex</td>
<td>Et 3N</td>
<td>70:30</td>
</tr>
<tr>
<td>4</td>
<td>Raney Ni (1.5:1)</td>
<td>EtOH</td>
<td>80:20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Raney Ni (2.7:1)</td>
<td>EtOH/AcOEt</td>
<td>70:30</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Raney Ni (1.5:1)</td>
<td>MeOH</td>
<td>85:15</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Raney Ni (1.5:1)</td>
<td>MeOH/H 2O</td>
<td>75:25</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Raney Ni (8:1)</td>
<td>MeOH</td>
<td>85:15</td>
<td></td>
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<tr>
<td>9</td>
<td>Raney Ni (20:1)</td>
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</tr>
<tr>
<td>10</td>
<td>Raney Ni (2:1)</td>
<td>MeOH</td>
<td>80:20</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Raney Ni (2:1)</td>
<td>MeOH</td>
<td>86:14</td>
<td></td>
</tr>
</tbody>
</table>

Reactions conducted at room temperature and 1 atm, using a concentration of 0.8%. Raney Ni as a 50% w/w slurry in H 2O (pH = 10). h 1% w/w of catalyst. i Determined by NMR. j Concentration = 10%.

hydroxymethyl moiety of 10 to carboxylic acid with Jones reagent in acetone provided Fmoc-protected trans-4-methylproline (dr = 95:5, ee = 96%).

Conclusions

We have developed a new direct route to trans-4-alkylprolines, using a substrate directed hydrogenation reaction for the synthesis of alcohol 5b. The route involves eight steps, renders only the trans diastereoisomer (after recrystallization), and should be applicable to other targets of the same family. We are currently investigating new approaches to improve the diastereoselectivity of the hydrogenation step. Moreover, the target trans-4-methylproline is being incorporated into small peptides in order to obtain backbone and side chain conformationally constrained peptides to mimic β-turns in proteins.

Experimental Section

General Methods. 1H NMR spectra were recorded on a Varian Unity-400 at 400 MHz and are reported in ppm downfield from SiMe 4. J values are given in Hz. 13C NMR spectra were recorded on a Varian Unity-400 at 100 MHz. HRMS were conducted on JEOL JMS-DX303 (EI+) and Micromass LCT (ES+) spectrometers. Optical rotations were measured on a Perkin-Elmer 343 polarimeter at room temperature, using a cell of 1 dm of length and λ = 598 nm. Data are reported as follows: [α] D (solvent, concentration in g/100 mL). HPLC analyses were performed using a Waters system with UV detector, on a Chiralpak AS (Daicel) column. Melting points (mp) were performed on a Gallenkamp apparatus, using open capillary tubes. Values are given in degrees Celsius (uncorrected). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with QF-254 indicator.
Visualization was accomplished with UV light, iodine or 1% KMnO₄ in H₂O. Flash chromatography was performed using Merck silica gel 60 (40–63 μm). The detector wavelength, flow rate and solvents were as denoted. The retention times (tR) for the enantiomers are reported.

Solvents were dried using standard procedures. 16 β-Serine was purchased from Fluka. DiBAL-H [1 M in toluene] was obtained from Alrich and KHMDS [0.5 M in toluene] was obtained from Fluka. 10% Pt/C, PtO₂, and Raney Nickel (50% w/w slurry in H₂O, pH = 10) were purchased from Alrich, and 5% Ir/C from Alfa. Garner’s aldehyde 17 and phosphorane 2 were synthesized as described in the literature.

In a 1 L three-necked round-bottomed flask under argon (C-carbethoxymethyldiene)triphenylphosphine (1.44 g, 5.54 mmol, 110 mol %) and the mixture cooled to −5 °C was added. The mixture was stirred at room temperature for 18 h. The solution was washed with hexane (2 × 100 mL). The solvent was filtered at reduced pressure. The residue was purified by flash chromatography (silica, Hex/AcOEt 5:1). A clear oil was obtained (12.0 g, 44.2 mmol, 88%).

In a 250 mL two-necked round-bottomed flask under argon was placed [2R,3S(4S)]-2-methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (5b).

2L three-necked round-bottomed flask were placed Raney Ni (13.0 g, 50% w/w slurry in water, 50 mol %) and [2R,3S(4S)]-2-methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (13.0 g, 46.8 mmol) in MeOH (1300 mL). The flask was filled with hydrogen, the mixture was stirred at room temperature for 18 h and filtered through a pad of Celite, and the solvent was eliminated under reduced pressure. The residue was taken up in Et₂O (100 mL) and washed with H₂O (2 × 25 mL). The mixture was dried (MgSO₄) and filtered and the solvent removed under reduced pressure. 5 was obtained as a clear oil (12.1 g, 44.4 mmol, 95%) with τR = 86:14 (two rotamers): [α]D₉⁺ = +32.6 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14.

[2R,3S(4S)]-1-Chloro-2-methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (6a).

In a 1 L three-necked round-bottomed flask under argon placed [2R,3S(4S)]-2-methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (12.0 g, 44.2 mmol) of dr = 86:14 in acetonitrile (650 mL), K₂CO₃ (12.3 g, 89.7 mmol, 200 mol %), Ph₃P (29.6 g, 164.9 mmol, 250 mol %), and CCl₄ (43 mL) were added. The mixture was stirred at room temperature for 1 h and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, Hex/AcOEt 4:1 and 2:1). Two fractions were obtained: the target molecule (6a) as an oil (1.8 g, 6.0 mmol, 14%) and the hemiaminal cleaved product (7a) also as an oil (5.4 g, 21.4 mmol, 48%). 6a (two rotamers): [α]D₉⁺ = +22.5 (c = 1.13, CHCl₃); [α]D₉⁻ = −34.5 (c = 1.06, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c = 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14; [α]D₉¹ = +3.1 (c 0.98, CHCl₃) for τR = 70:30; [α]D₉⁻ = −34.5 (c 1.06, CHCl₃) for τR = 86:14.

[2R,3S(4S)]-2-Methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (5b).

In a 10 mL two-necked round-bottomed. flask under argon was placed [2R,3S(4S)]-2-methyl-3-[N-(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl)propanol (5b) in dry CH₂Cl₂ (50 mL) and the mixture cooled to 30 °C. The solution was filtered at reduced pressure. The residue was purified by flash chromatography (silica, Hex/AcOEt 4:1). A clear oil was obtained (3.6 g 58% yield).
(25R,4R)-2-Amino-N-[(1,1-dimethyl)ethoxy carbonyl]-1-chloro-4-methylpentan-10(11)-ol (7a). In a 250 mL round-bottomed flask was placed [2R,3S]-1-bromo-2-methyl-3-N-[(1,1-dimethyl)ethoxy carbonyl]-2,2-dimethyl-1,3-azoxadindienyl propanate (3.5 g, 11.9 mmol) of dr = 86:14 in AcONH 80% (70 mL). The mixture was stirred at 50 °C during 1.5 h and evaporated to dryness at reduced pressure (without heating). The residue was dissolved in Et 2O (70 mL) and washed with 0.1 M NaHCO 3 (4 × 50 mL). The organic layer was dried (MgSO 4) and filtered and the solvent removed under reduced pressure. An oil was obtained (2.8 g, 11.1 mmol, 94%), which was used without further purification: R f = 0.25 (silica, Hex:AcOEt 1:1); [ä]D 20 = −17.5 (c = 0.76, CHCl 3) (dr = 86:14); 1H NMR (400 MHz, CDCl 3) δ 4.81, 4.61 (2 bs, 1H), 3.80–3.40 (m, 5H), 2.95–2.25 (15 bs, 1H), 1.92 (m, 1H), 1.85–1.55 (m, 11H), 1.46–1.32 (m, 10H), 1.08 (s, 3H), 1.07 (dd, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl 3) δ 136.2, 97.1, 67.5, 54.5, 50.2, 35.6, 31.8, 28.4, 18.5 (major diastereoisomer); 156.2, 79.7, 66.5, 53.8, 38.8, 33.5, 28.2, 19.1; HRMS calc for M + Na [(C 12H 14NO 3Na + Na) 342.1681, found 342.1655.

(25R,4R)-2-(Benzyloxymethyl)-4-methyl-N-[(1,1-dimethyl)ethoxy carbonyl]pyrrolidine (9). In a three-necked round-bottomed flask under argon was placed (25R,4R)-2-amino-N-[(1,1-dimethyl)ethoxy carbonyl]-1-benzyloxycarbonyl-1-chloro-4-methylpentan-10(11)-ol (300 mg, 0.84 mmol) (dr = 95:5) in dry THF (50 mL). The solution was cooled to 0 °C, and KHMDS (0.5 M in Tol, 1.8 mL, 0.92 mmol, 110 mol %) was added dropwise. The mixture was stirred at 0 °C for 15 min and treated with saturated NH 4 Cl solution (60 mL). The layers were separated, and the aqueous one was extracted with Et 2O (3 × 25 mL). The combined organic extracts were washed with H 2O (2 × 50 mL), dried (MgSO 4), and filtered, and the solvent was removed under reduced pressure. A yellow viscous liquid was obtained (190 mg, 0.60 mmol, 71%), which was used without further purification. An analytic sample was obtained by filtration over silica with the aid of the hexane and then AcOEt: R f = 0.56 (silica, Hex:AcOEt 4:1); [ä]D 20 = −21.3 (c = 0.4, CHCl 3) for dr = 95:5; 1H NMR (400 MHz, CDCl 3) δ 8.00 (m, 2H), 7.50 (m, 1H), 7.24 (m, 1H), 3.92 (dd, J = 11.6, 7.6 Hz, 3H), 2.83 (dd, J = 11.6, 7.6 Hz, 3H), 2.69 (dd, J = 11.6, 7.6 Hz, 3H), 2.68 (dd, J = 11.6, 7.6 Hz, 3H), 1.92 (m, 3H); HRMS calc for M + H [(C 12H 14NO 3Na + Na) 342.1681, found 342.1655.

(25R,4R)-N-9-Fluorphenylmethoxycarbonyl-2-hydroxy-methyl-4-methylpyrrolidine (10). (a) In a 100 mL round-bottomed flask was placed (25R,4R)-2-(benzyloxymethyl)-4-methyl-N-[(1,1-dimethyl)ethoxy carbonyl]pyrrolidine (160 mg, 0.50 mmol) and 1 N HCl (30 mL). The mixture was stirred overnight at 100 °C, cooled to room temperature and extracted with Et 2O (3 × 15 mL). The solvent was removed from the aqueous layer under reduced pressure, and the residue was suspended in a mixture of dioxane (0.6 mL) and 10% Na 2CO 3 (3 mL). The heterogeneous mixture was cooled to 0 °C, and a solution of 9-fluoromethylchloroformate (135 mg, 0.52 mmol, 105 mol %) in dioxane (1 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1.5 h, diluted with H 2O (10 mL), and extracted with Et 2O (4 × 10 mL). The organic extracts were washed with H 2O (3 × 10 mL), dried (MgSO 4), and filtered, and the solvent was removed under reduced pressure. An oil was obtained (160 mg, 0.48 mmol, 96%), which was used directly. An analytic sample was obtained by flash chromatography (silica, Hex:AcOEt 2:1), resulting in a white foam: R f = 0.29 (silica, Hex:AcOEt 1:2).

(b) In a 100 mL three-necked round-bottomed flask under argon was placed (25R,4R)-2-amino-N-[(1,1-dimethyl)ethoxy carbonyl]-1-benzyloxycarbonyl-1-chloro-4-methylpentan-10(11)-ol (300 mg, 0.51 mmol) in dry THF (30 mL). The solution was cooled to 0 °C, and KHMDS (0.5 M in Tol, 3.0 mL, 1.50 mmol, 294 mol %) was added dropwise. The mixture was stirred at 0 °C for 15 min, the solvent was eliminated under reduced pressure, and the residue was washed with 1 N HCl (30 mL). The mixture was stirred at 100 °C for 3 h, cooled to room temperature, and extracted with Et 2O (3 × 15 mL). The aqueous phase was concentrated under reduced pressure, and the residue was treated as described above. 10 was obtained as a white foam (150 mg, 0.45 mmol, 88%) after flash chromatography (silica, Hex:AcOEt 2:1); [ä]D 20 = −19.8 (c = 1.42, CHCl 3); 1H NMR (400 MHz, CDCl 3) δ (two rotamers) 7.77 (d, J = 6.6 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.39 (d, J = 7.0 Hz, 2H), 7.32 (pdt, J = 6.8, 2.1, 2.1 Hz, 2H), 2.03 (d, J = 6.8 Hz, 2H), 2.42 (d, J = 6.8 Hz, 1H), 4.24–4.00 (m, 2H), 3.64 (m, 2H), 3.55 (dd, J = 10.4, 6.8 Hz, 1H), 3.05 (dd, J = 10.4, 7.6 Hz, 1H), 2.33 (m, 1H), 1.80–1.60 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl 3) δ (two rotamers) 157.1, 143.8, 141.3, 127.7, 127.0, 125.0, 124.7, 119.9, 67.5, 67.1, 66.4, 64.0,
(2S,4R)-trans-N-(9-Fluorenlymethoxycarbonyl)-4-methylproline (11). In a 25 mL two-necked round-bottomed flask was placed (2S,4R)-N-(9-fluorenlymethoxycarbonyl)-2-hydroxymethyl-4-methylpyrrolidine (120 mg, 0.36 mmol) in 10 mL of dry acetone. Jones reagent (0.5 mL) was added dropwise at room temperature, and the mixture was stirred vigorously for 1 h. Acetone was removed under reduced pressure, and the residue was dissolved in AcOEt (15 mL) and washed with H2O (3 x 10 mL). The organic layer was extracted with 5% NaHCO3 (4 x 10 mL) cooled to 0 °C, which was washed with AcOEt (10 mL) and acidified to pH = 2 with 1 N HCl (aprox. 20 mL). The product was extracted with CHCl3 (4 x 10 mL), which was washed with brine (2 x 10 mL), dried (MgSO4), and filtered, and the solvent was removed under reduced pressure. An amorphous solid was obtained (75 mg, 0.21 mmol, 59%) (two rotamers): Rf = 0.29 (silica, Hex/AcOEt 1:2); mp = 65–67 °C; [a]20D = −49.3 (c = 0.3, CHCl3); 1H NMR (400 MHz, CDCl3) δ 9.8–8.8 (bs, 1H), 7.77–7.66 (m, 2H), 7.62–7.51 (m, 2H), 7.45–7.22 (m, 4H), 4.50–4.28 (m, 3H), 4.24, 4.12 (2t, J = 7.2 Hz, 1H rotamers), 3.74 (dd, J = 9.6, 8.0 Hz, 1H), 3.05 (dd, J = 9.6, 9.2 Hz, 1H), 2.50–2.30 (m, 1H), 2.30–2.24 and 2.20–2.10 (2m, 1H rotamers), 1.93–1.76 (m, 1H), 1.07, 1.03 (2d, J ≈ 6.4 Hz, 3H rotamers); 13C NMR (100 MHz, CDCl3) δ 178.0, 176.2, 155.8, 154.4, 144.0, 143.8, 143.7, 143.7, 141.4, 141.3, 141.2, 140.1, 128.3, 127.7, 127.6, 127.4, 127.0, 127.0, 125.7, 125.1, 125.0, 124.9, 124.8, 120.1, 120.0, 119.9, 67.9, 67.4, 59.5, 58.8, 53.6, 53.4, 47.2, 38.5, 36.9, 32.2, 31.0, 17.1; HRMS calcd for M+ (C21H21NO4) 351.1465, found 351.1395.

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Supporting Information Available: Copies of 1H and 13C NMR spectra of compounds 3–11. This material is available free of charge via the Internet at http://pubs.acs.org.

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