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 **3** was used to control the diastereoselective formation of the new stereocenter on the hydrogenation of allylic alcohol **4**. 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 **8**, which after recrystallization afforded the syn diastereoisomer in dr = 95:5. Protected *trans*-4-methylproline **11** 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 Rapoport[1a] 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. *trans*-4-Phenylproline has also been synthesized from 4-hydroxyproline[1b] by tosyl formation and further substitution of that group with lithium diphenylcuprate.[1c,d] Although the reaction proceeds with retention of configuration at the carbon bearing the tosyloxy group, participation of the *N*-Boc protecting group results in the epimerization 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)[1e] and from 4-ketoproline (*cis*-4-phenylproline was obtained pure and the trans diastereomer as a 9:1 mixture).[1f] Thottathil and co-workers[1g] reported the synthesis of *trans*-4-cyclohexylproline from pyroglutamic acid, in good yield and complete diastereoselectivity. Recently, Sasaki and co-workers[1h] 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.[3] In connection with our studies on the structure and biosynthesis of collagen,[4] we needed an efficient synthesis of *trans*-4-methylproline,[5] suitable for incorporation in automated peptide synthesis. The free amino acid was isolated from apples by Hulme and Arthington in 1954,[5a,b] and its first synthesis was reported in 1962 by Gray and Fowden.[5c] Those authors hydrogenated the naturally occurring 4-methyleneproline with Adam's catalyst, obtaining *cis*-4-methylproline as the major diastereoisomer. Later on, Lavergne and co-workers[5d] obtained a 1:1

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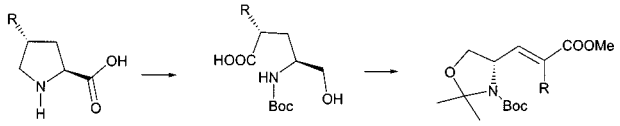
Scheme 1. Retrosynthetic Analysis of 4-Substituted Prolines



mixture of *cis*- and *trans*-4-methylproline by cyclization of *δ*-chlorinated compounds obtained by irradiating *N*-chloro-L-amino acids. In 1988, Belokon and co-workers[5e] 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 α-enoates, as outlined in Scheme 1.

Some of our preliminary results on the hydrogenation of *E*-enoates derived from fully protected serinal[6] prompted 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).[7]

A Wittig reaction between phosphorane **2** and the Garner's aldehyde (**1**) provided α,*β*-unsaturated ester **3**[6] in 72% yield, with the *E*/*Z* ratio ≥96:4 (the *Z*-enoate was not observed by ^{1}H NMR), as we have already described.[6] The enantiomeric excess of **3** was determined following the method described by Mann and co-workers.[8] 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.[9] Analysis of the resulting Mosher ester by HPLC (Chiralcel OD column, Hex/IPA 95:5, 1 mL/min, 254 nm; $t_{R(R)}$=16.8 min, $t_{R(S)}$=19.0 min) and ^{1}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,[8] 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 syn/anti diastereomeric ratio for the corresponding saturated ester (using Pt/C in Hex).[6] The moderate diastereoselectivity was rationalized on the basis of a hydrogen migration, which results in the isomerization of the double bond.[4] 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% 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,[6] 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.[10] Platinum oxide was used instead. Although it is known that platinum promotes less hydrogen migration than palladium,[10] only a 75:25 syn/anti ratio was afforded with platinum oxide (Table 1, entry 1). The use of iridium was attempted, as according to Rylander,[11] 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).[10] As the diastereoselectivity increased only to a maximum of 86:14 syn/anti ratio, 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 syn/anti) by chloride (PPh_3, K_2CO_3, CCl_4 in MeCN)[12] 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% AcOH at 50 °C (91%).[13] Benzoylation of the alcohol group of **7a** and **7b** (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 (2*R*,4*S*)-**8** in dr = 95:5. The diastereomeric purity of compound **8b** was also increased by recrystallization (the conditions were not optimized).

Cyclization of (2*R*,4*S*)-**8** (dr = 95:5) was carried out in tetrahydrofuran, using KHMDS as the base. The yield

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Scheme 2. Synthesis of Fmoc-Protected *trans*-4-Methylproline

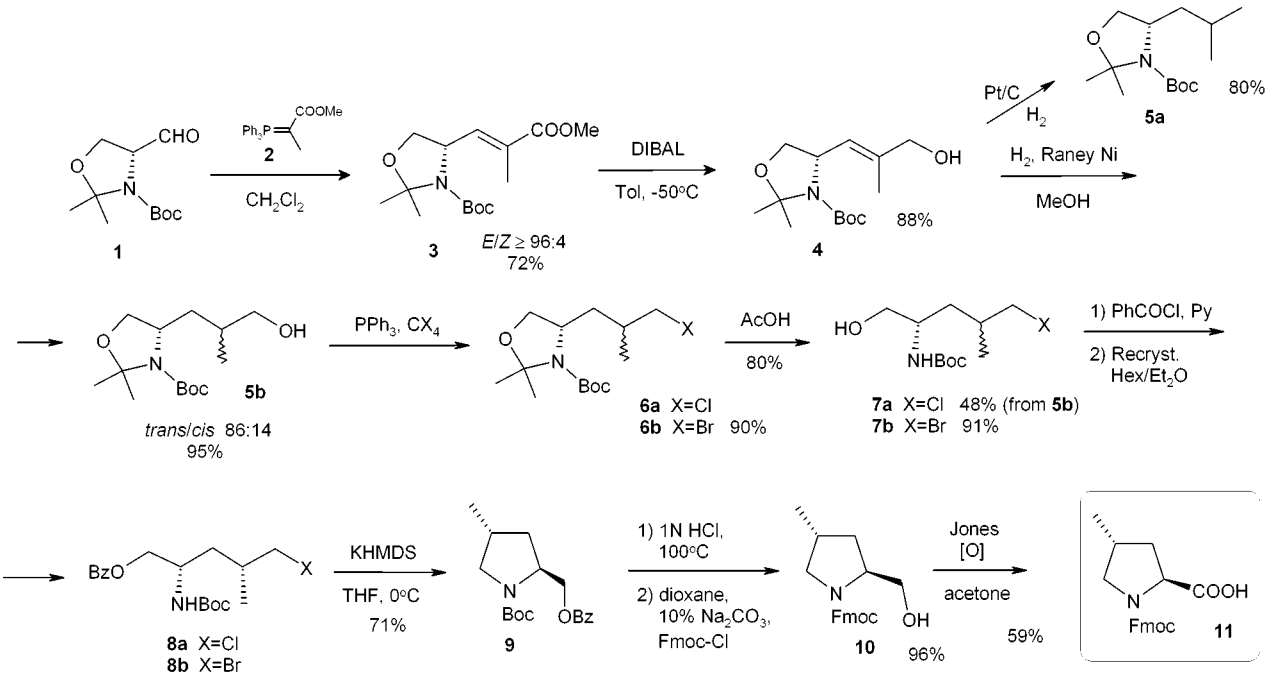

Table 1. Hydrogenation of Allylic Alcohol 4

entry[a]	metal catalyst (substrate/catalyst)	solvent	additive[b]	syn/anti ratio[c]
1	Pt_2O (4:1)	EtOH	$NaNO_2$	75:25
2	Pt_2O (4:1)	Hex	Et_3N	70:30
3	Pt_2O (8:1)	Hex	Et_3N	70:30
4	Raney Ni (1.5:1)	EtOH		80:20
5	Raney Ni (2.7:1)	EtOH/AcOEt 20:80		70:30
6	Raney Ni (1.5:1)	MeOH		85:15
7	Raney Ni (1.5:1)	MeOH/H_2O 20:80		75:25
8	Raney Ni (8:1)	MeOH		85:15
9	Raney Ni (20:1)	MeOH[d]		80:20
10	Raney Ni (2:1)	MeOH[d]		80:20
11	Raney Ni (2:1)	MeOH		86:14

[a] 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). [b] 1% w/w of catalyst. [c] Determined by NMR. [d] Concentration = 10%.

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 crude amino alcohol hydrochloride obtained was converted quantitatively into Fmoc-protected amino alcohol **10** under Schotten−Baumann conditions.[14] Compound **10** can be obtained directly from **8a** (without isolation of **9**) in 88% yield. Finally, oxidation of the hydroxymethyl moiety of **10** to carboxylic acid with Jones reagent in acetone[15] 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. ^{1}H 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. ^{13}C 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: $[\alpha]^T_D$ (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.

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Visualization was accomplished with UV light, iodine or 1% $KMnO_4$ in H_2O. 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 (t_R) for the enantiomers are reported.

Solvents were dried using standard procedures.[16] D-Serine was purchased from Fluka. DIBAL-H (1 M in toluene) was obtained from Aldrich and KHMDS (0.5 M in toluene) was obtained from Fluka. 10% Pt/C, Pt_2O, and Raney Nickel (50% w/w slurry in H_2O, pH = 10) were purchased from Aldrich, and 5% Ir/C from Alfa. Garner's aldehyde[7,17] and phosphorane **2**[18] were synthesized as described in the literature.

[2*E*,3(4*S*)]-2-Methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propenoic Acid Methyl Ester (3). In a 1 L three-necked round-bottomed flask was placed under argon (α-carbomethoxyethylidene)triphenylphosphorane (38.6 g, 110 mmol, 110 mol %) in dry CH_2Cl_2 (500 mL). The solution was cooled to 0 °C, and (4*R*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (22.9 g, 100 mmol) in dry CH_2Cl_2 (200 mL) was dropwise added. The ice/water bath was removed, and the mixture was stirred at room temperature for 18 h. The solution was concentrated under reduced pressure. The residue (150 mL) was treated with hexane (500 mL), cooled to 0 °C, and stirred at that temperature for 30 min. The solid was filtered washed with hexane (2 × 100 mL). The solvent was evaporated from the filtrate at reduced pressure, and the residue was purified by flash chromatography (silica, Hex/AcOEt 5:1). A clear oil was obtained (21.5 g, 71.9 mmol, 72%): R_f = 0.41 (silica, Hex/AcOEt 5:2); $[\alpha]^{20}_D$ +19.3 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (bs, 1H), 4.78−4.59 (bs, 1H), 4.12 (dd, *J* = 8.8 Hz, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, *J* = 8.8, 3.0 Hz, 1H), 1.91 (m, 3H), 1.63 (m, 3H), 1.55−1.40 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 152.0 (rotamer), 151.7, 140.9, 140.6 (rotamer), 128.8 (rotamer), 127.8, 94.4, 93.8 (rotamer), 80.4 (rotamer), 80.0, 67.6, 55.3, 51.8, 28.3, 27.2 (rotamer), 26.2, 25.0 (rotamer), 24.1, 12.5; HRMS calcd for M^+ ($C_{15}H_{25}NO_5$) 299.1726, found 299.1733.

[2*E*,3(4*S*)]-2-Methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propenyl Alcohol (4). In a 250 mL two-necked round-bottomed flask under argon was placed DIBAL-H (1 M in toluene, 90 mL, 90 mmol, 180 mol %) and the mixture cooled to −50 °C. A solution of [2*E*,3-(4*S*)]-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propenoic acid methyl ester (15.0 g, 50.3 mmol) in dry toluene (15 mL) was dropwise added. The mixture was stirred at −50 °C for 5 h, quenched with acetone (60 mL), and allowed to warm to room temperature by removal of the dry ice/$CHCl_3$ bath. When the mixture started to jellify, it was poured into a solution of sodium potassium tartrate (113 g) in H_2O (300 mL), with the aid of Et_2O (2 × 10 mL). The biphasic mixture was stirred vigorously at room temperature for 1 h, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (silica, Hex/AcOEt 3:1). A clear oil was obtained (12.0 g, 44.2 mmol, 88%): R_f = 0.34 (silica, Hex/AcOEt 1:1); $[\alpha]^{20}_D$ −16.5 (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46, 5.27 (d, *J* = 9.2 Hz, 1H), 4.72−4.52 (bs, 1H), 4.07 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.02 (s, 2H), 3.66 (dd, *J* = 8.8, 3.2 Hz, 1H), 1.80−1.34 (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 137.1, 135.9 (rotamer), 125.5 (rotamer), 125.2, 93.9, 80.1, 68.6, 68.0, 55.1, 28.5, 27.1 (rotamer), 26.4, 25.2 (rotamer), 24.0, 13.8; HRMS calcd for M^+ ($C_{14}H_{25}NO_4$) 271.1777, found 271.1709.

[2*R*,3(4*S*)]-2-Methyl-3-[N-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propanol (5b). In a 2 L three-necked round-bottomed flask were placed Raney Ni (13.0 g, 50% w/w slurry in water, 50 mol %) and [2*E*,3(4*S*)]-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propenyl alcohol (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 Et_2O (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent removed under reduced pressure. **5** was obtained as a clear oil (12.1 g, 44.4 mmol, 95%) with dr = 86:14 (two rotamers): $[\alpha]^{20}_D$ +32.6 (*c* 0.98, $CHCl_3$) for dr = 70:30; $[\alpha]^{20}_D$ = +34.5 (*c* 1.06, $CHCl_3$) for dr = 86:14; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20−4.00 (bs, 1H), 4.00−3.80 (m, 1H), 3.80−3.64 (m, 1H), 3.60−3.38 (bs, 2H), 3.24−3.00 (bs, 1H), 1.80−1.66 (m, 2H), 1.66−1.50 (m, 4H), 1.50−1.34 (m, 12H), 1.02−0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.4, 161.6, 93.6, 93.2, 93.1, 80.4, 79.5, 68.5, 68.2 67.9, 67.6, 67.2, 67.0, 55.8 (minor diastereoisomer), 55.6 and 55.1 (major diastereoisomer), 38.1 (minor diastereoisomer), 37.4 and 37.1 (major diastereoisomer), 33.6, 33.0, 32.9, 28.5, 28.4, 27.7, 26.6, 26.9, 24.5, 24.4, 23.2, 18.4 and 18.1 (minor diastereoisomer), 16.5 and 16.0 (major diastereoisomer); HRMS calcd for M^+ ($C_{14}H_{27}NO_4$) 273.1933, found 273.1938.

[2*R*,3(4*S*)]-1-Chloro-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (6a). In a 1 L three-necked round-bottomed flask under argon was placed [2*R*,3(4*S*)]-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). K_2CO_3 (12.3 g, 89.7 mmol, 200 mol %), Ph_3P (29.6 g, 164.9 mmol, 250 mol %), and CCl_4 (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): $[\alpha]^{20}_D$ +22.5 (*c* = 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 45 °C) δ 4.15−3.77 (bs, 1H), 3.91 (m, 1H), 3.70 (d, *J* = 8.8 Hz, 1H), 3.44 (bs, 2H), 1.85−1.60 (bs, 3H), 1.55 (m, 3H), 1.46−1.40 (m, 12H), 1.04 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.5, 93.7, 93.2, 80.0, 79.7, 66.9, 66.8, 55.5, 55.5, 51.3, 51.2, 38.0, 37.3, 33.4, 28.4, 27.7 (rotamer), 26.9, 24.5 (rotamer), 23.2, 17.4, 17.1; HRMS calcd for M^+ ($C_{14}H_{26}NO_3Cl$) 291.1575, found 291.1578.

[2*R*,3(4*S*)]-1-Bromo-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (6b). In a 25 mL two-necked round-bottomed flask under argon was placed [2*R*,3(4*S*)]-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propanol (280 mg, 1.03 mmol) of dr = 80:20 in dry THF (10 mL). Ph_3P (538 mg, 2.06 mmol, 200 mol %) and CBr_4 (682 mg, 2.06 mmol, 200 mol %) were added, followed by (^{i}Pr)$_2$EtNH (359 μL, 2.06 mmol, 200 mol %). The mixture was stirred at room temperature for 1 h, diluted with Et_2O (75 mL), and extracted with 0.5 N H_3PO_4 (2 × 25 mL), saturated Na_2CO_3 (25 mL), and brine (25 mL). The acidic and neutral extracts were washed with Et_2O (2 × 25 mL), the combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure. The residue was treated with Hex/AcOEt 4:1 (10 mL), cooled to 0 °C, and filtered. The solid was washed with Hex/AcOEt 4:1 (5 mL), and the combined filtrates were evaporated to dryness under reduced pressure. The residue was filtered through a short pad of silica with the aid of Hex/AcOEt 4:1 (50 mL). The target molecule was obtained as an oil (310 mg, 0.92 mmol, 90%) (two rotamers): $[\alpha]^{20}_D$ = −14.2 (*c* = 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06−3.80 (bs, 1H), 3.92 (m, 1H), 3.73 (dd, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H), 3.52−3.24 (bs, 2H), 2.00−1.60 (bs, 3H), 1.60−1.50 (m, 3H), 1.50−1.40 (m, 12H), 1.08 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.5, 93.7, 93.3, 80.1, 79.7, 66.9, 65.7, 55.5, 55.5, 50.1, 41.4, 40.9, 39.4, 38.9, 38.3, 36.8, 36.5, 33.0, 31.6, 28.5, 28.4, 28.3, 27.8 (rotamer), 26.9, 24.5 (rotamer), 23.2, 20.1, 19.8, 18.5, 18.2; HRMS calcd for M^+ − 71 ($C_{10}H_{19}NO_2Br$) 264.0595, found 264.0566.

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(2*S*,4*R*)-2-Amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-5-chloro-4-methylpentanol (7a). In a 250 mL round-bottomed flask was placed [2*R*,3(4*S*)]-1-chloro-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (3.5 g, 11.9 mmol) of dr = 86:14 in AcOH 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 saturated $NaHCO_3$ (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); $[\alpha]^{20}_D = -17.5$ (c = 0.76, $CHCl_3$) (dr = 86:14); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71, 4.61 (2 bs, 1H), 3.80−3.40 (m, 5H), 2.50−2.20 (bs, 1H), 1.96 (m, 1H), 1.70−1.58 (m, 1H), 1.45 (s, 9H), 1.44−1.30 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 79.7, 65.6, 51.4, 50.5, 35.5, 32.0, 28.3, 18.3 (major diastereoisomer). 156.2, 79.7, 66.5, 51.0, 50.2, 35.8, 32.6, 28.3, 17.5 (minor diastereoisomer); HRMS calcd for M^+ ($C_{11}H_{22}NO_3Cl$) 251.1283, found 251.1280.

(2*S*,4*R*)-2-Amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-5-bromo-4-methylpentanol (7b). Following the same procedure described for **7a**, with [2*R*,3(4*S*)]-1-bromo-2-methyl-3-[*N*-[(1,1-dimethyl)ethoxycarbonyl]-2,2-dimethyl-1,3-oxazolidin-4-yl]propane (280 mg, 0.83 mmol) of dr = 80:20 in AcOH 80% (10 mL), an oil was obtained (225 mg, 0.76 mmol, 91%), which was used without further purification: R_f = 0.35 (silica, Hex/AcOEt 1:1); $[\alpha]^{20}_D = -14.1$ (c = 1.01, $CHCl_3$) (dr = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70, 4.63 (2 bs, 1H), 3.80−3.30 (m, 5H), 2.25−2.15 (bs, 1H), 1.92 (m, 1H), 1.80−1.55 (m, 1H), 1.55−1.32 (m, 10H), 1.08, 1.07 (2d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 79.7, 65.7, 54.5, 50.2, 35.6, 31.6, 28.4, 18.5 (major diastereoisomer). 156.2, 80.2, 66.6, 54.5, 50.6, 36.9, 32.3, 28.4, 17.8 (minor diastereoisomer); HRMS calcd for M^+ ($C_{11}H_{22}NO_3Br$) 295.0778, found 295.0742

(2*S*,4*R*)-2-Amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-1-benzoyloxy-5-chloro-4-methylpentanol (8a). In a 250 mL round-bottomed flask under argon was placed (2*S*,4*R*)-2-amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-5-chloro-4-methylpentanol (4.85 g, 19.3 mmol) of dr = 86:14 in dry pyridine (80 mL). Benzoyl chloride (2.24 mL, 19.3 mmol, 100 mol %) was dropwise added, and the mixture was stirred at room temperature for 2.5 h. The solvent was eliminated under reduced pressure, and the residue was taken up in Et_2O (100 mL), washed with 5% $NaHCO_3$ (2 × 25 mL), 3% HCl (2 × 25 mL), 5% $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent removed under reduced pressure. A cream-colored solid was obtained (6.35 g, 17.8 mmol, 92%), which was recrystallized twice from Hex/Et_2O 4:6 (45 mL) to render **8a** (dr = 95:5) as a white microcrystalline solid: R_f = 0.26 (silica, Hex/AcOEt 4:1); mp = 94.5−95.0 °C; $[\alpha]^{20}_D = -29.7$ (c = 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 4.61 (d, J = 9.6 Hz, 1H), 4.31 (d, J = 4.8 Hz, 2H), 4.11 (m, 1H), 3.65 (dd, J = 10.8 Hz, J = 5.2 Hz, 1H), 3.53 (dd, J = 10.8 Hz, J = 4.8 Hz, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.48−1.37 (m, 1H), 1.41 (s, 9H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 155.4, 133.2, 129.8, 129.7, 128.4, 79.7, 66.9, 50.3, 47.5, 35.8, 31.9, 28.3, 18.3; HPLC (Chiralpak AS, Hex/IPA 95:5, 254 nm, 1.0 mL/min): $t_{R[(2R,4S)-12]}$ = 12.5 min, $t_{R[(2R,4R)-12]}$ = 14.4 min. Anal. Calcd for $C_{18}H_{26}NO_4Cl$: C, 60.75; H, 7.36; N, 3.94. Found: C, 60.43; H, 7.42; N, 3.71.

(2*S*,4*R*)-2-Amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-1-benzoyloxy-5-bromo-4-methylpentanol (8b). Following the same procedure described for **8a**, with (2*S*,4*R*)-2-amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-5-bromo-4-methylpentanol (180 mg, 0.61 mmol) of dr = 80:20 in dry pyridine (3 mL) and benzoyl chloride (71 μL, 0.61 mmol, 100 mol %), a white solid was obtained (229 mg, 0.57 mmol, 94%): R_f = 0.52 (silica, Hex/AcOEt 1:1); mp = 91−92 °C (dr = 80:20); $[\alpha]^{20}_D = -15.3$ (c = 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.60 (d, J = 9.6 Hz, 1H), 4.31 (d, J = 4.8 Hz, 2H), 4.11 (m, 1H), 3.57 (dd, J = 10.0, 4.8 Hz, 1H), 3.45 (dd, J = 10.0, 4.4 Hz, 1H), 1.99 (m, 1H), 1.79 (m, 1H), 1.48−1.38 (m, 1H), 1.41 (s, 9H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 155.4, 133.1, 130.4, 129.7, 128.4, 79.7, 66.9, 47.6, 40.7, 36.9, 31.4, 28.3, 19.3 (major diastereoisomer); HPLC (Chiralpak AS, Hex/IPA 90:10, 254 nm, 1.0 mL/min): $t_{R[(2R,4S)-12]}$ = 9.1 min, $t_{R[(2R,4R)-12]}$ = 10.3 min; HRMS calcd for M^+ ($C_{18}H_{26}NO_4Br$) 399.1039, found 399.1026.

(2*S*,4*R*)-2-(Benzoyloxymethyl)-4-methyl-*N*-[(1,1-dimethyl)ethoxycarbonyl]pyrrolidine (9). In a three-necked round-bottomed flask under argon was placed (2*S*,4*R*)-2-amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-1-benzoyloxy-5-chloro-4-methylpentanol (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_4Cl 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 hexane and then AcOEt: R_f = 0.56 (silica, Hex/AcOEt 4:1); $[\alpha]^{20}_D = -21.3$ (c = 0.4, $CHCl_3$) for dr = 95:5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.50 (m, 1H), 7.41 (m, 2H), 4.52 (m, 1H), 4.10−4.02 (m, 1H), 4.08 (dd, J = 10.0, 4.0 Hz, 1H), 3.87 (dd, J = 11.6, 7.6 Hz, 1H), 2.69 (dd, J = 11.6, 6.0 Hz, 1H), 2.12 (m, 1H), 1.79−1.66 (m, 2H), 1.60 (s, 9H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 161.6, 132.4, 132.0, 129.4, 128.1, 80.9, 68.5, 57.6, 53.8, 38.8, 33.5, 28.2, 19.1; HRMS calcd for M + Na ($C_{18}H_{25}NO_4$ + Na) 342.1681, found 342.1655.

(2*S*,4*R*)-*N*-(9-Fluorenylmethoxycarbonyl)-2-hydroxymethyl-4-methylpyrrolidine (10). (a) In a 100 mL round-bottomed flask was placed (2*S*,4*R*)-2-(benzoyloxymethyl)-4-methyl-*N*-[(1,1-dimethyl)ethoxycarbonyl]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-fluorenylmethylchloroformate (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 analytical 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 (2*S*,4*R*)-2-amino-*N*-[(1,1-dimethyl)ethoxycarbonyl]-1-benzoyloxy-5-chloro-4-methylpentanol (180 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 suspended in 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): $[\alpha]^{20}_D = -19.8$ (c = 1.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (two rotamers) 7.77 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.41 (pt, J = 7.6 Hz, 2H), 7.32 (ptd, J = 7.2, 0.8 Hz, 2H), 4.42 (d, J = 6.8 Hz, 2H), 4.24 (t, J = 6.8 Hz, 1H), 4.15−4.00 (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); ^{13}C 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,

60.2, 59.0, 54.0, 47.2, 36.6, 36.1, 31.6, 30.6, 17.9, 17.6; HRMS calcd for M^+ ($C_{21}H_{23}NO_3$) 337.1672, found 337.1633.

(2*S*,4*R*)-*trans*-*N*-(9-Fluorenylmethoxycarbonyl)-4-methylproline (11). In a 25 mL two-necked round-bottomed flask was placed (2*S*,4*R*)-*N*-(9-fluorenylmethoxycarbonyl)-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 H_2O (3 × 10 mL). The organic layer was extracted with 5% $NaHCO_3$ (4 × 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 $CHCl_3$ (4 × 10 mL), which was washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. An amorphous solid was obtained (75 mg, 0.21 mmol, 59%) (two rotamers): R_f = 0.29 (silica, Hex/AcOEt 1:2); mp = 65−67 °C; $[\alpha]^{20}_D = -49.3$ (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^+ ($C_{21}H_{21}NO_4$) 351.1465, found 351.1395.

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Supporting Information Available: Copies of ^{1}H and ^{13}C 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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