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Asymmetric Hydrogenations for the Synthesis of Boc-Protected 4-Alkylprolinols and Prolines

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The utility of 4-substituted prolinols and their corresponding prolines in peptides, peptidomimetics, and natural products has motivated researchers to find new and efficient routes for their preparation. Herein, we report a general approach to the synthesis of Boc-protected 4-alkylprolinols and prolines via a divergent asymmetric hydrogenation strategy. Intermediate exocyclic olefins were prepared by Wittig-type reactions with ketone **6** and subjected to hydroxyl and sterically directed reductions. The Crabtree catalyst (Ir[COD]PyPCy$_3$PF$_6$) proved to be highly effective in diastereoselective hydrogenations to give trans-substituted pyrrolidines (**9**). Good facial selectivities were also observed in heterogeneous hydrogenations with Raney-nickel to obtain cis-substituted pyrrolidines (**11**). Employing this strategy, we describe the synthesis of novel prolinol and proline-based building blocks for incorporation into biologically relevant peptidomimetics.

Introduction

The proline residue is the only secondary amine among the 20 proteinogenic amino acids and thus exhibits unique conformational properties.[1] Substituted prolines have been used extensively to influence the conformation of the peptide backbone and to induce desired turns in host structures.[2] The amide-bond geometry of the proline *N*-terminus is crucial in the activity and reactivity of a number of peptides[3] and substituted analogues have been shown to affect the energetic barrier to amide-bond rotation and the rotameric equillibrium dramatically.[4] In many cases, proline-induced turns in peptides can be found in close proximity to pharmacophores that are essential for biological recognition.[5] As a result, chimeric residues, featuring biologically relevant substituents, have been utilized to project desired functionalities into defined regions of space.[6] Incorporation of these derivatives into peptides and peptidomimetics continues to be a powerful tool for identifying and elucidating structure−activity relationships.

In addition to the various peptidic applications of functionalized proline residues, substitued 2-hydroxymethylpyrrolidines have featured as valuable precursors and key components of natural products[7] and other biologically active compounds.[8] For these reasons, much effort has been devoted to the design and synthesis of substituted prolinols and their amino acid counterparts. Still, new and facile methods for their diastereoselective preparation are desirable.

We have been particularly interested in the synthesis of 4-substituted prolinols and prolines for use in our peptidomimetic research programs because of their ac-

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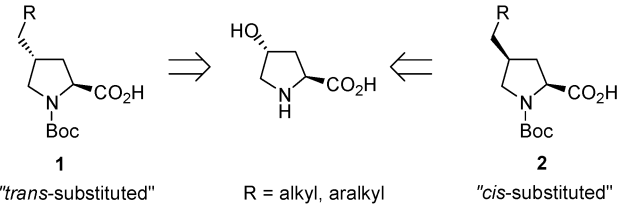

FIGURE 1. *N*-Boc-*cis*- and *trans*-4-alkylprolines.

cessibility from naturally abundant *trans*-4-hydroxproline (Figure 1). Prolines functionalized with the appropriate pharamacophores at the 4-position have found wide application in medicinal chemistry and feature in therapeutic agents such as inhibitors of angiotensin-converting enzyme (ACE)[9] and potential inhibitors of proline dehydrogenase.[10]

The synthesis of a variety of 4-alkylprolines are present in the literature, but many of the methods involve glutamate or pyroglutamate alkylations that meet with varying success depending on the nature of the electrophile.[11] To some degree, substrate-directed hydrogenations have been employed to prepare primarily cis-substituted prolines and pyroglutamates under heterogeneous conditions.[9b,12] Despite these reports, most protocols do not offer an entry into each diastereomer of a given proline derivative, requiring equillibration of epimers, difficult separations, or entirely different synthetic routes to obtain other isomers. There is no general investigation of substrate-directed hydrogenations in the literature for the synthesis of 4-alkylprolinols and prolines.

In the present work, we provide a versatile approach to the preparation of 4-alkylprolinols and prolines via substrate-directed hydrogenations of exocyclic olefin intermediates. In most cases, we have found this strategy offers a diastereoselective entry into each isomer of a given prolinol derivative. This approach has been successfully applied to the synthesis of novel 4-substituted prolinols and prolines for incorporation into biologically relevant peptidomimetics.

Results and Discussion

Recently, we communicated the synthesis of 4-trifluoromethylprolines by asymmetric hydrogenation of the pyrrolines shown in Figure 2.[13] Our divergent approach utilizes the protecting group on the hydroxymethyl substituent to dictate the facial selectivity of the hydrogenations. When protected as the silyl ether, delivery of hydrogen from the less hindered face of the molecule provides primarily the cis-substituted pyrrolidine under heterogeneous conditions. Conversely, reduction of the deprotected hydroxymethyl moeity affords the trans-isomer by homogeneous hydrogenation with the Crabtree catalyst (Ir[COD]PyPCy$_3$PF$_6$).[14] Utilizing the Ir(I) complex, we observed remarkable diastereoselectivity (>99:1 trans:cis) resulting from coordination of the catalyst to the directing hydroxyl group.

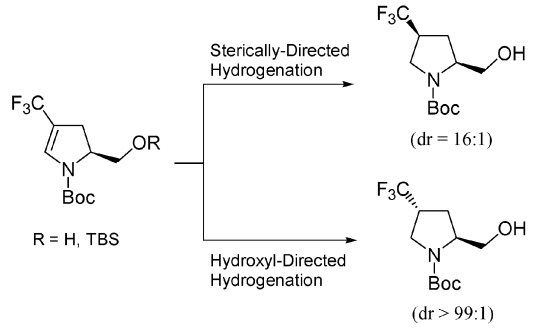

FIGURE 2. Asymmetric Hydrogenations in the Synthesis of *cis*- and *trans*-4-trifluoromethylprolinol.

In an effort to extend this strategy to the synthesis of 4-alkylprolines we sought to prepare a family of structures based on those shown in Figure 1. Beyond our investigation of the described methodology, we desired a facile preparation of novel 4-arylalkyl-substituted prolinols for our somatostatin research programs. Thus, a route amenable to the introduction of a diverse array of aromatic pharmacophores was of particular interest. We envisioned that the most efficient way of arriving at functionalized olefin intermediates for hydrogenation would be Wittig-type reactions with a suitably protected 4-prolinone derivative.

Our synthesis of the target compounds begins with the preparation of the desired ketone intermediate (**6**) starting from *trans*-4-hydroxyproline (Scheme 1). Although the synthesis of the monoprotected diol **5** has been described,[15] we found the ester reduction step to be somewhat inconvenient on a large scale. As an alternative, we chose to Boc-protect the free amino acid and carry out the reduction of a mixed anhydride formed in situ. The anhydride reduction required considerably less solvent than ester reduction with $LiBH_4$ and resulted in a less complicated workup. Selective protection of the primary alcohol with TBDMSCl, as reported previously, gave compound **5**, which was then oxidized with trichloroisocyanuric acid and catalytic TEMPO[16] to afford pyrrolidinone **6** in 88% yield.

Reaction of pyrrolidinone **6** with various triphenylphosphoranes gave the desired olefins **7a**−**d** in good yields.[17]

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(15) For the previously reported preparation and characterization of compound **5** see: Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 13045. Diol **4** has been prepared and characterized as described in: Rajeev, K. G.; Sanjayan, G. J.; Ganesh, K. N. *J. Org. Chem.* **1997**, *62*, 5169.

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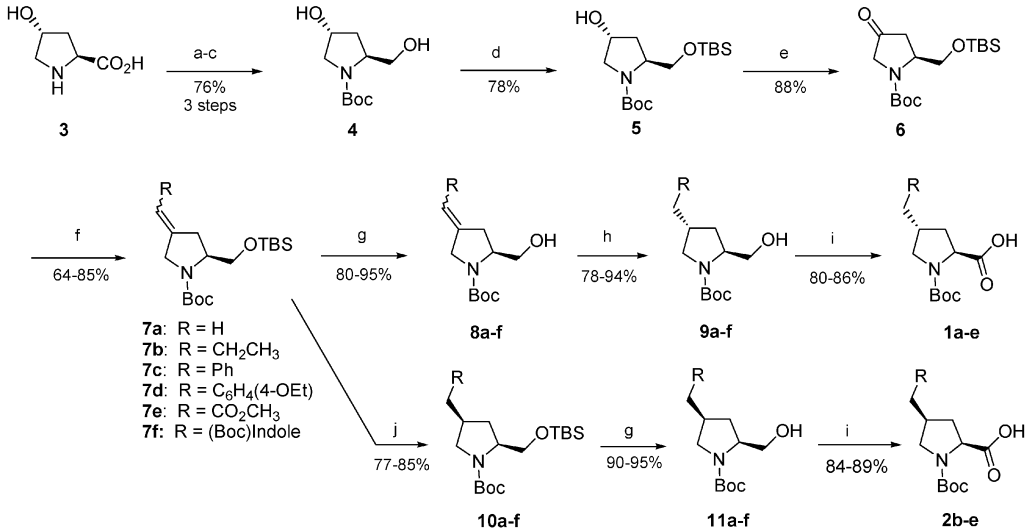
(17) For compounds **7b**−**f**, the *E* and *Z* isomeric products were unresolvable by column chromatography.

SCHEME 1. Synthesis of 4-Alkylprolines 1 and 2[a]



[a] Reagents and conditions: (a) Boc_2O, 10% aq Na_2CO_3/dioxane; (b) isobutyl chlorofomate, NMM, DME; (c) $NaBH_4$ in H_2O; (d) TBDMSCl, TEA, DMAP (cat.), DCM; (e) trichoroisocyanuric acid, TEMPO (cat.), DCM; (f) ylide, THF; (g) 0.5 M TBAF in THF; (h) 3 mol % of $Ir(COD)PyPCy_3PF_6$, H_2, DCM; (i) $NaClO_2$, NaClO (cat.), TEMPO, pH 6.7 phosphate buffer (0.67 M NaH_2PO_4)/MeCN; (j) Raney-Ni, MeOH, H_2.

Likewise, Horner−Wadsworth−Emmons olefination with diethyl methylphosphonoacetate proceeded to give the α-*β* unsaturated ester **7e** as a mixture of *E*- and *Z*-isomers. To obtain **7f,** Boc-indolyltriphenylphosphonium bromide was prepared from the corresponding (3-bromomethyl)indole[18] and reacted with ketone **6** under standard Wittig conditions. As expected, attempts to react **6** with the ylide derived from cyclohexyltriphenylphosphonium bromide failed to give any of the tetrasubstituted olefin. Compounds **7b**−**f** were used in subsequent reactions as mixtures of *E*- and *Z*-isomers. Following hydrogenation and silyl ether deprotection, the diastereomeric ratios for prolinols **9** and **11** were determined by ^{1}H NMR analysis of concentrated samples.[19]

To obtain trans-substituted 4-alkylprolinols, silyl ether deprotection of compounds **7a**−**f** was first carried out to unmask the hydroxyl directing groups. Treatment of the resulting olefins (**8**) with 3 mol % of the Crabtree catalyst, under H_2 atmosphere, gave good to excellent selectivities for the trans-substituted pyrrolidines (Table 1). In most cases, the undesired diastereomers were undetected by ^{1}H NMR. There appeared to be no significant compromise in selectivity in moving from the endocyclic olefin of our trifluoromethylpyrrole derivative to the exocyclic olefins of compounds **8a**−**f**. The range of substrates and consistently high selectivities obtained in these hydrogenations suggest that reduction utilizing the Crabtree catalyst is an attractive method for setting the C4 stereochemistry.

Although homogeneous hydrogenation of **8e** (entry 5) gave good facial selectivity, the diastereomeric ratio was reproducibly lower than that obtained with other substrates. We hypothesize that this is due to competing coordination of the catalyst with the ester side-chain of **8e**, instead of with the directing hydroxyl group. The ability for the Crabtree catalyst to coordinate to a variety of polar functionalities is well-documented[20] and was confirmed, in our case, upon hydrogenation of **7b** under homogeneous conditions. Despite the presence of the TBDMS protecting group, the reduction resulted in a 4:1 diastereomeric ratio in favor of the trans-substituted isomer (**9b**) after silyl ether deprotection.

In our efforts to obtain the cis-substituted pyrrolidines, sterically directed hydrogenations were carried out under a variety of conditions (Table 2). Although Pd/C-catalyzed reduction of the trifluoromethylpyrroline derivative had proceeded with good selectivity, reduction of olefins **7a**−**c** (entries 1−3) exhibited low preference for the cis-substituted products. These results are in agreement with existing reports on the reduction of 4-methyleneproline derivatives with Pd/C.[21] The disparity in selectivity highlights a marked difference between the heterogeneous hydrogenation of endocyclic and exocyclic olefins in similar systems. In the case of **7f**, hydrogenation with Pd/C also resulted in undesired reduction of the C2−C3 indole double bond. After hydrogenation of **7e** in the presence of Mg/MeOH met with low diastereoselectivity, we turned to the less commonly employed Raney-nickel.

In using Raney-nickel as the hydrogenation catalyst we observed an increase in selectivity over Pd/C for the reduction of **7a**−**d**. The diastereomeric ratios obtained in the reduction of **7b**−**f** (entries 2−6) clearly demonstate the utility of Raney-nickel in preparing cis-substituted pyrrolidines. While hydrogenation of **7f** (entry 6) again resulted in over-reduction when left to react for extended

(18) See Supporting Information for the experimental procedure. For the preparation of *N*-Boc-(3-bromomethyl)indole see: Venkatachalam, T. K.; Mzengeza, S.; Diksic, M. *Org. Prep. Proced. Int.* **1993**, *25*, 249.

(19) In comparing the NMR spectra of each diastereomeric pair of prolinols, clearly discernible proton resonances were chosen for integration. Samples for NMR analysis were 100 mg/mL in concentration and consisted of the diastereomeric mixture **9** + **11**. The limit of detection of the NMR at this concentration was determined to be ~1% by doping experiments. Integration values for the impurity peak were determined to be accurate and reproducible to 2.5 mol % by the same experiments. Thus, in cases where the minor diastereomer was <2.5% abundant or undetected, we assume the d.r. to be >40:1.

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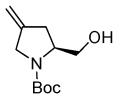
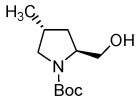
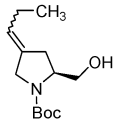
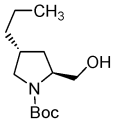
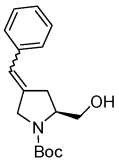
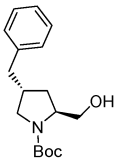
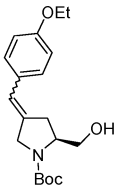
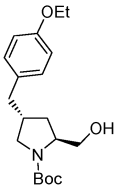
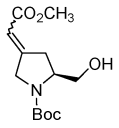
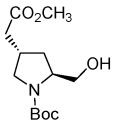
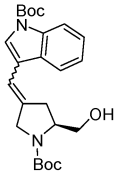
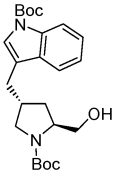
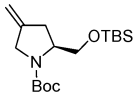
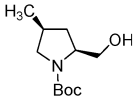
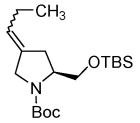
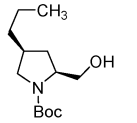
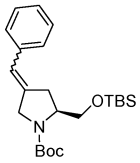
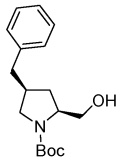
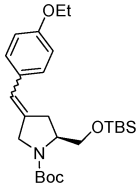
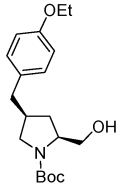
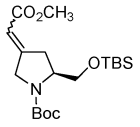
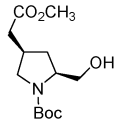
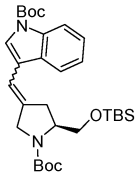
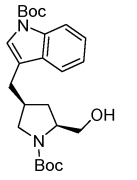
TABLE 1. Diastereoselectivity in Homogeneous Hydrogenations of 8a−f with Ir(COD)PyPCy$_3$PF$_6$

Entry	Olefin	Product	dr [a]	% Y [b]
1	 **8a**	 **9a**	> 40 : 1	90
2	 **8b**	 **9b**	> 40 : 1	95
3	 **8c**	 **9c**	> 40 : 1	93
4	 **8d**	 **9d**	> 40 : 1	90
5	 **8e**	 **9e**	16 : 1	92
6	 **8f**	 **9f**	> 40 : 1	94

[a] Ratio of **9**:**11** determined by ^{1}H NMR. [b] Isolated yield of **9** + **11**.

TABLE 2. Diastereoselectivity of Heterogeneous Hydrogenations of 7a−f

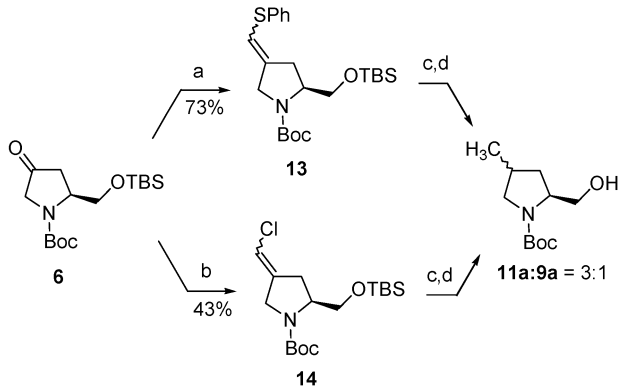
Entry	Olefin	Product [a]	dr [b]	% Y [c]
1	 **7a**	 **11a**	Pd/C (2.5 : 1) Rh/C (3 : 1) Ra-Ni (3 : 1)	74 70 70
2	 **7b**	 **11b**	Pd/C (3 : 1) Ra-Ni (13 : 1)	73 82
3	 **7c**	 **11c**	Pd/C (3 : 1) Ra-Ni (15 : 1)	75 85
4	 **7d**	 **11d**	Pd/C (2.5 : 1) Ra-Ni (16 : 1) [d]	66 63
5	 **7e**	 **11e**	$Mg_{(s)}$ (3 : 1) [e] Ra-Ni (15 : 1)	83 68
6	 **7f**	 **11f**	Ra-Ni (22 : 1) [f]	66

[a] After TBS ether cleavage. [b] Ratio of **11**:**9** determined by ^{1}H NMR. [c] Isolated yield of **9** + **11** over 2 steps. [d] Refluxed in MeOH under Ar. [e] Mg in MeOH. [f] NMR revealed ~ 3% of the over-reduced product.

periods of time (>4 h), reduction of the indole double bond occurred slowly and could be largely avoided with close monitoring; after 45 min a >20:1 cis:trans ratio was obtained with ~3% of the over-reduced species detected by NMR.

Hydrogenation of compound **7a** proved to be resistant to sterically directed selectivity under a variety of conditions (entry 1). Because we believed the terminal nature of the olefin to be responsible for the low selectivity, attempts were made to take advantage of the desulfurization and dehalogenation capabilities of Raney-nickel. Compounds **13** and **14** were prepared and subjected to one-pot olefin reduction and carbon−heteroatom hydrogenolysis conditions (Scheme 2). After silyl ether cleavage, both cases resulted in formation of the desired *N*-Boc-4-methylprolinol product with only 3:1 cis:trans

SCHEME 2. Alternate Route to 11a[a]



[a] Reagents and conditions (see Supporting Information): (a) $Ph_2P(O)CH_2SPh$, *n*-BuLi, THF; (b) $Ph_2P(O)CH_2Cl$, *n*-BuLi, THF; (c) Raney-Ni, MeOH, reflux; (d) 0.5 M TBAF in THF.

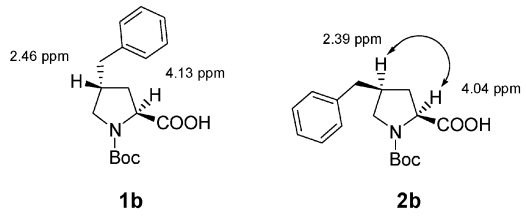


FIGURE 3. NOE correlation from the ROESY spectrum of **2b** (in DMSO-d_6).

selectivity. This suggests that the reactions first lead to intermediate **7a**, which is then hydrogenated in situ.

The overall success of our hydrogenation strategy yielded the cis- and trans-isomers of each 4-arylalkylprolinol (**9c**,**d**,**f** and **11c**,**d**,**f**) in suitable diastereomeric purity. These building blocks are currently being incorporated into nonpeptidic somatostatin mimetics and utilized as key components of novel, bicyclic peptidomimetic scaffolds. In addition, 4-substituted prolines could also be obtained from the corresponding prolinols. Following the hydrogenations, the diastereomeric mixtures **9a**−**e** and **11b**−**e** were oxidized cleanly in the presence of TEMPO, bleach, and sodium chlorite[22] to give the desired amino acid derivatives (**1a**−**e**, **2b**−**e**) in good yields after extractive workup (Scheme 1).

Oxidations of the indolylprolinol derivatives (**9f** and **11f**) by this method were sluggish and resulted in the formation of various side products. Attempts to separate the complex product mixtures were unsuccessful. Despite exploring mild two-step protocols as an alternative, we were unable to obtain the indolylprolines in pure form. We presume that oxidation of the indole ring occurred simultaneously with that of the alcohol.

The configuration of the newly formed C4 stereocenters was confirmed by ROESY experiments performed on compounds **1b** and **2b** (Figure 3). The presence of a strong NOE correlation between the C2 and C4 protons of **2b** established the cis relationship between the substituents of the pyrrolidine ring. No such NOE was observed for compound **1b**, supporting our stereochemical assignments. In addition, we found good agreement in the comparison of ^{1}H NMR, ^{13}C NMR, and optical rotation data for **9a** with that obtained from a previously reported synthesis of *N*-Boc-*trans*-4-methylprolinol.[23] This serves as further evidence that compounds **9** and **11** are the expected products of hydroxy and sterically directed hydrogenations, respectively.

(22) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. *J. Org. Chem.* **1999**, *64*, 2564.

Conclusions

In summary, we have described the first general investigation of hydroxy and sterically directed hydrogenations in the synthesis of 4-alkylprolinols and prolines. The use of the Crabtree catalyst for hydroxyl-directed hydrogenations has proven to be convenient and effective for the preparation of *trans*-4-alkylprolinols. High diastereoselectivities and a tolerance for various olefins make homogeneous hydrogenation a viable alternative to the alkylation of pyroglutamate derivates. Only in the case of ester-substituted olefin **7e** did we observe a modest drop in selectivity. To the best of our knowledge, the described syntheses of trans-substituted prolines **1a**−**e** are among the most diastereoselective preparations to date.

Investigation of heterogeneous hydrogenations revealed that Raney-nickel generally gives rise to higher facial selectivities than other commonly used catalysts and is useful for obtaining some cis-substituted 4-alkylprolinols. Further investigation into the scope and utility of Raney-nickel in this capacity is warranted.

Last, we have applied this approach to the synthesis of novel 4-arylalkylprolinols and prolines for use in our peptidomimetic research program. The results described herein will find wide application in the synthesis of novel pyrrolidine-based building blocks.

Experimental Section

General. Unless otherwise indicated, all compounds and reagents were purchased from commercial suppliers and used without further purification. Proton and carbon nuclear magnetic resonance spectra are recorded at either 300 or 400 MHz in $CDCl_3$ and internally referenced to residual $CHCl_3$. All chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Electrospray and MALDI high-resolution mass spectra were obtained from the Scripps Research Institute Mass Spectrometry Facility. Optical rotations were measured with use of a 1.00 dm path length cell.

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-hydroxy-2-hydroxymethylpyrrolidine (4). A solution of *trans*-4-hydroxyproline (10.0 g, 76.2 mmol) in 80 mL of 10% aq Na_2CO_3 was added dropwise to a solution of Boc-anhydride (15.8 g, 72.4 mmol) dissolved in 40 mL of 10:1 THF/dioxane. The mixture was stirred for 18 h and the THF removed in vacuo. The mixture was then washed with Et_2O, cooled to 0 °C, and acidified carefully to pH 3 with concentrated HCl. The aqueous layer was extracted with EtOAc and the organic solution dried (Na_2SO_4) and concentrated to a white solid. The solid was then dissolved in 70 mL of 1,2-DME, cooled to −20 °C, and treated with 9.51 mL (72.4 mmol) of isobutyl chloroformate and 7.96 mL (72.4 mmol) of NMM. The reaction was stirred at −20 °C for 30 min and the resulting white suspension was rapidly filtered to remove the precipitate. After re-cooling the filtrate, a solution of $NaBH_4$ in 60 mL of H_2O was added to the reaction dropwise via an addition funnel and the reaction was stirred for 20 min. The DCE was then removed in vacuo and the residue was diluted with 1 M NaOH, extracted with EtOAc,

(23) Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron* **1998**, *54*, 15759.

dried (Mg_2SO_4), and concentrated. Purification by silica gel chromatography (95% EtOAc/Hex) afforded 11.96 g of **4** as a white solid (76%, three steps). The ^{1}H NMR and optical rotation data we obtained were in agreement with the values previously reported by Rajeev et al. (see ref 15). This compound was converted into the mono-TBS ether by the procedure described by Aoyagi et al. (ref 15).

(*S*)- 2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonylpyrrolidin-4-one (6). A solution of alcohol **5** (3.36 g, 10.0 mmol) in 50 mL of DCM was cooled to 0 °C and treated with 2.32 g (10.0 mmol) of trichloroisocyanuric acid. After 5 min, 156 mg (1.0 mmol) of TEMPO was added and the reaction was stirred at 0 °C for 1 h. The mixture was then diluted with DCM and washed with saturated aqueous $NaHCO_3$, 1 M HCl, and brine. Drying over $MgSO_4$ and concentration in vacuo gave the crude residue, which was purified by silica gel chromatography (20% EtOAc/Hex eluent) to afford 2.91 g of **6** as a colorless oil (88%). Molecular formula $C_{16}H_{31}NO_4Si$. Molecular weight 329.51; R_f 0.45 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 and 4.25 (2d, J = 9.6 Hz, 1H, rotamers), 4.03 (d, J = 10.0 Hz, 1H), 3.88−3.74 (m, 1H), 3.67−3.49 (m, 2H), 2.69−2.58 (m, 1H), 2.43 and 2.37 (2s, 1H, rotamers), 1.46 and 1.45 (2s, 9H, rotamers), 0.81 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 156.7, 80.1, 65.5, 64.9, 55.7, 55.2, 54.0, 53.4, 40.8, 40.2, 28.4, 25.7, 18.1, −3.4, −5.5, −5.5. ES-MS: 330 $[MH]^+$, 352 $[MNa]^+$. $[\alpha]^{20}_D$ +2.5 (*c* 1.0, $CHCl_3$).

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonyl-4-methylenepyrrolidine (7a). A suspension of methyltriphenylphosphonium bromide (2.710 g, 7.59 mmol) in 15 mL of dry THF was placed under Ar and treated with 851 mg (7.59 mmol) of potassium *tert*-butoxide. The mixture quickly became bright yellow and was stirred at room temperature for 1 h. A solution of ketone **6** (1.00 g, 3.04 mmol) in 10 mL of dry THF was then added to the mixture via cannula and stirred until no more starting material was being consumed (1−4 h). The mixture was poured into water, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by silica gel chromatography (5% EtOAc/Hex eluent) to afford 776 mg of **7a** as a colorless oil (78%). Molecular formula $C_{17}H_{33}NO_3Si$. Molecular weight 327.54; R_f 0.33 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93−4.96 (m, 2H), 4.05−3.89 (m, 2H), 3.80 and 3.76 (2d, 1H, J = 2.4 Hz, rotamers), 3.60 and 3.58 (2d, 1H, J = 3.6 Hz, isomers), 3.57 and 3.33 (2t, 1H, J = 8.8 Hz, rotamers), 2.58 (m, 2H), 1.42 (s, 9H), 0.83 (s, 9H), −0.01 (m, 6H). ES-MS: 350 $[MNa]^+$. $[\alpha]^{20}_D$ −20.0 (*c* 1.0, $CHCl_3$).

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonyl-4-propylenepyrrolidine (7b). Following the procedure described for the preparation of **7a**, a suspension of propyltriphenylphosphonium bromide (1.17 g, 3.04 mmol) in 5 mL of dry THF was treated with 341 mg (3.04 mmol) of potassium *tert*-butoxide, stirred 1 h, then treated with a solution of ketone **6** (400 mg, 1.214 mmol) in 5 mL of dry THF. After workup the crude material was purified by silica gel chromatography (5% EtOAc/Hex eluent) to afford 306 mg of colorless oil **7b** as a mixture of *E* and *Z* isomers (71%). Molecular formula $C_{19}H_{37}NO_3Si$. Molecular weight 355.56; R_f 0.49 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (br s, 1H), 3.96 (d, 1H, J = 14.8 Hz), 3.86 (m, 2H), 3.34 (m, 1H), 2.57 and 2.49 (2m, 2H), 1.94 (m, 2H), 1.46 (s, 9H), 0.94 (m, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ES-MS: 378 $[MNa]^+$.

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonyl-4-(phenyl)methylenepyrrolidine (7c). Following the procedure described for the preparation of **7a**, a suspension of benzyltriphenylphosphonium bromide (3.29 g, 7.59 mmol) in 25 mL of dry THF was treated with 851 mg (7.59 mmol) of potassium *tert*-butoxide, stirred 1 h, then treated with a solution of ketone **6** (1.00 g, 3.04 mmol) in 10 mL of dry THF. After workup the crude material was purified by silica gel chromatography (5% EtOAc/Hex eluent) to afford 860 mg of colorless oil **7b** as a mixture of *E* and *Z* isomers (70%). Molecular formula $C_{23}H_{37}NO_3Si$. Molecular weight 403.64; R_f 0.35 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.10 (m, 5H), 6.38 (2br s, 1H), 4.22−3.87 (m, 3H), 3.71−3.32 (2m, 2H), 2.97−2.68 (m, 2H), 1.47 (s, 9H), 0.84 and 0.78 (2s, 9H), 0.02−0.00 (M, 6H). ES-MS: 426 $[MNa]^+$.

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonyl-4-(4′-ethoxyphenyl)methylenepyrrolidine (7d). Following the procedure described for the preparation of **7a**, a suspension of (4-ethoxy)benzyltriphenylphosphonium bromide (1.81 g, 3.79 mmol) in 5 mL of dry THF was treated with 426 mg (3.79 mmol) of potassium *tert*-butoxide, stirred 1 h, then treated with a solution of ketone **6** (500 mg, 1.517 mmol) in 5 mL of dry THF. After workup the crude material was purified by silica gel chromatography (5% EtOAc/Hex eluent) to afford 468 mg of colorless oil **7d** as a mixture of *E* and *Z* isomers (69%). Molecular formula $C_{25}H_{41}NO_4Si$. Molecular weight 447.69; R_f 0.38 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−6.82 (m, 4H), 6.33 (br s, 1H), 4.38−4.00 (complex m, 3H), 4.02 (m, 2H), 3.66−3.37 (m, 2H), 2.93−2.73 (m, 1H), 1.50 (s, 9H), 1.43 (m, 3H), 0.88 and 0.83 (2s, 9H), 0.52 and −0.25 (2d, 6H, J = 3.2 H). ES-MS: 448 $[MH]^+$, 446 $[M-H]^-$, 470 $[MNa]^+$.

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*-*tert*-butyloxycarbonyl-4-(carboxymethyl)methylenepyrrolidine (7e). Following the procedure described for the preparation of **7a**, a solution of methyldiethylphosphonoacetate (280 μL, 1.52 mmol) in 5 mL of dry THF was placed under Ar and treated with 61 mg (1.52 mmol) of 60% NaH (dispersion in mineral oil) followed by addition of ketone **6** (250 mg, 759 μmol) in 5 mL of dry THF. After workup the crude material was purified by silica gel chromatography (15% EtOAc/Hex eluent) to afford 249 mg of pale yellow oil **7c** as a mixture of *E* and *Z* isomers (85%). Molecular formula $C_{19}H_{35}NO_5Si$. Molecular weight 385.58; R_f 0.44 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 and 5.74 (2s, 1H, isomers), 4.46 (s, 1H), 4.27−3.75 (m, 2H), 3.71 and 3.70 (2s, 3H), 3.65 (m, 1H), 3.32 (m, 1H), 3.00−2.85 (m, 1H), 2.73−2.68 (m, 1H), 1.47 (s, 9H), 0.83 (s, 9H), 0.00 (s, 6H). ES-MS: 386 $[MH]^+$, 408 $[MNa]^+$.

(*S*)-2-*tert*-Butyldimethylsilyloxymethyl-*N*,*N*′-di-*tert*-butyloxycarbonyl-4-(3′-indolyl)methylenepyrrolidine (7f). Following the procedure described for the preparation of **7a**, a suspension of (*N*-Boc)-indolyltriphenylphosphonium bromide (1.22 g, 2.12 mmol) in 3 mL of dry THF was placed under Ar and treated with 244 mg (2.18 mmol) of potassium *tert*-butoxide followed by addition of ketone **6** (350 mg, 1.06 mmol) in 2 mL of dry THF. After workup, purification by silica gel chromatography (5% EtOAc/Hex eluent) gave 369 mg of white foam **7d** as a mixture of *E* and *Z* isomers (64%). Molecular formula $C_{30}H_{46}N_2O_5Si$. Molecular weight 542.31; R_f 0.42 (10% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (t, 1H, J = 8.1 Hz), 7.59−7.24 (m, 4H), 6.52 and 6.51 (2br s, 1H), 4.29−4.03 (m, 3H), 3.71−3.35 (m, 2H), 2.99−2.80 (m, 2H), 1.69 and 1.68 (2s, 9H), 1.51 (s, 9H), 0.91 (m, 9H), −0.03 (m, 6H). ES-MS: 543 $[MH]^+$, 565 $[MNa]^+$.

General Procedure for Silyl Ether Deprotection and Homogeneous Olefin Hydrogenation: Preparation of *N*-Boc-*trans*-4-alkylprolinols (9a−f). The appropriate olefin was treated with 2.0 equiv of a 0.5 M solution of TBAF in THF at room temperature. After being stirred for 6 h, the solution was concentrated in vacuo and the crude oil was purified by silica gel chromatography (note: care must be taken to remove residual TBAF as we found that it can effectively diminish or destroy the activity of the catalyst in the next step). The alcohol was then taken up in dry DCM (0.2 M substrate concentration) and treated with 3 mol % of $Ir(COD)PyPCy_3PF_6$. The solution was promptly put under H_2 atmosphere (1 atm), stirred at room temperature for 18 h, and concentrated to give an orange oil. The products were purified as described below to isolate the isomeric mixture (**9** + **11**) for NMR analysis. In each case, chemical shifts are given for the major diastereomer.

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-methylpyrrolidine (9a). Yield of **8a** (after silyl ether depro-

tection): 85%. After hydrogenation the residue was purified by silica gel chromatography (50% EtOAc/Hex eluent) to give a pale orange oil (90%, dr >40:1). Molecular formula $C_{11}H_{21}NO_3$. Molecular weight 215.29; R_f 0.33 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 3.95 (m, 1H), 3.58−3.57 (m, 2H), 3.42 (dd, 1H, J_a = 10.0 Hz, J_b = 6.4 Hz), 2.88 (t, J = 8.4 Hz, 1H), 2.30 (m, 1H), 1.65 (m, 1H), 1.55 (m, 1H), 1.41 (s, 9H), 0.96 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 80.3, 67.8, 60.0, 54.7, 36.9, 31.9, 28.7, 18.1. ES-MS: 216 $[MH]^+$. $[\alpha]^{20}_D$ −38.2 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-propylpyrrolidine (9b). Yield of **8b** (after silyl ether deprotection): 80%. After hydrogenation the residue was purified by silica gel chromatography (50% EtOAc/Hex eluent) to give a pale orange oil (95%, dr >40:1). Molecular formula $C_{13}H_{25}NO_3$. Molecular weight 243.35; R_f 0.22 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (br s, 1H), 3.98 (br s, 1H), 3.61−3.42 (m, 3H), 2.91 (m, 1H), 2.15 (m, 1H), 1.69 (m, 1H), 1.61 (m, 1H), 1.43 (s, 9H), 1.28 (m, 4H), 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 80.0, 67.8, 59.5, 52.8, 36.9, 35.9, 34.5, 28.4, 21.2, 14.2. ES-MS: 244 $[MH]^+$. $[\alpha]^{20}_D$ −30.0 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-benzyl-2-hydroxymethylpyrrolidine (9c). Yield of **8c** (after silyl ether deprotection): 81%. After hydrogenation the residue was purified by silica gel chromatography (50% EtOAc/Hex eluent) to give a colorless oil (93%, dr >40:1). Molecular formula $C_{17}H_{25}NO_3$. Molecular weight 291.39; R_f 0.42 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.08 (m, 5H), 4.54 (br s, 1H), 4.05 (m, 1H), 3.57 (m, 2H), 3.39 (dd, 1H, J_a = 10.4 Hz, J_b = 6.4 Hz), 3.13 (dd, 1H, J_a = 11.2 Hz, J_b = 7.2 Hz), 2.61 (m, 2H), 2.43 (s, 1H, J = 7.6 Hz), 1.83−1.60 (complex m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 140.1, 128.8, 128.4, 126.4, 80.5, 67.8, 59.7, 52.6, 39.8, 39.6, 34.5, 28.8. ES-MS: 292 $[MH^+]$, 314 $[MNa]^+$. $[\alpha]^{20}_D$ −13.6 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-(4′-ethoxy)benzyl-2-hydroxymethylpyrrolidine (9d). Yield of **8d** (after silyl ether deprotection): 77%. After hydrogenation the residue was purified by silica gel chromatography (25% EtOAc/Hex eluent) to give a pale orange oil (90%, dr >40:1). Molecular formula $C_{19}H_{29}NO_4$. Molecular weight 335.44; R_f 0.16 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, 2H, J = 8.0 Hz), 6.83 (d, 2H, J = 8.4 Hz), 4.52 (br s, 1H), 4.00 (m, 3H), 3.58 (m, 2H), 3.38 (dd, 1H, J_a = 10.4 Hz, J_b = 6.8 Hz), 3.12 (dd, 1H, J_a = 11.2 Hz, J_b = 7.2 Hz), 2.55 (d, 2H, J = 6.4 Hz), 2.39 (m, 1H), 1.74−1.62, (m, 2H), 1.46 (s, 9H), 1.40 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 131.7, 129.3, 114.4, 114.3, 80.6, 67.8, 63.3, 59.4, 52.2, 39.1, 38.3, 34.1, 28.5, 14.9. ES-MS: 336 $[MH]^+$, 358 $[MNa]^+$. $[\alpha]^{20}_D$ −12.9 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-(methoxycarbonyl)methylpyrrolidine (9e). Yield of **11e** (after silyl ether deprotection): 80%. After hydrogenation the residue was purified by silica gel chromatography (50% EtOAc/Hex eluent) to give an pale yellow oil (92%, dr 16:1). Molecular formula $C_{13}H_{23}NO_5$. Molecular weight 273.33; R_f 0.20 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (2br s, 1H), 3.94 (m, 1H), 3.60 (s, 3H), 3.53 (m, 3H), 2.96 (t, 1H, J = 8.0 Hz), 2.54 (m, 1H), 2.30 (m, 2H), 1.78 (m, 1H), 1.63 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.6, 80.5, 67.1, 59.4, 52.6, 51.9, 37.9, 35.4, 34.4, 33.9, 28.8. ES-MS: 274 $[MH]^+$, 296 $[MNa]^+$. $[\alpha]^{20}_D$ −20.2 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*,*N*′-Di-*tert*-butyloxycarbonyl-2-hydroxymethyl-4-(3′-indolylmethyl)pyrrolidine (9f). Yield of **8f** (after silyl ether deprotection): 83%. After hydrogenation the residue was purified by silica gel chromatography (25% EtOAc/Hex eluent) to give a white foam (94%, dr >40:1). Molecular formula $C_{24}H_{34}N_2O_5$. Molecular weight 430.55; R_f 0.24 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.49−7.21 (m, 4H), 4.58 (m, 1H), 4.09 (m, 1H), 3.59 (m, 2H), 3.45 (dd, 1H, J_a = 10.4 Hz, J_b = 6.4 Hz), 3.20 (dd, 1H, J_a = 10.0 Hz, J_b = 6.4 Hz), 2.70 and 2.68 (2s, 2H, rotamers), 2.58 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.66 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.4, 135.1, 130.1, 124.1, 122.7, 122.2, 118.6, 115.1, 83.4, 80.2, 67.5, 64.7, 59.3, 52.4, 37.1, 34.8, 28.4, 28.2. ES-MS: 431 $[MH]^+$, 453 $[MNa]^+$. $[\alpha]^{20}_D$ −12.4 (*c* 1.0, $CHCl_3$).

General Procedure for Raney-Nickel Olefin Hydrogenation and Silyl Ether Deprotection: Preparation of *N*-Boc-*cis*-4-alkylprolinols (11b−f). To a 0.1 M solution of the appropriate olefin in MeOH was added Raney-Ni (10:1 w/w Raney-Ni/olefin) that had been washed successively with MeOH. The mixture was placed under H_2 atmosphere (1 atm) and stirred at room temperature for 18 h (note: the mixture was refluxed in the case of **7d**; reaction time was 45 min in the case of **7f**). The mixture was then filtered through a pad of Celite and rinsed successively with DCM (**Caution!** the filter cake should not be allowed to dry during filtration as Raney-nickel can rapidly ignite). The organic solution was dried over $MgSO_4$, concentrated in vacuo, and treated with 2 equiv of 0.5 M TBAF solution in THF. After being stirred at room temperature for 6 h, the solution was concentrated to give a bronze oil. The products were purified as described below to isolate the isomeric mixture (**9** + **11**) for NMR analysis. In each case, chemical shifts are given for the major diastereomer.

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-propylpyrrolidine (11b). Yield of **10b** (after hydrogenation): 87%. After silyl ether deprotection the residue was purified by silica gel column (20% EtOAc/Hex eluent) to give a colorless oil (94%, dr 13:1). Molecular formula $C_{13}H_{25}NO_3$. Molecular weight 243.35; R_f 0.26 (25% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (br s, 1H), 3.85 (m, 1H), 3.58 (m, 3H), 2.72 (t, 1H, J = 10.8 Hz), 2.10 (m, 1H), 1.97 (m, 1H), 1.41 (s, 9H), 1.26 (m, 4H), 0.85 (m, 1H), 0.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 80.0, 67.6, 61.0, 53.1, 37.1, 35.5, 35.0, 28.5, 21.2, 15.3. ES-MS: 244 $[MH^+]$ calcd, 242 $[M - H]^-$, 266 $[MNa^+]$. $[\alpha]^{20}_D$ −43.5 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-benzyl-2-hydroxymethylpyrrolidine (11c). Yield of **10c** (after hydrogenation): 95%. After silyl ether deprotection the residue was purified by silica gel chromatography (40% EtOAc/Hex eluent) to give a colorless oil (89%, dr 16:1). Molecular formula $C_{17}H_{25}NO_3$. Molecular weight 291.39; R_f 0.44 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.12 (m, 5H), 5.36 (br s, 1H), 3.89 (q, J = 8.0 Hz, 1H), 3.68−3.55 (m, 3H), 2.92 (t, J = 10.4 Hz, 1H), 2.72−2.55 (m, 2H), 2.31 (m, 1H), 2.06 (m, 1H), 1.47 (s, 9H), 1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 140.0, 129.0, 128.4, 128.6, 126.4, 80.6, 67.9, 61.5, 53.3, 39.5, 35.6, 28.8. ES-MS: 292 $[MH^+]$, 314 $[MNa^+]$. $[\alpha]^{20}_D$ −65.1 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-(4′-ethoxy)benzyl-2-hydroxymethylpyrrolidine (11d). Yield of **10d** (after hydrogenation): 80%. After silyl ether deprotection the residue was purified by silica gel chromatography (25% EtOAc/Hex eluent) to give a colorless oil (79%, dr 16:1). Molecular formula $C_{19}H_{29}NO_4$. Molecular weight 335.44; R_f 0.20 (30% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, 2H, J = 7.6 Hz), 6.81 (d, 2H, J = 8.4 Hz), 5.29 (d, 1H, J = 8.0 Hz), 4.01 (q, 2H, J = 6.8 Hz), 3.90 (q, 1H, J = 8.0 Hz), 3.62 (m, 3H), 2.91 (t, 1H, J = 10.0 Hz), 2.66−2.55 (m, 2H), 2.28 (m, 1H), 2.08 (m, 1H), 1.48 and 1.46 (2s, 9H, rotamers), 1.41 (t, 3H, J = 7.2 Hz), 1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 131.8, 129.5, 129.3, 114.2, 80.3, 67.7, 63.3, 61.2, 52.9, 39.3, 38.1, 35.2, 28.4, 14.9. ES-MS: 336 $[MH]^+$, 358 $[MNa]^+$. $[\alpha]^{20}_D$ −33.8 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-4-(methoxycarbonyl)methylpyrrolidine (11e). Yield of **8e** (after hydrogenation): 85%. After silyl ether deprotection the residue was purified by silica gel chromatography (50% EtOAc/Hex eluent) to give a colorless oil (80%, dr 15:1). Molecular formula $C_{13}H_{23}NO_5$. Molecular weight 273.33; R_f 0.15 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br s, 1H), 3.93 (q, 1H, J = 7.2 Hz), 3.78 (t, 1H, J = 8.0 Hz), 3.65 (s, 3H), 3.56 (m, 1H), 2.84 (t, 1H, J = 10.4 Hz), 2.45 (m, 1H), 2.36 (m, 2H), 2.21 (m, 1H), 1.43 (s, 9H), 1.15 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 172.0, 157.0, 80.4, 67.3, 60.9, 52.6, 51.6, 37.0, 35.1, 33.6, 28.4. ES-MS: 274 $[MH]^+$, 296 $[MNa]^+$. $[\alpha]^{20}_D$ −32.3 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*,*N*′-Di-*tert*-butyloxycarbonyl-2-hydroxymethyl-4-(3′-indolylmethyl)pyrrolidine (11f). Yield of **8f** (after hydrogenation): 84%. After silyl ether deprotection the residue was purified by silica gel chromatography (20% EtOAc/Hex eluent) to give a colorless oil (78%, dr 22:1. Molecular formula $C_{24}H_{34}N_2O_5$. Molecular weight 430.55; R_f 0.21 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 7.5 Hz), 7.20−7.50 (m, 4H), 5.30 (br s, 1H), 3.91 (m, 1H), 3.76−3.55 (m, 3H), 2.95 (m, 1H), 2.73 (m, 2H), 2.49 (m, 1H), 2.16 (m, 1H), 1.66 (s, 9H), 1.56 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 149.8, 135.6, 130.5, 124.6, 123.0, 122.6, 119.0, 115.5, 83.8, 80.7, 68.0, 61.5, 53.5, 37.6, 35.9, 31.9, 28.8, 28.4, 23.0, 21.0, 14.5. ES-MS: 431 $[MH]^+$, found 431. $[\alpha]^{20}_D$ −28.3 (*c* 1.0, $CHCl_3$).

Representative Procedure for Oxidation of *N*-Boc-4-alkylprolinols: Preparation of *N*-Boc-4-alkylprolines (1a−e and 2b−e). Two oxidant solutions were prepared prior to carrying out the reaction. The first consisted of 84 mg (742 μmol) of 80% $NaClO_2$ dissolved in 0.4 mL of water (∼2 M). The second was comprised of 22 μL of bleach diluted with 0.4 mL of water. The desired alcohol (371 μmol) was dissolved in 5 mL of a 3:2 mixture of MeCN:NaH_2PO_4 buffer (pH 6.6, 0.67 M) and warmed to 45 °C. The reaction mixture was treated with 6 mg (37 μmol) of TEMPO followed by the dropwise, simultaneous addition (over 1 h) of the two oxidant solutions described above. Stirring was maintained at 45 °C until TLC showed complete consumption of starting material (usually 24 h). The reaction was cooled to room temperature and a saturated Na_2SO_3 solution was added dropwise until the reaction mixture became colorless. The MeCN was removed in vacuo and the resulting mixture basified to pH >10 with 1 M NaOH and washed twice with Et_2O. The solution was then carefully acidified with 1 M HCl to pH <3 and extracted 6 times with Et_2O. The organic layers were dried over Na_2SO_4 and concentrated to give the carboxylic acid products.

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-methylproline (1a). Yield: colorless oil (84%, dr >40:1). Molecular formula $C_{11}H_{19}NO_4$. Molecular weight 229.28; R_f 0.42 (75% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (br s, 1H), 4.36 and 4.24 (2d, 1H, J = 8.0 Hz, rotamers), 3.71 and 3.54 (2dd, 1H, J_a = 10.4 Hz, J_b = 7.6 Hz, rotamers), 2.83−2.96 (2t, 1H, J = 8.8 Hz, rotamers), 2.35 (m, 1H), 2.09−2.29 (m, 1H), 1.72−1.89 (m, 1H), 1.48 and 1.38 (2s, 9H, rotamers), 1.00 and 1.02 (2s, 3H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 175.4, 155.7, 153.6, 81.0, 80.2, 59.2, 53.7, 59.0, 38.3, 36.6, 32.1, 31.2, 29.7, 28.4, 17.4, 17.1; HR-FTMS $[MNa]^+$ calcd for **1a** 252.1206, found 252.1200 $[MNa]^+$; $[\alpha]^{20}_D$ −74.7 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-propylproline (1b). Yield: white solid (81%, dr >40:1). Molecular formula $C_{13}H_{23}NO_4$. Molecular weight 257.33; R_f 0.23 (50% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 4.38 and 4.26 (2d, 1H, J = 7.2 Hz, rotamers), 3.73 and 3.58 (2dd, 1H, J_a = 10.0 Hz, J_b = 8.4 Hz, rotamers), 2.94 and 2.84 (2t, 1H, J = 9.6 Hz, rotamers), 2.33−2.25 (m, 2H), 1.71−1.67 (m, 1H), 1.46−1.23 (m, 14H), 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 178.9, 175.8, 156.2, 153.9, 81.4, 80.5, 59.4, 52.6, 52.0, 35.4, 35.3, 35.0, 30.0, 28.7, 28.2, 21.5, 14.5; HR-FTMS $[MNa]^+$ calcd for **1b** 280.1519, found 280.1518; $[\alpha]^{20}_D$ −33.7 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-4-Benzyl-*N*-*tert*-butyloxycarbonylproline (1c). Yield: colorless oil (86%, dr >40:1). Molecular formula $C_{17}H_{23}NO_4$. Molecular weight 305.37; R_f 0.48 (75% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (br s, 1H), 7.31−7.13 (m, 5H), 4.40 and 4.26 (2d, 1H, J = 7.2 Hz, rotamers), 3.71 and 3.50 (2dd, 1H, J_a = 10.4 Hz, J_b = 7.2 Hz), 3.02 and 3.15 (2t, 1H, J = 10.0 Hz, rotamers), 2.55−2.71 (m, 3H), 1.81−2.30 (m, 2H), 1.44 and 1.39 (2s, 9H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 175.5, 156.0, 153.8, 139.6, 128.7, 126.5, 81.5, 80.6, 72.4, 59.3, 59.1, 52.2, 51.7, 39.5, 38.7, 37.9, 36.4, 34.8, 29.5, 28.7, 28.3, 20.9, 15.8; HR-FTMS $[MNa]^+$ calcd for **1c** 328.1519, found 328.1529; $[\alpha]^{20}_D$ −36.7 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-(4′-ethoxy)benzylproline (1d). Yield: white solid (80%, dr >40:1). Molecular formula $C_{19}H_{27}NO_5$. Molecular weight 349.43; R_f 0.16 (50% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (br s, 1H), 7.06 (m, 2H), 6.70 (m, 2H), 4.39 and 4.26 (2d, 1H, J = 5.7 Hz, rotamers), 4.02 (m, 2H), 3.67 and 3.50 (2m, 1H), 3.11 and 3.03 (2m, 1H, J = 6.9 Hz, rotamers), 2.60 (m, 3H), 2.34 and 2.04 (2m, 1H), 2.05 and 1.82 (2m, 1H), 1.47−1.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 175.0, 157.5, 155.6, 131.6, 129.7, 114.6, 81.7, 80.5, 63.7, 59.0, 52.2, 51.6, 39.7, 38.4, 36.4, 34.5, 28.7, 21.6, 15.2; HR-FTMS $[MNa]^+$ calcd for **1d** 372.1781, found 372.1791; $[\alpha]^{20}_D$ −19.6 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-(methoxycarbonyl)methylproline (1e). Yield: colorless oil (84%, dr 16:1). Molecular formula $C_{13}H_{21}NO_6$. Molecular weight 287.31; R_f 0.46 (75% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 4.37 and 4.24 (2d, 1H, J = 8.4 Hz, rotamers), 3.76 (m, 1H), 3.65 and 3.68 (2s, 3H, rotamers), 3.03 (m, 1H), 2.67 (m, 1H), 2.41 (m, 2H), 2.24 (m, 1H), 1.80−1.97 (m, 1H), 1.37 and 1.42 (2s, 9H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 175.1, 172.0, 155.3, 153.6, 81.1, 80.5, 58.6, 51.8, 51.1, 37.0, 36.0, 34.6, 33.7, 32.9, 28.3; HR-FTMS $[MNa]^+$ calcd for **1e** 310.1261, found 310.1253; $[\alpha]^{20}_D$ −24.5 (*c* 1.0, MeOH).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-propylproline (2b). Yield: white solid (85%, dr 13:1). Molecular formula $C_{13}H_{23}NO_4$. Molecular weight 257.33; R_f 0.24 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H), 4.26 and 4.17 (2s, 1H, rotamers, J = 8.0 Hz), 3.78 and 3.66 (2dd, 1H, rotamers,, J_a = 10.4 Hz, J_b = 8.0 Hz), 2.96 (m, 1H), 2.43 (m, 1H), 2.13 (m, 1H), 1.71−1.55 (m, 2H), 1.48 and 1.39 (2s, 9H, rotamers), 1.35 (m, 4H), 0.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 153.4, 80.7, 80.3, 59.3, 52.5, 51.9, 38.2, 37.8, 37.2, 35.6, 34.8, 28.4, 28.2, 21.3, 14.4; HR-FTMS $[MNa]^+$ calcd for **2b** 280.1519, found 280.1525; $[\alpha]^{20}_D$ −86.8 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-4-Benzyl-*N*-*tert*-butyloxycarbonylproline (2c). Yield: colorless oil (89%, dr 15:1). Molecular formula $C_{17}H_{23}NO_4$. Molecular weight 305.37; R_f 0.48 (75% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (br s, 1H), 7.12−7.32 (m, 5H), 4.30 and 4.16 (2t, 1H, J = 8.0 Hz), 3.60 and 3.75 (2dd, 1H, J_a = 10.0 Hz, J_b = 7.2 Hz), 3.11 (m, 1H), 2.72 (m, 2H), 2.30−2.47 (complex m, 2H), 1.71−1.92 (m, 1H), 1.46 and 1.39 (2s, 9H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 176.3, 153.7, 139.8, 129.0, 128.7, 126.5, 81.4, 80.8, 59.5, 52.6, 52.1, 40.5, 40.2, 39.1, 37.1, 35.3, 28.7, 28.6; HR-FTMS $[MNa]^+$ calcd for **2c** 328.1519, found 328.1524; $[\alpha]^{20}_D$ −65.1 (*c* 1.0, $CHCl_3$).

(2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-(4′-ethoxy)benzylproline (2d). Yield: white solid (85%, dr 16:1). Molecular formula $C_{19}H_{27}NO_5$. Molecular weight 349.43; R_f 0.20 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (m, 2H), 6.81 (m, 2H), 4.29 and 4.18 (2t, 1H, J = 8.0 Hz, rotamers), 4.00 (m, 2H), 3.72−3.60 (m, 1H), 3.09 (m, 1H), 2.63 (m, 2H), 2.34 (m, 2H), 1.90 and 1.69 (2m, 1H), 1.48−1.38 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 176.4, 157.5, 131.8, 129.7, 129.6, 114.7, 63.7, 59.5, 52.6, 52.1, 40.4, 38.2, 37.1, 35.0, 28.7, 21.1, 15.2; HR-FTMS $[MNa]^+$ calcd for **2d** 372.1781, found 372.1786; $[\alpha]^{20}_D$ −42.7 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-(methoxycarbonyl)methylproline (2e). Yield: colorless oil (84%, dr 15:1). Molecular formula $C_{13}H_{21}NO_6$. Molecular weight 287.31; R_f 0.46 (75% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 4.33 and 4.20 (2t, 1H, J = 7.2 Hz), 3.81 (m, 1H), 3.66 and 3.68 (2s, 3H,, rotamers), 3.06 (m, 1H), 2.57 (m, 1H), 2.46 (m, 3H), 1.91 and 1.65 (2m, 1H, rotamers), 1.39 and 1.48 (2s, 9H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 175.0, 172.0, 155.6, 153.3, 81.5, 80.6, 58.9, 52.1, 51.8, 51.5, 37.0, 36.6, 34.6, 34.3, 34.1, 33.9, 29.7, 28.4, 28.3; HR-FTMS $[MNa]^+$ calcd for **2e** 310.1261, found 310.1263; $[\alpha]^{20}_D$ −60.4 (*c* 1.0, MeOH).

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Supporting Information Available: Experimental procedures and spectroscopic data for **13** and **14**, ^{1}H NMR spectra for compounds **1b**−**e**, **2a**−**e**, **6**, **7a**, **9b**−**f**, and **11a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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