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Full Paper

Studies on the Synthesis of *cis*-4-Hydroxy-L-proline

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A high yielding practical three-step procedure, which relies on an extractive work-up procedure, has been developed to convert *N*-phenylsulfonyl-*trans*-4-hydroxy-L-proline to *N*-phenylsulfonyl-*cis*-4-hydroxy-L-proline methyl ester in 82 % yield over three steps.

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Trans-4-hydroxy-L-proline is a naturally occurring, non-proteinogenic amino acid. The synthesis of hydroxyproline derivatives is important because these compounds have proven to be useful building blocks in medicinal chemistry. For example, MK-1220 **1** is a highly active hepatitis C virus NS3/4A protease inhibitor,[1] while GAP-134 **2** is small molecule gap-junction modifier for the treatment of atrial fibrillation (Fig. 1).[2] These compounds possess a *trans*-4-hydroxyproline and a *trans*-4-aminoproline core, respectively, as key structural templates upon which are tethered functional and structural motifs. Access to *trans*-4-hydroxyproline derivatives often proceeds via an initial stereoinversion at the hydroxy group of readily available *trans*-4-hydroxy-L-proline to *cis*-4-hydroxy-L-proline, followed by an S_N2 reaction at that centre to install desired functionality and re-establish the *trans* configuration.

The *N*-phenylsulfonyl group is an excellent functional group for the construction of small-molecule libraries.[3] As such, we sought a practical conversion of the *N*-phenylsulfonyl-*trans*-4-hydroxyproline acid **3** to the corresponding *N*-phenylsulfonyl-*cis*-4-hydroxyproline methyl ester **4** (Fig. 2).

Early synthetic studies on this conversion were reported by Patchett and Witkop, who demonstrated inversion of the C4 alcohol through activation of the *trans*-hydroxyl as the tosylate and subsequent internal displacement by the carboxylic acid to form the corresponding lactone (Eqn 1, Fig. 3).[4–6] Portoghese and coworkers reported a similar activation step enroute to the 2,5-diazabicyclo[2.2.1]heptanes,[7] while Robertson and Simpson also evoked the formation of a bicyclic species to explain the formation of *cis*-4-hydroxy amide derived from the *trans*-4-bromo-L-proline (Eqn 2).[8] Employing the Mitsunobu reaction, Joullié and coworkers were successful in shortening the sequence to directly convert a variety of *N*-functionalized *trans*-4-hydroxy-L-proline derivatives to the bicyclic lactones (Eqn 3).[9] In a related manner, La Rosa and coworkers have demonstrated the formation of the enantiomeric lactone.[10] Direct intermolecular S_N2 inversion of C4 through the Mitsunobu reaction, or conversion to the mesylate, and subsequent displacement with oxygen and nitrogen nucleophiles has also been reported.[3,11,12] More recently, Silverman and coworkers demonstrated that the bicyclic lactone could be efficiently opened with MeOH in the presence of catalytic NaN_3 (Eqn 4).[13]

Despite these advances, the conversion of **3** to **4** via Joullié's route is laborious owing to the well established[14,15] difficulties in removing the Mitsunobu by-products: triphenyl phosphine oxide and the dialkyl hydrazine carboxylate. Purification required several chromatography operations. To overcome these difficulties, an efficient extractive procedure has been developed that greatly simplifies the purification process and is now reported.

To avoid the Mitsunobu reagents entirely, Patchett's approach was initially investigated (Scheme 1). Readily available *trans*-hydroxy-L-proline **5** was converted to the *N*-phenylsulfonyl derivative **3** in 89 % yield.[16] A recent modification of this procedure using microwave conditions is a convenient alternative for moderate scale preparations.[17] The *N*-phenylsulfonyl derivative **3** was subsequently converted to the corresponding *O*-tosylate **6** in

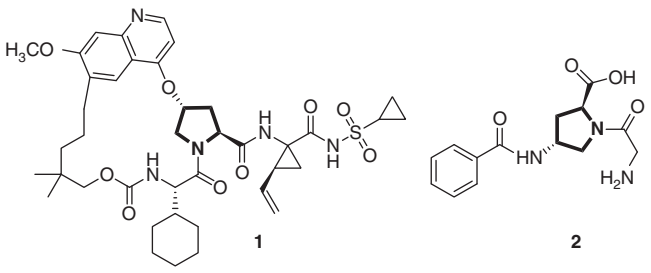


Fig. 1. Exploitation of hydroxyproline building blocks.

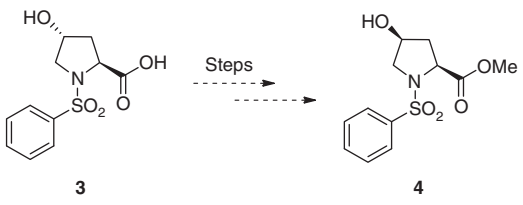


Fig. 2. Desired conversion.

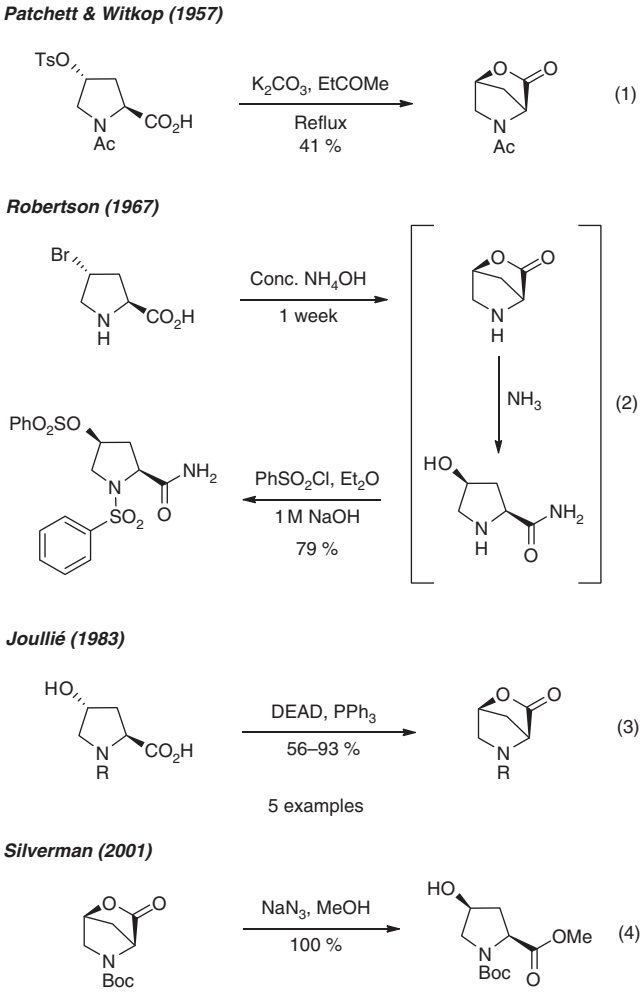
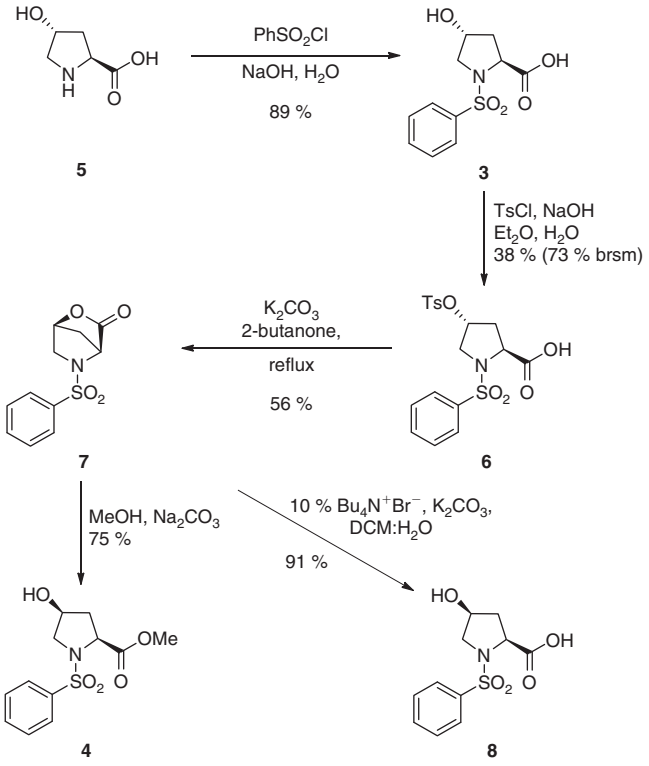


Fig. 3. Synthesis of *cis*-4-hydroxy proline derivatives.

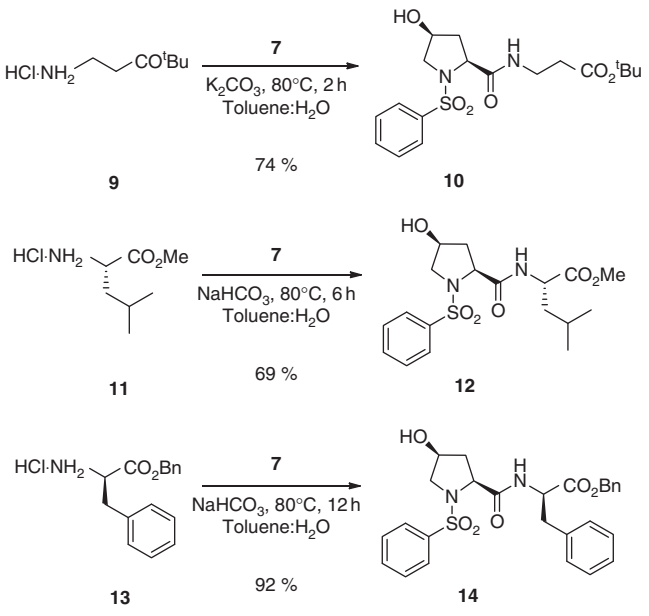
38 % yield.[7] The conversion of *O*-tosylate **6** to the lactone **7** on treatment with K_2CO_3 in 2-butanone at reflux proceeded smoothly in 56 % yield. Although this sequence proceeded in modest overall yield, the lactone **7** was obtained in essentially pure form and required little additional purification. Recent reports employing the corresponding mesylate derivative provide an alternative method for exploiting this strategy.[5,6] The lactone **7** is a versatile intermediate that could be converted to the *cis*-4-hydroxy ester **4** in 75 % yield by treatment with Na_2CO_3 in methanol.[18] Alternatively, treatment of the lactone **7** with 10 % tetrabutyl ammonium bromide (TBAB) and K_2CO_3, in a biphasic dichloromethane (DCM)/water system, delivered the *cis*-4-hydroxy acid **8** in 91 % yield.

Lactones that are structurally related to compound **7** have been used as activated esters in peptide synthesis and we found that biphasic conditions were excellent conditions for this reaction.[12,19,20] For example, treatment of β-alanine *tert*-butyl ester **9** with lactone **7**, in the presence of one equivalent of K_2CO_3 gave the amide **10** in 74 % yield. Employing K_2CO_3 with more hindered amines such as L-leucine **11** and D-phenylalanine **13** led predominantly to the acid **8** demonstrating the susceptibility of lactone **7** to hydrolysis. However, employing a stoichiometric equivalent of $NaHCO_3$ delivered amides **12** and **14** in 69 and 92 % yield, respectively (Scheme 2).

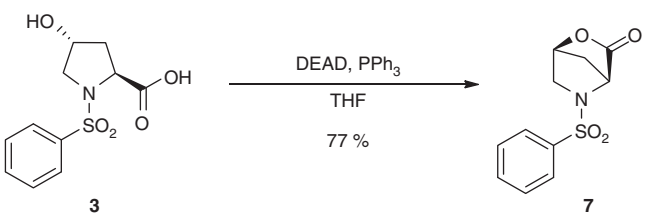
Although the *O*-tosylate approach was a feasible method for synthesizing the desired *cis*-4-hydroxy-L-proline methyl ester **4**,



Scheme 1. Initial tosylate-displacement approach.

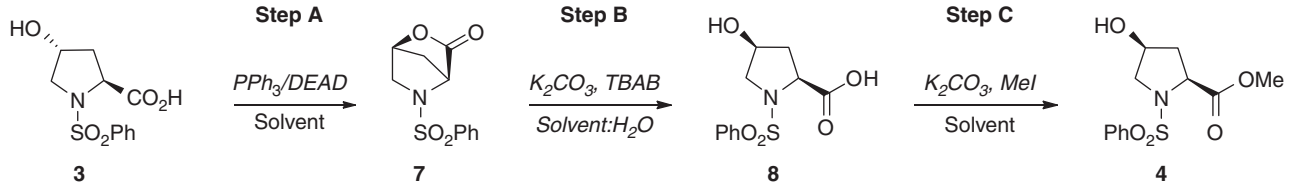


Scheme 2. Amide bond formation under biphasic conditions.

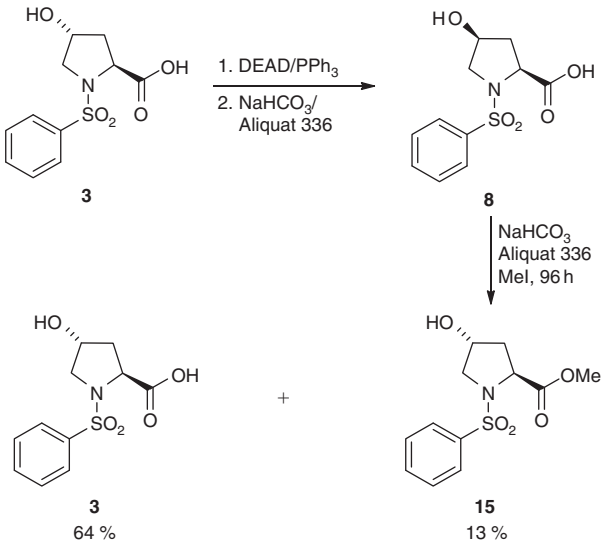


Scheme 3. The Mitsunobu approach.

Table 1. Optimization of the process for synthesis of *cis*-4-hydroxy-L-proline methyl ester 4



Entry	Solvent	Operation	Solvent	Operation	Conditions	Yield	*cis*:*trans*
1	THF	Remove THF	Toluene	Discard toluene. Add DCM	DCM:H_2O 18 h	37	1:0
2	THF	Remove THF	Toluene	Discard toluene. Add DCM	DCM:H_2O 72 h	65	1:1
3	THF	Remove THF	Toluene	Acidify aqueous, extract	Acetone	75	1:0
4	DCM	Add H_2O	DCM	Acidify aqueous, extract	Acetone	82	1:0



Scheme 4. Complete stereo-reversion of **8**.

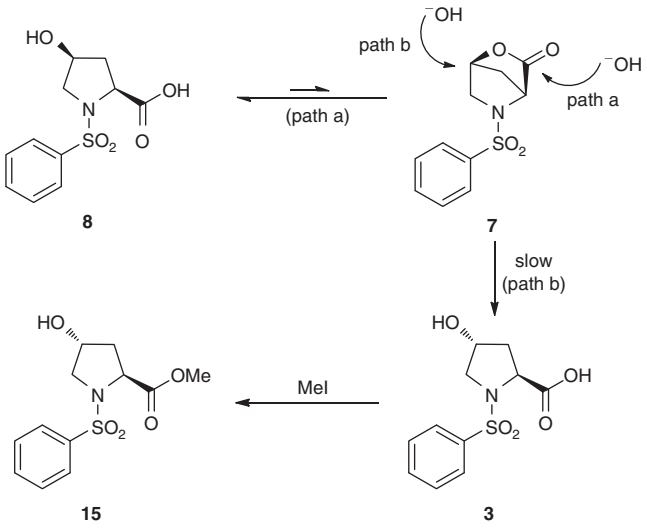


Fig. 4. Reaction mechanism for the stereo-reversion of **8**.

the low yields and long reactions times of the tosylate formation and subsequent cyclization were discouraging. Despite the aforementioned difficulties, the Mitsunobu reaction applied to this system gave excellent conversion and treatment of **3** with DEAD/PPh_3 delivered the lactone **7** in 77 % yield (Scheme 3). Unsurprisingly, the remainder of the material could be accounted for as impure lactone **7** contaminated with triphenyl phosphine oxide and dialkyl hydrazine carboxylate by-products.

However, the efficient conversion of the lactone **7** to the *cis*-4-hydroxy acid **8** (Scheme 1) suggested that the crude Mitsunobu product could be subjected to similar biphasic conditions. This process would selectively extract the *cis*-4-hydroxy acid **8** into the water phase. Further, it seemed reasonable that removal of the organic layer and recharging with fresh solvent, MeI, and phase-transfer catalyst (PTC) would lead to the formation of the desired ester **4**.[21] Initial attempts to employ a similar strategy through methanolysis of lactone **7** did not lead to a significant difference in polarity and was therefore not useful for enhancing separation from the by-products by chromatography.

The development of this extractive approach is outlined in Table 1. Thus, treatment of *trans*-4-hydroxy-L-proline **3** under the Mitsunobu conditions outlined above lead to the formation of the lactone **7**. The THF was removed and toluene, water, K_2CO_3, and TBAB added to give the acid **8.** The toluene/water mixture was partitioned and the organic layer containing the unwanted Mitsunobu adducts was discarded and replaced with fresh DCM and MeI to give the desired ester **4** in 37 % yield (Entry 1). No alkylation was observed in the absence of TBAB. Prolonging the final methylation step (Entry 2) resulted in an increase of the ester **4** to 65 % yield, but as a 1:1 mixture of the desired *cis*-hydroxy-L-proline methyl ester **4** and curiously the diastereomer, *trans*-4-hydroxy-L-proline methyl ester **15**.

The formation of *trans*-4-hydroxy-L-proline **3** in this reaction suggests a mechanism whereby the *cis*-4-hydroxy-L-proline **8** is in equilibrium with the lactone **7**, which can be ring-opened via attack on the carbonyl carbon (path a) or the less favoured, but irreversible, attack on the γ-carbon (path b) to give *trans*-4-hydroxy-L-proline **3**, and then subsequent alkylation leading to the corresponding ester **15** (Fig. 4).

Even in the presence of 0.5 equivalents of K_2CO_3 (data not shown), significant stereoinversion was observed. In fact, complete stereoinversion of C4 could be affected in the presence of Aliquat 336 (a tetraalkylammonium PTC with C-8 and C-10 alkyl chains) [19] over 96 h, delivering *trans*-hydroxy-L-proline methyl ester **15** and the *trans*-hydroxy-L-proline acid **3** ($[\alpha]_D^{25}$ −100.7 (*c* 1.4 in EtOH); lit. $[\alpha]_D^{25}$ −96.2 (2.5 in EtOH))[8] in 13 and 64 % yield, respectively (Scheme 4).

Although the PTC alkylation approach was initially attractive owing to its simplicity, the potential for stereochemical leakage in this step made it untenable. Therefore the acid **8** was

isolated after Step B and methylated in the standard fashion (K_2CO_3, MeI, acetone), which delivered the desired ester product **4** in 75 % yield over the three steps (Entry 3). Finally, by substituting DCM for THF in Step A, removal of the solvent after the Mitsunobu reaction was not required and this resulted in an increased overall yield (82 %) over the three steps (Entry 4).

Conclusion

A high yielding practical procedure has been successfully developed to convert the *trans*-4-hydroxy-L-proline derivative **3** to the *cis*-hydroxy-L-proline derivative **4** in 82 % over three steps. For comparison, the traditional stepwise route of **3** to **4**, through methanolysis of lactone **7** (Scheme 1), proceeds in 58 % over two steps. Moreover, this sequence requires an intermediate chromatography operation that is technically difficult on a larger scale. Although PTC alkylation of *cis*-hydroxy-L-proline **8** could be achieved in modest yield, these reaction conditions lead to significant stereo-reversion to the *trans*-hydroxy-L-proline derivative **3** through nucleophilic attack on the γ-carbon of lactone **7**. Finally, simple biphasic conditions have been developed for employing lactone **7** as an active ester for use in amide bond formation.

Experimental

Reaction flasks were oven-dried and solvents employed were HPLC grade. NMR spectra were recorded on either a 400 or 200 MHz spectrometer. Spectra were recorded as solutions in $CDCl_3$ [$\delta_H = 7.26$, $\delta_C = 77.26$ as internal standards], d_6-DMSO [$\delta_H = 2.50$, $\delta_C = 39.5$ as internal standards], or d_6-acetone [$\delta_H = 2.05$, $\delta_C = 29.9$ as internal standards]. The data are reported as integration, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet or unresolved, br = broad, obs = obscured, coupling constant(s) in Hz. Mass spectra were recorded using electrospray ionization (ESI) employing 35 eV cone voltage, employing lock spray and sodium iodide as a reference sample. Specific rotations were determined at the sodium D line at 25°C using a 10-cm length tube. Melting points were determined using a variable heater apparatus and values are uncorrected. FTIR spectra were obtained using a Thermo Nicolet 6700 spectrometer using a SmartATR (attenuated total reflectance) attachment fitted with a diamond window.

N-*Phenylsulfonyl*-trans-*4-tosyloxy-proline Methyl Ester* ***6***

N-Phenylsulfonyl-*trans*-4-hydroxy proline **3** (2 g, 7.38 mmol) was dissolved in 2 M NaOH (10 mL, 20 mmol) and a solution of TsCl (5.7 g, 29.5 mmol) in Et_2O (10 mL) added. The mixture was stirred at room temperature for 4 days over which time the precipitate completely dissolved. The Et_2O layer was then extracted with 1 M NaOH (2 × 10 mL). The aqueous layers were then combined and the water removed under reduced pressure. The resulting residue was then taken up in EtOH, filtered, and the solvent again removed under reduced pressure. The residue was then dissolved in 10 % butan-2-ol/ethyl acetate (20 mL) and washed with H_2O and brine. The organic layer was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give an oil which was chromatographed on silica gel (5 % MeOH/DCM with 0.5 % AcOH) to give the *N*-phenylsulfonyl-*trans*-4-tosyloxy-proline methyl ester **6** (1.2 g, 38 %) as a white solid (mp 120.9–121.0°C) and *N*-phenylsulfonyl-*trans*-4-hydroxy proline **3** (700 mg, 35 %). $[\alpha]_D^{25}$ −58.4 (*c* 2.5 in EtOH). δ_H (400 MHz, d_4-MeOH) 2.16 (m, 1H), 2.34 (m, 1H), 2.44 (s, 3H), 3.54 (d, *J* 12.9, 1H), 3.63 (dd, *J* 12.8, 3.6, 1H), 4.16 (dd, *J* 9.1, 7.6, 1H), 5.00 (br s, 1H), 7.39 (d, *J* 8.0, 2H), 7.52 (m, 5H), 7.82 (d, *J* 7.5, 2H). δ_C (100 MHz, d_4-MeOH) 20.2, 37.1, 54.1, 59.4, 79.3, 127.5, 127.3, 128.9, 129.8, 133.1, 133.2, 137.1, 145.5, 173.4. ν_{max}(film)/cm^{-1} 1734. *m/z* (HR-EI+) found 448.0480; $C_{18}H_{19}NO_7NaS_2$ requires 448.0501.

Lactone ***7***

Method A: A mixture of *N*-phenylsulfonyl-*trans*-4-tosyloxy-proline methyl ester **6** (200 mg, 0.47 mmol), K_2CO_3 (64 mg, 0.47 mmol), and 2-butanone (10 mL) was heated at reflux for 2 h over which time a white precipitate formed. The reaction was allowed to cool and was diluted with DCM (20 mL) and H_2O (20 mL). The organic layer was washed with brine and the aqueous layer re-extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed over silica gel eluting with petroleum spirits/EtOAc (1:1) to give lactone **7** as a white solid (67 mg, 56 %).

Method B: N-Phenylsulfonyl-*trans*-4-hydroxy proline **3** (2.16 g, 7.96 mmol) was dissolved in anhydrous THF (140 mL) under a nitrogen atmosphere and triphenylphoshine (2.19 g, 8.36 mmol) was added. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (1.32 mL, 8.36 mmol) added dropwise over 1 h. After complete addition, the resulting mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed under reduced pressure affording a sticky residue, which was purified by chromatography over silica gel eluting with DCM/EtOAc (4:1). The lactone **7** was isolated as a white powder, mp 118.7–119.5°C (1.55 g, 77 %). $[\alpha]_D^{25}$ +33.4 (*c* 1.0 in $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 2.03 (dd, *J* 1.9, 10.9, 1H), 2.23 (dq, *J* 1.3, 10.9, 1H), 3.27 (br d, *J* 10.0, 1H), 3.68 (dd, *J* 2.0, 10.0, 1H), 4.52 (q, *J* 1.3, 1H), 5.03 (br t, *J* 0.8, 1H), 7.49–7.68 (m, 3H), 7.83–7.90 (m, 2H). δ_C (100 MHz, $CDCl_3$) 39.4, 51.1, 59.5, 78.6, 128.0, 129.3, 133.7, 136.5, 169.4. ν_{max}(film)/cm^{-1} 1787, 1586. *m/z* (ESI) 286 (M+Na, 100%), 254 (M+H, 50), 226 (30). *m/z* (HR-EI+) found: 276.0303; $C_{11}H_{11}NO_4S$+Na requires 276.0306.

N-*Phenylsulfonyl*-cis-*4-hydroxy Proline* ***8***

Lactone **7** (475 mg, 1.88 mmol), K_2CO_3 (428 mg, 3.09 mmol), and $Bu_4N^+Br^-$ (61 mg, 0.19 mmol) were dissolved in DCM (10 mL) and water (10 mL) and the biphasic reaction mixture stirred for 16 h at room temperature. The reaction mixture was acidified with 1M HCl and extracted with DCM:^{i}PrOH (4:1). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified over silica gel eluting with CH_3CN:H_2O (1:1) to give the title acid **8** as a white solid, mp 113.1–114.3°C (lit.[7] 113.5–114.5°C), (472 mg, 91 %). $[\alpha]_D^{25}$ −84.9 (*c* 1.5 in EtOH) (lit.[7] $[\alpha]_D^{25}$ −72.4 (2.5 EtOH)). δ_H (400 MHz, d_6-DMSO) 1.87 (dt, *J* 4.0, 12.8, 1H), 2.00 (m, 1H), 3.11 (dd, *J* 4.0, 10.5, 1H), 3.28 (dt, *J* 5.0, 10.5, 1H), 3.95 (quin, *J* 5.0, 1H), 4.23 (dd, *J* 4.6, 9.1, 1H), 4.34 (br s, 1H), 7.59–7.64 (m, 2H), 7.67–7.72 (m, 1H), 7.83–7.87 (m, 2H). δ_C (50 MHz, d_6-DMSO) 38.3, 55.4, 59.5, 68.5, 127.2, 129.4, 133.1, 137.6, 172.8. ν_{max}(film)/cm^{-1} 3241, 1691. *m/z* (ESI) 272 (M+H, 100 %), 226 (30). *m/z* (HR-EI+) found: 294.0398; $C_{11}H_{13}NO_5S$+Na requires 294.0412.

N-*Phenylsulfonyl*-cis-*4-hydroxy Proline Methyl Ester* **4**

Lactone **7** (1.0 g, 3.95 mmol) and Na_2CO_3 (2.09 g, 19.8 mmol) were combined in MeOH (25 mL) and stirred for 8 h at room temperature. The MeOH was removed under reduced pressure, the residue taken up in EtOAc and filtered through a small plug of silica gel. The title compound **4** was obtained as a white powder, mp 104.4–104.7°C (lit.[7] 104–105°C), (852 mg, 75 %). $[\alpha]_D^{25}$ −65.2 (*c* 1.5 in $CHCl_3$) (lit.[7] $[\alpha]_D^{25}$ −70.3 (2.5 $CHCl_3$)). δ_H (400 MHz, $CDCl_3$) 2.10 (dt, *J* 1.6, 14.1, 1H), 2.17 (m, 1H), 3.40 (dd, *J* 4.2, 10.3, 1H), 3.55 (dt, *J* 1.3, 10.3, 1H), 3.77 (s, 3H), 4.34 (m, 1H), 4.38 (dd, *J* 2.0, 9.7, 1H), 7.42–7.56 (m, 2H), 7.56–7.69 (m, 1H), 7.85–7.90 (m, 2H). δ_C (100 MHz, $CDCl_3$) 38.7, 53.0, 56.9, 59.1, 70.9, 127.8, 129.2, 133.2, 137.6, 174.1. ν_{max}(film)/cm^{-1} 3523, 1726. *m/z* (ESI): 286 (M+H, 100%), 226 (20). *m/*z (HR-EI+) found: 308.0577; $C_{12}H_{15}NO_5S$+Na requires 308.0569.

^{t}*Butyl-3-((2S,4S)-4-hydroxy-1-(phenylsulfonyl)pyrrolidine-2-carboxamido)-propanoate* **10**

To a solution of lactone **7** (500 mg, 1.9 mmol) in toluene (5 mL) was added β-alanine *tert*-butyl ester · HCl (429 mg, 2.4 mmol) and K_2CO_3 (325 mg, 2.4 mmol) in H_2O (1 mL). The biphasic mixture was heated to 80°C for 2 h. The reaction was then cooled and toluene (5 mL) added. The organic layer was washed with H_2O and brine. The aqueous layer was re-extracted with EtOAc and the combined organic extracts dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed over silica gel eluting with DCM/MeOH (initial eluent 1 % MeOH increasing to 5 % MeOH) to give the title compound **9** as a white solid, mp 131.9–132.0°C (560 mg, 74 %). $[\alpha]_D^{25}$ −81.1 (*c* 2.5 in $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 1.44 (s, 9H), 1.79 (m, 1H), 2.20 (d, *J* 14.0, 1H), 2.43 (m, 2H), 3.59–3.39 (m, 3H), 4.18 (d, *J* 8.9, 1H), 4.28 (m, 2H), 7.20 (t, *J* 5.7, 1H), 7.52 (m, 2H), 7.60 (m, 1H), 7.80 (m, 2H). δ_C (100 MHz, $CDCl_3$) 28.1, 34.9, 35.5, 37.8, 57.9, 61.5, 70.6, 81.3, 127.6, 129.3, 133.3, 136.4, 171.5, 172.1. ν_{max}(film)/cm^{-1} 1722, 1654. *m/z* (HR-EI+) found 421.1367; $C_{18}H_{26}N_2O_6NaS$ requires 421.1409.

Methyl-(S)-2-((2S,4S)-4-hydroxy-1-(phenylsulfonyl) pyrrolidine-2-carboxamido)-4-methylpentanoate **12**

To a solution of lactone **7** (50 mg, 0.19 mmol) in toluene (0.5 mL) was added L-leucine methyl ester · HCl (35 mg, 0.2 mmol) and $NaHCO_3$ (16 mg, 0.2 mmol) in H_2O (0.1 mL). The biphasic mixture was heated to 80°C for 6 h. The reaction was then cooled and EtOAc (10 mL) added. The organic layer was washed with 2 % w/v citric acid (×2) and brine. The aqueous layer was re-extracted with EtOAc and the combined organic extracts dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed over silica gel eluting with DCM/MeOH (initial eleunt 1 % MeOH increasing to 5 % MeOH) to give the title compound **12** as a white solid, mp 142.4°C (54 mg, 69%). $[\alpha]_D^{22}$ –75.5 (*c* 1.0 in $CHCl_3$). δH (400 MHz, d_6-Acetone/0.3 % D_2O) 0.89 (d, *J* 6.6, 6H), 1.60 (m, 2H), 1.80 (m, 1H), 1.94 (m, 2H), 3.26 (dd, *J* 9.9, 4.3, 1H), 3.40 (d, *J* 10.3, 1H), 3.66 (s, 3H), 4.14 (br s, 1H), 4.27 (dd, *J* 7.4, 4.3, 1H), 4.49 (dd, *J* 9.3, 5.6, 1H), 7.61 (t, *J* 7.7, 2H), 7.69 (t, *J* 7.3, 1H), 7.88 (d, *J* = 7.7, 2H). δ_C (100 MHz, d_6-Acetone/0.3 % D_2O) 21.0, 22.3, 24.2, 37.9, 40.6, 50.7, 51.5, 57.6, 60.9, 69.8, 127.6, 129.3, 133.2, 136.9, 172.4, 172.5. ν_{max}(film)/cm^{-1} 3355, 1743, 1655, 1534. *m/z* (HR-EI+) found 421.1396; $C_{18}H_{26}N_2O_6NaS$ requires 421.1409.

Benzyl-(R)-2-((2S,4S)-4-hydroxy-1-(phenylsulfonyl) pyrrolidine-2-carboxamido)-3-phenylpropanoate **14**

To a solution of lactone **7** (100 mg, 0.4 mmol) in toluene (1 mL) was added D-phenylalanine benzyl ester · HCl (429 mg, 0.24 mmol) and $NaHCO_3$ (33 mg, 0.4 mmol) in H_2O (0.2 mL). The biphasic mixture was heated to 80°C for 12 h. The reaction was then cooled and EtOAc (10 mL) added. The organic layer was washed with 2 % w/v citric acid (×2) and brine. The aqueous layer was re-extracted with EtOAc and the combined organic extracts dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed over silica gel eluting with DCM:MeOH (initial eluent 1 % MeOH increasing to 5 % MeOH) to give the title compound **14** as a white clear oil (186 mg, 91 %). $[\alpha]_D^{25}$ –38.8 (*c* 1.0 in $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 1.69 (m, 1H), 2.16 (d, *J* 14.0, 1H), 3.12 (m, 2H), 3.22 (dd, *J* 10.7, 4.1, 1H), 3.90 (br s, 1H), 4.23 (m, 1H), 4.25 (d, *J* 8.9, 1H), 4.86 (dd, *J* 13.8, 6.1, 1H), 5.13 (ABd, *J* 12.0, 2H), 7.12 - 7.34 (m, 11H), 7.50 (t, *J* 7.3, 2H), 7.60 (t, *J* 7.4, 1H), 7.78 (m, 2H). δ_C (100 MHz, $CDCl_3$) 37.6, 37.9, 53.8, 57.7, 61.3, 67.2, 70.5, 127.1, 127.6, 128.5, 128.5, 128.6, 128.6, 129.4, 129.6, 133.4, 135.1, 135.6, 136.3, 170.7, 171.9. ν_{max}(film)/cm^{-1} 3373, 1740 1657, 1524. *m/*z (HR-EI+) found 531.1523; $C_{27}H_{28}N_2O_6NaS$ requires 531.1566.

Preferred Three-step One-pot Procedure for Conversion of N-*phenylsulfonyl*-trans-*hydroxy-L-proline* **3** *to* N-*phenylsulfonyl*-cis-*hydroxy-L-proline Methyl Ester* **4**

N-Phenylsulfonyl-*trans*-4-hydroxy proline **3** (500 mg, 1.85 mmol) was dissolved in anhydrous DCM (20 mL) under a nitrogen atmosphere and triphenylphoshine (678 mg, 2.58 mmol) was added. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (407 µL, 2.58 mmol) added dropwise over 20 min. After complete addition, the resultant mixture was allowed to warm to room temperature and stirred for 4 h. Water (20 mL), K_2CO_3 (280 mg, 2.03 mmol) and $Bu_4N^+Br^-$ (59 mg, 0.19 mmol) were added to the reaction mixture and the biphasic solution stirred for 16 h at room temperature. The DCM layer was discarded and the aqueous layer washed with DCM/^{i}PrOH (4:1) (20 mL × 3) to remove the diethyl hydrazine dicarboxylate by-product. The aqueous layer was acidified with 1M HCl and extracted with DCM/^{i}PrOH (4:1). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. Acetone (20 mL) was added to the residue along with K_2CO_3 (255 mg, 1.85 mmol), methyl iodide (234 µL, 3.69 mmol), and the mixture heated at reflux for 6 h. The reaction was cooled to room temperature and the acetone removed under reduced pressure. DCM was added to the residue and the organic layer was washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified over C-18 silica gel eluting with water/acetonitrile (7:3) affording the title ester **4** as white crystals (430 mg, 82 %).

Complete Stereo-reversion of N-*phenylsulfonyl*-cis-*hydroxy-L-proline 8 to* N-*phenylsulfonyl*-trans-*hydroxy-L-proline* **3**

N-Phenylsulfonyl-*trans*-4-hydroxy proline **3** (250 mg, 0.92 mmol) was dissolved in anhydrous DCM (10 mL) under a nitrogen atmosphere and triphenylphosphine (338 mg, 1.29 mmol) was added. The reaction mixture was cooled to 0°C and diethyl azodicarboxylate (175 µL, 1.29 mmol) added dropwise over 20 min. After complete addition, the resultant

mixture was allowed to warm to room temperature and stirred for 6 h. Water (10 mL), $NaHCO_3$ (78 mg, 0.92 mmol), and Aliquat 336 (420 μL, 0.92 mmol) were added to the reaction mixture and the biphasic mixture stirred for 16 μLh at room temperature. The DCM layer was discarded and the aqueous layer washed with DCM (2 × 20 mL). DCM (40 mL) and methyl iodide (118 μL, 1.85 mmol) were added to the aqueous layer and the biphasic mixture stirred for 16 h at room temperature. After this time additional $NaHCO_3$ (78 mg, 0.92 mmol), Aliquat 336 (420 μL, 0.92 mmol), and methyl iodide (586 μL, 9.22 mmol) were added and the mixture stirred at room temperature for a further 96 h. At this point LCMS indicated only a small amount of a methyl ester had been formed and the reaction was terminated. The aqueous layer was acidified with 1M HCl and extracted with DCM/^{i}PrOH (4:1). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude material was purified by flash chromatography over C-18 silica gel eluting with water/acetonitrile (8:2). Methyl ester **10** was isolated as a white solid, mp 114.8–116.1°C (lit.[22] 121–122°C) (34 mg, 13 %). $[\alpha]_D^{25}$ −98.2 (*c* 0.7 in $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 2.08–2.16 (m, 1H), 2.19–2.17 (m, 1H), 3.42 (d, *J* 11.3, 1H), 3.61 (dd, *J* 3.6, 11.3, 1H), 3.74 (s, 3H), 4.45 (t, *J* 8.3, 1H), 4.43–4.48 (m, 1H), 7.53 (t, *J* 7.6, 2H), 7.60 (t, *J* 7.6, 1H), 7.90 (d, *J* 7.6, 2H). δ_C (100 MHz, $CDCl_3$) 39.8, 52.8, 56.6, 59.6, 70.4, 127.9, 129.3, 133.3, 138.1, 172.6. ν_{max}(film)/cm^{-1} 3468, 1712. *m/z* (ESI) 286 (M+H, 100 %), 226 (30). *m/z* (HR-EI+) found: 308.0576; $C_{12}H_{15}NO_5S$+Na requires 308.0569.

N-Phenylsulfonyl-*trans*-4-hydroxy proline **3** was also isolated as a white glass, mp 152.7–152.8°C (lit.[7] 150–151°C) (160 mg, 64 %). $[\alpha]_D^{25}$ −100.7 (*c* 1.4 in EtOH) (lit.[7] $[\alpha]_D^{25}$ −96.2 (2.5 EtOH)). δ_H (400 MHz, d_6-DMSO) 2.05–2.09 (m, 2H), 3.24 (ddd, *J* 0.9, 2.7, 10.5, 1H), 3.54 (dd, *J* 4.4, 10.5, 1H), 4.22 (t, *J* 7.7, 1H), 4.33 (quin, *J* 3.8, 1H), 4.34 (br s, 1H), 7.41–7.45 (m, 2H), 7.48–7.52 (m, 1H), 7.82–7.84 (m, 2H). δ_C (100 MHz, d_6-DMSO) 39.5, 56.4, 59.8, 69.5, 127.8, 128.9, 132.7, 138.0, 174.1. ν_{max}(film)/cm^{-1} 3394, 1709. *m/z* (ESI) 272 (M+H, 100 %), 226 (30). *m/z* (HR-EI+) found: 294.0388; $C_{11}H_{13}NO_5S$+Na requires 294.0412.

Accessory Publication

^{1}H NMR and ^{13}C NMR spectra for compounds **4**, **6**, **7**, **10**, **12**, **14**, and **15** can be found on the Journal's website.

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