Asymmetric Synthesis of the Four Stereoisomers of 4-Hydroxypipecolic Acid

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Abstract: The asymmetric synthesis of all four stereoisomers of 4-hydroxypipecolic acid (**1**) from the polyfunctionalized chiral building blocks δ-amino β-keto esters (S_S,*R*)-(+)-**5** or (R_S,*S*)-(-)-**5** is described. Key steps in the synthesis are the stereoselective reductions of b-phenylpiperidine-2,4-dione (**6**) and *N*-sulfinyl δ-amino β-keto esters **5** to *cis* 4-hydroxy 2-piperidinone **7** and *syn*-δ-amino β-hydroxy ester **9**, respectively. The only protecting/deprotecting group chemistry required is related to the oxidation step.

Key words: stereoselective reductions, hydrides, cyclization, asymmetric synthesis, piperidines

Interest in the synthesis of cyclic α-amino acids stems from the effects these acids have on biological activity once incorporated into peptides.[1] The 4-hydroxypipecolic acids **1** are of particular relevance because naturally occurring *cis*-(2*S*,4*R*)-(−)-**1** is found in cyclodepsipeptide antibiotics such as virginiamycin S_2,[2] which is used in the synthesis of *N*-methyl-D-aspartic acid (NMDA) receptor antagonists[3a] and in the synthesis of the palinavir, a new class of HIV protease inhibitor.[4] Its enantiomer (2*R*,4*S*)-(+)-**1** is an intermediate in the synthesis of 4-(phosphononoalkyl)-2-piperidinecarboxylic acids which are potent NMDA receptor antagonists of interest for the treatment of CNS disorders.[3a] *trans*-(2*S*,4*S*)-4-Hydroxypipecolic acid (**1**) was isolated from leaves of the *Acacia* species,[5] and its 4-sulfate is also a selective NMDA receptor agonist.[6] In addition, these cyclic amino acids are of importance as building blocks for the synthesis of piperidine alkaloids.[7]

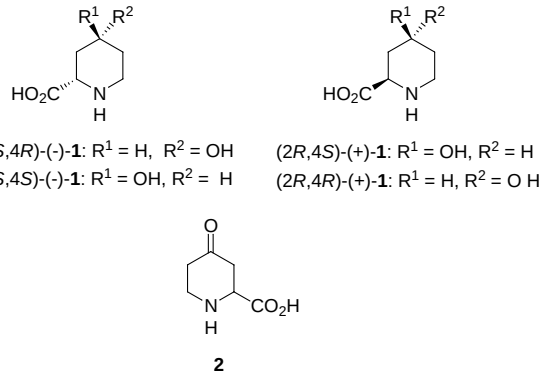
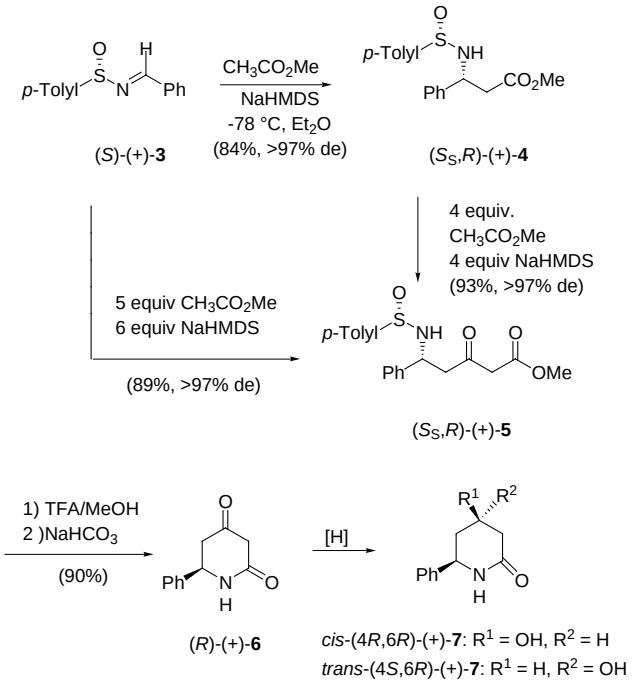


Figure 1 Structures of 4-Hydroxypipecolic acids **1** and 4-oxopipecolic acid (**2**)

Only a few syntheses of enantiomerically enriched 4-hydroxypipecolic acids (**1**) have been described.[8] These include the transformation of 4-oxopipecolic acid (**2**),[9] a constituent of the virginiamycins family of cyclopeptides,[10] cyclization of chiral *N*-acyliminium ions[11] and other procedures which start from D-glucoheptono-1,4-lactone,[12] glycidol,[13] or a chiral 1-acylpyridinium salt.[14] Unfortunately many of these methods suffer from limitations which include classical resolutions,[15] inefficient separation of diastereoisomers, expensive reagents and/or lengthy synthetic procedures. Furthermore, none of these syntheses provide easy access to all four stereoisomers of **1**.

As part of a program to design and synthesize polyfunctionalized chiral building blocks, we recently introduced *N*-sulfinyl δ-amino β-keto esters for alkaloid synthesis.[16,17] These building blocks are prepared from sulfinimines (*N*-sulfinyl imines)[18] and are used in the highly efficient asymmetric synthesis of (*R*)-(+)-2-phenylpiperidine, (−)-SS20846A,[16] and the quinolizidine alkaloid (−)-lasubine II.[17] In particular (S_S,*R*)-(+)-methyl 3-oxo-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (**5**) was prepared in one-pot by treatment of sulfinimine (*S*)-(+)-**3** with an excess of the sodium enolate of methyl acetate in THF/Et_2O (Scheme 1).[16] Alternatively, **5** can be prepared from the β-amino acid (S_S,*R*)-(+)-**4**. Treatment of (+)-**5** with trifluoroacetic acid (TFA)/MeOH, passing the solution through a short plug of silica gel to remove the sulfinate byproduct, and addition of aqueous saturated $NaHCO_3$ solution in THF afforded (*R*)-(+)-6-phenylpiperidine-2,4-dione (**6**) in 90% yield for the two steps. Our plan then consisted of stereoselectively reducing the 4-oxo group in **6** to the *cis* or *trans* hydroxy derivatives **7** and using the phenyl group as a carboxylic acid equivalent.[19] Herein we describe the asymmetric synthesis of all four stereoisomers of 4-hydroxypipecolic acid **1** from (S_S,*R*)-(+)-**5** and its enantiomer (R_S,*S*)-(−)-**5**.

It appears that there have been no reports on the stereoselective reduction of piperidine-2,4-diones such as **6**. In contrast, several studies on the reduction of 2-substituted and 2,6-disubstituted 4-oxo piperidines have appeared. In one study a 2-substituted NH 4-oxo piperidine with L-Selectride gave the *cis*-product (*cis*/*trans* = 90:10), while an *N*-protected derivative afforded the *trans*-isomer (*cis*/*trans* = 5:95).[20] In another study a 2-substituted *N*-PMP-4-oxopiperidine gave a 89:11 *cis/trans* ratio of products with L-Selectride, and with $NaBH_4/CeCl_3$ the ratio was reversed (*cis*/*trans* = 30:70).[21] On the other hand 2,6-disubstituted 4-oxo piperidines give the *cis*- and *trans*-products



Scheme 1

with $NaBH_4$ and L-Selectride, respectively.[22] Despite these encouraging results all attempts to produce the *trans*-isomer (4*S*,6*R*)-**7** as the major product were unsuccessful (Table). Indeed all reducing reagents tested afforded a predominance of the *cis*-isomer (4*R*,6*R*)-**7** with maximum selectivity (97:3) being observed with $NaBH_4$ and $Zn(BH_4)_2$ (Entries 1, 4 and 5). It proved impossible to remove the minor isomer by chromatography, and crystallization from *i*-PrOH/pentane gave (4*R*,6*R*)-**7** in only 50% yield. For this reason it was found more efficient to move on to the next step with crude material, where the minor isomer was eliminated (see below). The maximum amount of the *trans*-(4*S*,6*R*)-**7** was observed with L-Selectride, but the 1:1 *cis*/*trans* ratio was synthetically unacceptable (Entry 8). We believe that axial attack is particularly favorable in **8**, not only because torsional strain is relieved, but a bulky reducing reagent encounters a single 5-axial hydrogen on approach. Flattening of the piperidine ring, as a consequence of enolate-elongation due to the acidity of the 3 protons, may also enhance axial attack.

While a nitrogen substituent may alter the conformation of the piperidine-2,4-dione ring to minimize $A^{1,3}$ strain, and favor equatorial (*trans*) attack, this would require additional steps.[23] For this reason we explored the *syn* and

Table Reduction of (*R*)-(+)-**6** and (S_S,*R*)-(+)-**5**

Entry	Reducing Agents/Conditions	From (*R*)-(+)-**6** *cis*/*trans* **7**[a] (% yield)	From (S_S,*R*) (+)-**5** *syn*/*anti* **9**[a] (% yield)
1	$NaBH_4$/THF, −78 °C, 2 h (42 h)[b]	97:3 (92) [51][c]	66:34 (90)
2	$NaBH_4$/AcOH, −78 °C, 2 h	85:15 (92)	
3	$NaBH_4$/$CeCl_3$/MeOH, −78 to 0 °C, 10 min (1.5 h)	95:5 (82)	67:33 (15)
4	$Zn(BH_4)_2$, THF, −78 °C, 1 h (5 h)	97:3 (90)	77:23 (90) [69][c]
5	$Zn(BH_4)_2$/CH_2Cl_2, −78 °C, 1 h (4 h)	97:3 (90)	88:12 (90)
6	L-Selectride (5 equiv)/THF, −78 °C, 6 h (6 h)	no reaction	no reaction
7	L-Selectride (5 equiv)/CH_2Cl_2, −78 °C, 6 h	70:30 (98)	
8	L-Selectride (5 equiv)/THF, r.t., 6 h	1:1 (70)	
9	DIBAL-H/THF, −78 °C, 6 h (6 h)	no reaction	89:11 (20)
10	DIBAL-H/$ZnCl_2$/THF, −78 °C, 6 h		complex mixture
11	Ph_2MeSiH/THF/TFA, r.t., 12 h	70:30 (30)	
12	Me_4NBH_4/THF, −78 °C, 2 h		45:55 (85)
12	$LiEt_3BH$/THF, −78 °C, 5 h		33:67 (50)
14	$LiEt_3BH$/Et_2O, −78 °C, 8 h		9:91 (46)
15	$LiEt_3BH$/*t*-BuOH/THF, −78 °C, 6 h		no reaction
16	$NaEt_3BH$/THF, −78 °C, 6 h		55:43 (42)

[a] Determined from the NMR of the crude mixtures.
[b] Time for reduction of (+)-**5**.
[c] Isolated yield of the major diastereoisomer.

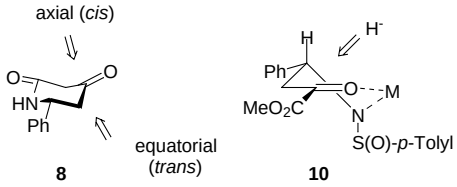
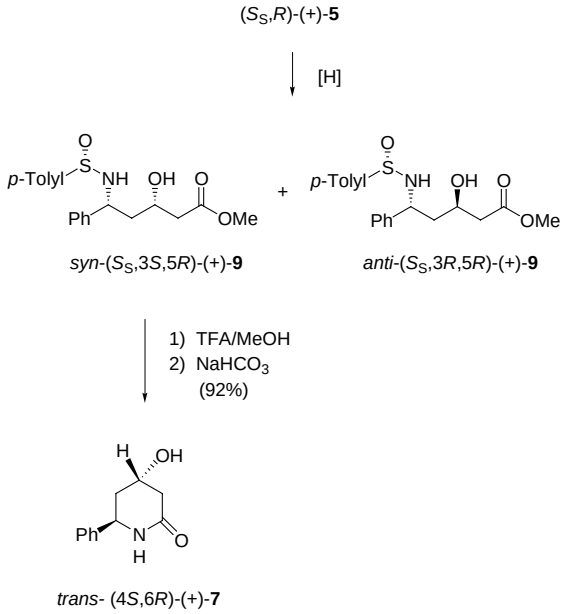


Figure 2 Proposed structure **8** for the preferential formation of *trans*-(4*S*,6*R*)-**7** in the reduction with L-Selectride and the structure of the six-membered chelate **10**

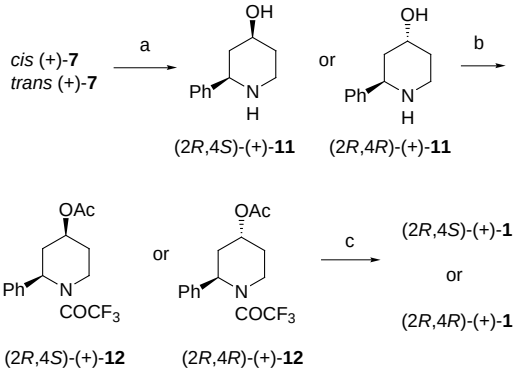
anti reduction of δ-amino β-keto ester **5** to δ-amino β-hydroxy ester **9** (Scheme 2). Although there are many studies on the reduction of acyclic β-hydroxy ketones[21] there are no reports on the reduction of δ-amino β-keto esters and only a few studies on the reduction of acyclic β-amino ketones.[24,25] For the reduction of acyclic β-hydroxy ketones, high *syn* selectivity was observed with reagents that deliver an external hydride ion [$NaBH_4$, $Zn(BH_4)_2$], and *anti* selectivity was observed when hydride was delivered intramolecularly ($LiAlH_4$).[21] In our case, we needed *syn*-**9** because on cyclization it gives the desired *trans* isomer (4*S*,6*R*)-(+)-**7**. The choice of reducing reagent was limited to those that were unlikely to cleave the sulfinyl group and/or reduce the ester functionality. These results are summarized in the Table.



Scheme 2

Good *syn* selectivity was observed only for $Zn(BH_4)_2$ (77:23) (Entries 1 and 4), which afforded, after flash chromatography, (S_S,3*S*,5*R*)-(+)-**9** in 69% yield (entries 4). This result is consistent with formation of a six-membered chelate **10** and external delivery of hydride. Treatment of *syn*-(+)-**9** with TFA/MeOH followed by $NaHCO_3$ gave (4*S*,6*R*)-(+)-**7** in 97% yield. The best *anti* selectivity was observed for lithium triethylborohydride to give a *syn*/*anti* ratio of 9:91 (Entry 14). However, it was difficult to obtain reproducible results, particularly in larger scale reactions, because the sulfinyl and/or methoxycarbonyl groups were being reduced.

Reduction of *cis*- and *trans*-**7** with $LiAlH_4$ for 36 hours gave diastereomerically pure *cis*- and *trans*- **11** in 62 and 64% yields, respectively (Scheme 3). Differential protection of the amino and hydroxy groups was accomplished by sequential treatment of **11** with trifluoroacetic anhydride (TFAA) and acetic anhydride to give **12**.[13,26] Oxidation of the phenyl groups in **12** was accomplished using $NaIO_4/RuCl_3$, followed by deprotection of the hydroxyl and amino groups with K_2CO_3/MeOH.[13] 4-Hydroxypipecolic acids *cis*-(2*R*,4*S*)-(+)-**1** and *trans*- (2*R*,4*R*)-(+)-**1** were isolated by ion exchange (Dowex 50W X8 resin) in 61% and 79% yields, respectively. Their properties were in agreement with literature values.



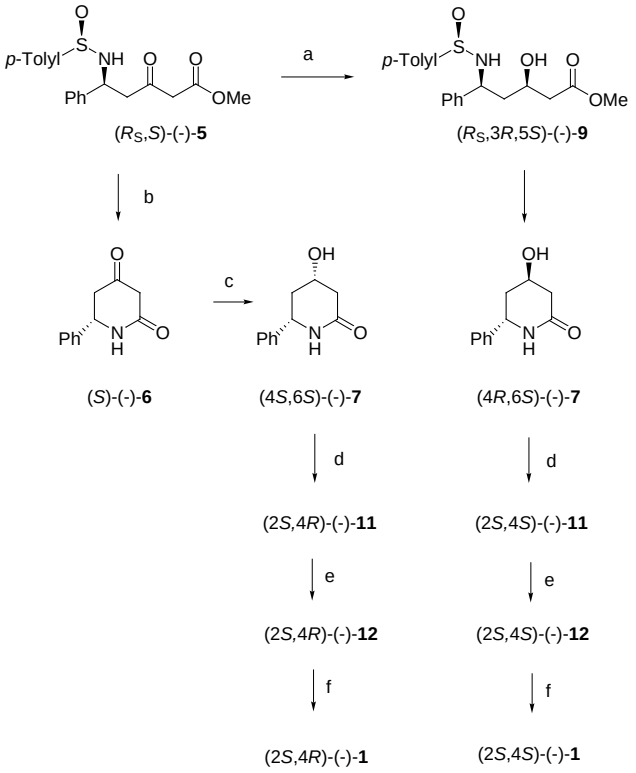
Reagents and conditions: (a) $LiAlH_4$, 36 h, (*cis* or *trans*: 62 or 64%); (b) i) TFAA/Et_3N, ii) K_2CO_3/THF, iii) Ac_2O/Et_3N/DMAP (83% or 80%); (c) i) $NaIO_4/RuCl_3/CCl_4$/MeCN/H_2O, ii) K_2CO_3, iii) Dowex 50 X8 resin (79% or 61% yield)

Scheme 3

The advantage of using δ-amino β-keto esters as chiral building blocks for alkaloid synthesis is that both enantiomers are easily available. Thus, beginning with δ-amino β-keto ester (R_S,*S*)-(−)-**5**, 4-hydroxypipecolic acids *cis*-(2*S*,4*R*)-(−)-**1** and *trans*-(−)-(2*S*,4*S*)-(−)-**1** were prepared in a similar manner in 61% and 68% yields, respectively (Scheme 4).

In summary, the asymmetric synthesis of all four stereoisomers of 4-hydroxypipecolic acid **1** has been achieved from the polyfunctionalized chiral building blocks δ-amino β-keto esters (S_S,*R*)-(+)-**5** or (R_S,*S*)-(−)-**5**. It is noteworthy that the only protection/deprotection group chemistry necessary is related to the oxidation step, serving to illustrate the utility of these building blocks for the efficient asymmetric synthesis of alkaloids.

Column chromatography was performed on silica gel, Merck grade 60(230−400 mesh). Analytical and preparative TLC were performed on precoated silica gel plates (250 and 400 μm) purchased from Analtech Inc. TLC plates were visualized by quenching of UV



Reagents: (a) $Zn(BH_4)_2$ (72%); (b) i) TFA, ii) $NaHCO_3$ (91 and 96%); (c) $NaBH_4$ (96%); (d) LAH (64 and 59%); (e) i) TFAA/Et_3N, ii) K_2CO_3, iii) Ac_2O/Et_3N, (78 and 84%); (f) i) $NaIO_4/RuCl_3/CCl_4$/MeCN/H_2O, ii) K_2CO_3, iii) Dowex 50 X8 resin, (61 and 68% yield).

Scheme 4

fluorescence (λ_{max} 254 nm), staining with I_2 or with 0.5% ninhydin in EtOH. IR spectra were obtained using NaCl plates or KBr discs and recorded on a Mattson 4020 FTIR spectrometer. ^1H and ^{13}C NMR were recorded on a General Electric Omega 500, operating at 500 MHz and 125 MHz, respectively. The spectra were referenced to solvent residues as internal standards. HRMS analyses were performed in the Department of Chemistry, Drexel University, Philadelphia, PA using a Fissions ZAB HF double focusing mass spectrometer. Melting points were recorded on a MEL-TEMP apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

THF and Et_2O were freshly distilled under an inert atmosphere from a purple solution of sodium/benzophenone ketyl. Anhyd CH_2Cl_2 was obtained by refluxing over CaH_2 followed by distillation under an inert atmosphere. $Zn(BH_4)_2$ was prepared according to a literature procedure.[27] All other reagents were obtained from commercial sources and used without further purification. Reactions were performed under an inert atmosphere of argon unless otherwise stated and all glassware was vacuum or oven dried prior to use.

Methyl (*S*$_S$,*R*)-(+)-3-Oxo-5-phenyl-5-(*p*-toluenesulfinylamino)-pentanoate (5)

This procedure is a modification of an earlier procedure.[16] In a 100 mL one-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed a 1 M solution of NaHMDS in THF (12.1 mL, 12.1 mmol) in THF (10 mL) and cooled to −78 °C. Anhyd methyl acetate (0.96 mL, 12.1 mmol) was added slowly via syringe and stirred vigorously for 40 min. Et_2O (5.4 mL) was added followed by addition of (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide[28] (0.59 g, 2.42 mmol) in THF (5 mL) via cannula. The reaction mixture was stirred at −78 °C for 3 h and monitored by TLC. If the starting material was absent, but (+)-**4** was present, the reaction temperature was raised to −42 °C for an additional 3 h and quenched with aq sat NH_4Cl solution (5 mL). H_2O (5 mL) was added and the aq. phase was washed with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (30% EtOAc/hexane) to give 0.74 g (85%) of an oil in >98% de; R_f 0.12 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ 77.0 (*c* = 1.6, $CHCl_3$); [Lit.[16] $[\alpha]_D^{20}$ +73.6 (*c* = 1.63, $CHCl_3$)].

Methyl (*R*$_S$,*S*)-(−)-3-Oxo-5-(*p*-toluenesulfinylamino)-5-phenylpentanoate (5)

Yield: 81%; oil; >98% de; R_f 0.12 (40% EtOAc/Hexanes); $[\alpha]_D^{20}$ −79.6 (*c* = 1.5, $CHCl_3$). Spectral properties were identical to (+)-**5**.

(*R*)-(+)-6-Phenylpiperidine-2,4-dione (6)

In a 50 mL one-necked round-bottomed flask equipped with a magnetic stir bar was placed (*S*$_S$,*R*)-(+)-**5** (1.14 g, 3.16 mmol) in MeOH (20 mL). The mixture was cooled to 0 °C and TFA (1.22 mL, 15.8 mmol) was added. After stirring at r.t. for 1 h, the mixture was concentrated and residue was loaded onto a short pad of silica gel that was then washed with 30% EtOAc/hexane (40−50 mL) until the TLC indicated the absence of the methyl *p*-toluenesulfinate byproduct. Elution with MeOH (50 mL) and concentration gave a residue that was then dissolved in THF (20 mL) and treated with aq sat $NaHCO_3$ solution (5 mL). After stirring for 1 h, the solution was diluted with EtOAc (50 mL) and the aqueous layer was acidified with concd HCl to pH ~3. The mixture was washed with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to give 0.54 g (90%) of a white solid; mp 166−168 °C; R_f 0.17 (40% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ +123.4 (*c* = 0.35, $CHCl_3$); [Lit.[16] mp 167−169 °C; $[\alpha]_D^{20}$ +124.3 (*c* = 0.37, $CHCl_3$)].

(*S*)-(−)-6-Phenylpiperidine-2,4-dione (6)

Yield: 91%; R_f 0.17 (40% EtOAc/CH_2Cl_2); mp 166−168 °C; $[\alpha]_D^{20}$ −122.7 (*c* = 1.0, $CHCl_3$). Spectral properties were identical to (+)-**6**.

(4*R*,6*R*)-(+)-4-Hydroxy-6-phenylpiperidin-2-one (*cis*-7)

In a 50 mL one-necked round-bottomed flask equipped with a magnetic stir bar, rubber septum, and an argon balloon was placed (*R*)-(+)-**6** (0.32 g, 1.69 mmol) in THF (15 mL). The solution was cooled to −78 °C and $NaBH_4$ (0.70 g, 18.5 mmol) was added. After stirring at this temperature for 5 h, aq sat NH_4Cl solution (5 mL), and H_2O (5 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was crystallized from *i*-PrOH/hexanes to give 0.165 g (51%) of a solid in >98% de; mp 213 °C [Lit.[29] mp 212−214 °C for (±)-**7**]; $[\alpha]_D^{20}$ +52.3 (*c* = 0.88, MeOH).

^1H NMR (CD_3OD): δ = 1.60 (ddd, *J* = 11.7, 11.7, 11.4 Hz, 1 H), 2.23−2.31 (m, 2 H), 2.66−2.71 (ddd, *J* = 16.9, 5.5, 2.2 Hz, 1 H), 4.06−4.12 (m, 1 H), 4.48 (dd, *J* = 11.7, 4.4 Hz, 1 H), 7.23−7.38 (m, 5 H).

^{13}C NMR (CD_3OD): δ = 41.4, 42.6, 56.2, 65.5, 127.4, 129, 129.9, 143.5, 173.4.

(4*S*,6*S*)-(−)-4-Hydroxy-6-phenylpiperidin-2-one (*cis*-7)

Yield: 96%; mp 211−213 [Lit.[29] mp 212−214 °C for (±)-**7**]; $[\alpha]_D^{20}$ −51.9 (*c* = 0.56, MeOH). Spectral properties were identical to *cis*-(+)-**7**.

Methyl (S_S,3*S*,5*R*)-(+)-3-Hydroxy-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (*syn*-9)
In a 250 mL one-necked round-bottomed flask was placed (S_S,*R*)-(+)-**5** (1.04 g, 2.89 mmol) in Et_2O (30 mL) and THF (50 mL). The solution was cooled to −78 °C and $Zn(BH_4)_2$[27] (0.14 M in Et_2O, 41 mL, 5.74 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 5 h, quenched by addition of aq sat NH_4Cl solution (20 mL), H_2O (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give **9** as a 77:23 mixture of diastereomers. Purification by flash chromatography (20–40% EtOAc/CH_2Cl_2) afforded 0.725 g (69%) of *syn*-(+)-**9** as a colorless oil; R_f 0.18 (40% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ +63.6 (*c* = 01.1, $CHCl_3$).

IR (neat): ν = 3249, 3021, 2362, 1733, 1439, 1216, 1054, 760 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.80 (ddd, *J* = 14.3, 4.8, 1.8 Hz, 1 H), 1.98 (ddd, *J* = 14.3, 10.3, 8.8 Hz, 1 H), 2.30−2.46 (m, 5 H), 3.66 (s, 3 H), 3.90 (br s, 1 H), 4.17 (m, 1 H), 4.78 (m, 1 H), 5.42 (d, *J* = 2.6 Hz, 1 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.23−7.57 (m, 7 H).

^{13}C NMR ($CDCl_3$): δ = 22.03, 42.51, 45.18, 52.43, 58.30, 68.09, 126.12, 128.32, 129.40, 129.91, 130.81, 141.90, 142.79, 143.16, 173.17.

HRMS: *m*/*z* calcd for $C_{19}H_{23}NO_4S$ (M + H): 362.1426; found 362.1417.

Methyl (S_S,3*R*,5*R*)-(+)-3-Hydroxy-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (*anti*-9)
Yield: 0.221 g (21%); colorless oil; R_f 0.28 (40% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ +95.5 (*c* = 0.56, $CHCl_3$).

IR (neat): ν = 3265, 3029, 2952, 1733, 1439, 1057 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.80 (br s, 1 H), 1.89 (ddd, *J* = 14.7, 9.2, 3.3 Hz, 1 H), 2.01 (ddd, *J* = 14.7, 9.5, 4.0 Hz, 1 H), 2.40−2.45 (m, 4 H), 2.58 (dd, *J* = 16.5, 8.8 Hz, 1 H), 3.67 (s, 3 H), 4.15−4.20 (m, 1 H), 4.83 (m, 1 H), 4.98 (d, *J* = 6.6, 1 H), 7.26−7.40 (m, 7 H), 7.61(d, *J* = 8.4, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.0, 41.7, 44.9, 52.6, 56.6, 65.4, 126.2, 127.6, 128.1, 129.3, 130.4, 142.1, 142.9, 143.4, 173.4.

Methyl (R_S,3*R*,5*S*)-(−)-3-Hydroxy-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (*syn*-9)
Yield: 72%; R_f 0.18 (40% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ −62.8 (*c* = 1.1, $CHCl_3$). Spectral properties were identical to *syn*-(+)-**9**.

Methyl (R_S,3*S*,5*S*)-(−)-3-Hydroxy-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (*anti*-9)
In a 10 mL one-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (R_S,*S*)-(−)-**5** (0.027 g, 0.075 mmol) in Et_2O (1.5 mL) and cooled to −78 °C. $LiEt_3BH$ (Super-Hydride) (190 μL, 0.19 mmol), was added dropwise and the reaction mixture was stirred for 5 h. At this time the solution was quenched by addition of a few drops of MeOH followed by H_2O (5 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to give a 91:9 mixture of diastereomers that were separated by flash chromatography (20–40% EtOAc/CH_2Cl_2) affording 0.012 g (44%) of *anti*-**9** as a colorless oil; R_f 0.28 (40% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ −96.1 (*c* = 1.2, $CHCl_3$). Spectral properties were identical to *anti*-(+)-**9**.

(4*S*,6*R*)-(+)-4-Hydroxy-6-phenylpiperidine-2-one (*trans*-7)
In a 100 mL one-necked round-bottomed flask was placed *syn*-(+)-**9** (0.5 g, 1.38 mmol) in MeOH (30 mL). The mixture was cooled to 0 °C and TFA (0.53 mL, 6.86 mmol) was added. After stirring at r.t. for 1 h, the mixture was concentrated and residue was loaded onto a short pad of silica gel which was washed with 30% EtOAc/hexane (40−50 mL) until the TLC indicated the absence of methyl *p*-toluenesulfinate. Elution with MeOH (50 mL) and concentration gave a residue which was dissolved in THF (30 mL) and treated with aq sat $NaHCO_3$ solution (7.5 mL). The mixture was stirred at r.t. for 2 h, diluted with EtOAc (100 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give 0.256 g (97%) of a white solid; mp 195−198 °C; $[\alpha]_D^{20}$ +29.9 (*c* = 0.67, MeOH).

IR (KBr): ν = 3238, 1621, 1470, 1327, 1158, 1055 cm^{-1}.

^1H NMR (CD_3OD): δ = 1.84 (m, 1 H), 2.10 (m, 1 H), 2.38 (m, 1 H), 2.66 (dd, *J* = 18.0, 4.4 Hz, 1 H), 4.21 (m, 1 H), 4.78 (dd, *J* = 9.9, 4.8 Hz, 1 H), 7.38−7.26 (m, 5 H).

^{13}C NMR (CD_3OD): δ = 39.4, 40.0, 54.2, 63.8, 127.4, 128.8, 129.9, 143.9, 174.1.

HRMS: *m*/*z* calcd for $C_{11}H_{13}NO_2$ (M + Na) 214.0844, found 214.0843.

(4*R*,6*S*)-(−)-4-Hydroxy-6-phenylpiperidine-2-one (*trans*-7)
Yield: 98%; mp 196−198 °C; $[\alpha]_D^{20}$ −30.4 (*c* = 1.2, MeOH). Spectral properties were identical to (+)-**7**.

(2*R*,4*S*)-(+)-2-Phenylpiperidine-4-ol (*cis*-11)
In a 25 mL single neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum and argon-filled balloon was placed *cis*-(+)-**7** (0.433 g, 2.26 mmol) in THF (4 mL). The solution was cooled to −78 °C, and a 1 M solution of $LiAlH_4$ in THF (11.3 mL, 11.3 mmol) was added slowly via syringe, and the mixture was stirred at r.t. for 36 h. At this time the solution was cooled to 0 °C, quenched with aq sat Na_2SO_4 solution (2 mL), stirred for 0.5 h and filtered through Celite. The filtrate was washed with EtOAc (50 mL), and the organic phase was washed with 2 N NaOH (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (90:10:2, CH_2Cl_2/MeOH/28% NH_4OH) to afford 0.25 g (62%) of a white solid; mp 101−102 °C (Lit.[13] mp 101−102 °C for the enantiomer of *cis*-**11**); $[\alpha]_D^{20}$ 20.2 (*c* = 0.56, MeOH) [Lit.[13] $[\alpha]_D^{20}$ −10.9 (*c* = 0.53, MeOH) for its enantiomer (2*S*,4*R*)-**11**]. Physical and spectral properties were in agreement with literature values.[13]

(2*R*,4*R*)-(+)-2-Phenylpiperidine-4-ol (*trans*-11)
Following the same procedure described for the preparation of *cis*-(+)-**11**, *trans*-(+)-**7** gave 0.23 g (64%) of a white solid; mp 107−108 °C; $[\alpha]_D^{20}$ +65.6 (*c* = 0.5, $CHCl_3$).

IR (KBr): ν = 3427, 3170, 1455, 1316, 1115 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.65 (br s, 1 H), 1.74−1.93 (m, 4 H), 3.01 (ddd, *J* = 2.6, 4.8, 11.7 Hz, 1 H), 3.26 (dt, *J* = 2.9, 12.3 Hz, 1 H), 3.52 (s, 1 H), 4.11 (dd, *J* = 2.9, 11.4 Hz, 1 H), 4.30 (m, 1 H), 7.27−7.43 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 145.6, 129.1, 127.8, 127.4, 66.1, 56.2, 42.3, 42.1, 33.5.

HRMS: *m*/*z* calcd for $C_{11}H_{15}NO$ (M+H) 178.1232, found 178.1235.

(2*S*,4*R*)-(−)-2-Phenylpiperidine-4-ol (*cis*-11)
Yield: 64%; mp 101−102 °C; $[\alpha]_D^{20}$ −19.5 (*c* = 0.70, MeOH). Physical and spectral properties were in agreement with literature values.[13]

(2*S*,4*S*)-(−)-2-Phenylpiperidine-4-ol (*trans*-11)
Yield: 59%; mp 107−108 °C; $[\alpha]_D^{20}$ −64.8 (*c* = 0.81, $CHCl_3$). Spectral properties were identical to (2*R*,4*R*)-(+)-**11**.

(2*R*,4*S*)-(+)-4-Acetoxy-2-phenyl-1-trifluoroacetylpiperidine (*cis*-12)
This procedure is a modification of an earlier procedure.[13] To an ice cold solution of *cis*-(+)-**11** (0.104 g, 0.59 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) containing Et_3N (0.49 mL, 3.52 mmol, 6 equiv)

and 4-dimethylaminopyridine (3 mg) was added trifluoroacetic anhydride (0. 33 mL, 2.34 mmol, 4.0 equiv) via a syringe. After stirring at r.t. for 12 h, H_2O (1 mL) was added and the solution was washed with brine (5 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in THF (10 mL), K_2CO_3 (0.162 g (1.17 mmol, 2.0 equiv) and H_2O (0.8 mL) were added, and the mixture was stirred for 5 h. At this time H_2O (2 mL) was added, the solution was washed with CH_2Cl_2 (2 × 5 mL), and dried (Na_2SO_4). After filtering into a one-neck 25 mL round bottomed flask, Et_3N (0.33 mL, 2.37 mmol, 4.0 equiv) and dimethylaminopyridine (3 mg) were added. The mixture was cooled to 0 °C, Ac_2O (0.11 mL, 1.17 mmol, 2.0 equiv) was added and the solution was stirred at r.t. for 12 h. At this time H_2O (1 mL) was added, the solution was washed with brine (5 mL). The organic phases were dried (Na_2SO_4), filtered and concentrated to give an oil that was purified by preparative TLC (EtOAc/pentane, 30:70) to give 0.154 g (83%) of *cis*-(+)-**12** as a colorless oil; $[\alpha]_D^{20}$ 49.3 (*c* = 1.1, CH_2Cl_2); [Lit.[13] $[\alpha]_D^{20}$ −45.5 (*c* = 1.05, CH_2Cl_2) for the enantiomer].

^{1}H NMR ($CDCl_3$) (it existed as rotamers): δ = 1.44 (s, 0.9 H), 1.51 (s, 2.1 H), 1.72−1.96 (m, 2 H), 2.11−2.16 (m, 1 H), 2.87−2.99 (m, 1 H), 3.33 (m, 0.3 H), 3.68 (q, *J* = 12.8 Hz, 0.7 H), 3.92 (d, *J* = 13.6 Hz, 0.7 H), 4.54 (d, *J* = 11.7 Hz, 0.3 H), 5.07 (s, 1 H), 5.34 (br s, 0.3 H), 5.85 (d, *J* = 5.1 Hz, 0.7 H), 7.12−7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 171.0, 157.5 (m), 139.3, 138.8, 129.4, 127.5, 125.7, 117.3 (q, *J* = 288 Hz), 66.9, 54.5, 51.8, 38.5, 35.7, 32.6, 31.7, 30.8, 29.9, 21.2.

(2*S*,4*R*)-(−)-4-Acetoxy-2-phenyl-1-trifluoroacetylpiperidine (*cis*-12)
Yield: 78%; colorless oil; $[\alpha]_D^{20}$ −47.9 (*c* = 1.1, CH_2Cl_2). Physical and spectral properties were identical to (2*R*,4*S*)-(+)-**12**.

(2*R*,4*R*)-(+)-4-Acetoxy-2-phenyl-1-trifluoroacetylpiperidine (*trans*-12)
Yield: 80%; colorless oil; $[\alpha]_D^{20}$ +80.7 (*c* = 1.95, CH_2Cl_2).

IR (neat): ν = 1736, 1690, 1455, 1243, 1204, 1142, 1046 cm^{-1}.

^{1}H NMR ($CDCl_3$) (it existed as rotamers): δ = 1.63−1.71 (m, 1 H), 1.86−2.14 (m, 4 H), 2.75−3.12 (m, 2 H), 3.90 (br d, *J* = 14.7 Hz, 0.7 H), 4.51 (br d, *J* = 13.9 Hz, 0.3 H), 4.96−5.08 (m, 1 H), 5.43 (br s, 0.3 H), 6.04 (br s, 0.7 H), 7.26−7.42 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 171.1, 157.1 (q, *J* = 34.6 Hz), 137.0, 136.8, 131.0, 129.9, 128.5, 128.4, 127.0, 126.7, 117.3 (q, *J* = 288.9 Hz), 67.7, 56.2, 53.4, 40.8, 38.7, 34.0, 32.6, 32.3, 31.6, 21.7.

Anal. calcd for $C_{15}H_{16}F_3NO_3$: C 57.14; H, 5.12; N, 4.44. Found: C, 57.04; H, 5.36; N, 4.46.

2*S*,4*S*)-(−)-4-Acetoxy-2-phenyl-1-trifluoroacetylpiperidine (*trans*-12)
Yield: 84%; colorless oil; $[\alpha]_D^{20}$ −81.2 (*c* = 1.1, CH_2Cl_2).

IR (neat): ν = 1736, 1690, 1455, 1243, 1204, 1142, 1046 cm^{-1}.

^{1}H NMR ($CDCl_3$) (it existed as rotamers): δ = 1.63−1.71 (m, 1 H), 1.86−2.14 (m, 4 H), 2.75−3.12 (m, 2 H), 3.90 (br d, *J* = 14.7 Hz, 0.7 H), 4.51 (br d, *J* = 13.9 Hz, 0.3 H), 4.96−5.08 (m, 1 H), 5.43 (br s, 0.3 H), 6.04 (br s, 0.7 H), 7.26−7.42 (m, 5 H);

^{13}C NMR ($CDCl_3$): δ = 171.1, 157.1 (q, *J* = 34.6 Hz), 137.0, 136.8, 131.0, 129.9, 128.5, 128.4, 127.0, 126.7, 117.3 (q, *J* = 288.9 Hz), 67.7, 56.2, 53.4, 40.8, 38.7, 34.0, 32.6, 32.3, 31.6, 21.7.

(2*R*,4*S*)-(+)-4-Hydroxypipecolic Acid (*cis*-1)
In a 25 mL one-necked round bottom flask equipped with a magnetic stir bar was placed *cis*-(+)-**12** (0.14 g, 0.44 mmol), CCl_4 (2 mL), MeCN (2 mL), and H_2O (3 mL). $NaIO_4$ (1.42 g, 6.64 mmol) and $RuCl_2 \cdot H_2O$ (0.0046 g, 0.022 mmol), were added and the solution was stirred vigorously for 8 h. The solution was filtered through a Celite, and rinsed with CH_2Cl_2 (20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissolved in methanol (5 mL), 0.368 g (2.66 mmol) of K_2CO_3 was added, and the mixture was stirred at r.t. for 12 h. The solution was concentrated, acidified with 1 N HCl, purified using a Dowex 50W-X8 resin (50−100 mesh) and eluted with 5% NH_4OH (150 mL). The ninhydrin positive fractions were combined and evaporated in vacuo to give a solid which was washed with activated carbon (1.0 g) in hot H_2O (20 mL). Concentration and drying under vacuum gave 0.039 g (61%) of (*2R,4S*)-(+)-**1** as a white gum; $[\alpha]_D^{20}$ +19.3 (*c* = 0.7, H_2O) [Lit.[13] $[\alpha]_D^{22}$ −17.2 (*c* = 1.05, H_2O) for the enantiomer].

(2*S*,4*R*)-(−)-4-Hydroxypipecolic Acid (*cis*-1)
Yield: 61%; white gum; $[\alpha]_D^{20}$ −18.9 (*c* = 0.7, H_2O) [Lit.[13] $[\alpha]_D^{20}$ −17.2 (*c* = 1.05, H_2O)].

(2*R*,4*R*)-(+)-4-Hydroxypipecolic Acid (*trans*-1)
Yield: 79%; white gum; $[\alpha]_D^{20}$ +12.6 (*c* = 0.8, H_2O) [Lit.[5] $[\alpha]_D^{20}$ −13 ± 0.4 (1% in H_2O) for the enantiomer]. Spectral properties were in agreement with literature values.[30]

(2*S*,4*S*)-(−)-4-Hydroxypipecolic Acid (*trans*-1)
Yield: 68%; white gum; $[\alpha]_D^{20}$ −12.6 (*c* = 0.8, H_2O) [Lit.[5] $[\alpha]_D^{20}$ −13 ± 0.4 (1% in H_2O) for the enantiomer]. Spectral properties were in agreement with literature values.[30]

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