A Short and Convenient Synthesis of Enantiopure *cis*- and *trans*-4-Hydroxypipecolic Acid

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Abstract: The synthesis of (2*S*,4*R*)- and (2*R*,4*R*)-4-hydroxypipecolic acid has been realized from commercial ethyl (*R*)-4-cyano-3-hydroxybutanoate through palladium-catalyzed methoxycarbonylation of a 4-hydroxy-substituted lactam-derived vinyl phosphate followed by the stereocontrolled reduction of the enamine double bond. The stereoselective hydrogenation of the suitably 4-hydroxy-protected enantiomer afforded the *cis*-(2*S*,4*R*)-4-hydroxypipecolic acid product, obtained in 66% overall yield over seven steps. The *trans*-product (42% overall yield over 8 steps) was instead obtained by hydride conjugate addition to the same α,β-unsaturated ester.

Key word: amino acids, carbonylations, coupling, lactams, palladium

4-Hydroxypipecolic acids are naturally occurring non-proteinogenic α-amino acids often isolated as their hydroxylated derivatives which, in many cases, display interesting and potent biological activity. (2*S*,4*R*)-4-Hydroxypipecolic acid [(2*S*,4*R*)-**1**] (Figure 1), isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[1] is a constituent of the cyclodepsipeptide antibiotic virginiamycin S_2.[2] Its epimer (2*R*,4*R*)-**1**, first isolated from the leaves of *Acacia excelsa*,[3] is embedded in the structure of damipipecoline, a serotonine receptor antagonist isolated very recently from the *Axinella damicornis* sponge,[4] as well as in ovalin,[5] and in a sulfate derivative possessing NMDA (*N*-methyl-D-aspartic acid) receptor agonistic activity.[6]

4-Hydroxypipecolic acids are also useful scaffolds for the preparation of medicinally important compounds.[7] In particular, (2*R*,4*S*)-**1** has been used as an intermediate in the synthesis of CGS 20281 (Figure 1), which is one of the most potent and selective competitive NMDA receptor antagonists,[8] whereas (2*S*,4*R*)-**1** has been included in the structure of HIV-protease inhibitors such as palinavir,[9] and some antagonists of the cholecistokinin (CCK) hormone.[10]

As a consequence of their importance in medicinal chemistry, a number of enantioselective syntheses of 4-hydroxypipecolic acids have been reported,[7c,e,11,12] including our own which was focused on the preparation of (2*S*,4*R*)-**1**.[13] This synthesis, which started from commercially available ethyl (3*S*)-4-chloro-3-hydroxybutanoate, was based on the palladium-catalyzed methoxycarbonylation of a 4-methoxybenzyl-protected lactam-derived vinyl triflate **3** (R = PMB, X = Tf) (Scheme 1) followed by stereocontrolled hydrogenation of the enamine double bond. However, the preparation of hydroxy ester **2** included the use of relatively large amounts of nickel(II) chloride hexahydrate (proven animal carcinogenic substance of potential relevance to humans) in the reductive step leading to 4-hydroxy-δ-valerolactam **4**, as well as the expensive *N*-phenyltriflimide for the preparation of vinyl triflate **3** as the intermediate in the carbonylative step.

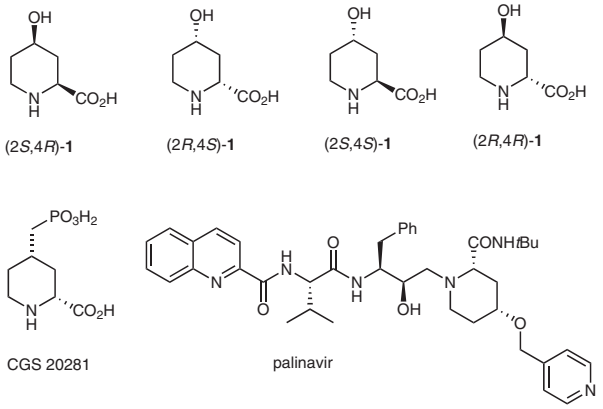
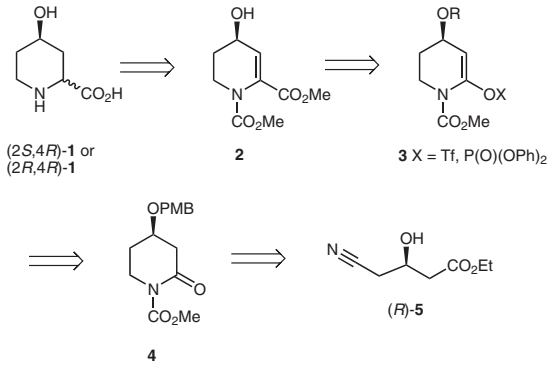


Figure 1 4-Hydroxypipecolic acids and some derivatives



Scheme 1 Retrosynthetic analysis

We present here a short and high-yielding synthesis of both *cis*-(2*S*,4*R*)- and *trans*-(2*R*,4*R*)-4-hydroxypipecolic acid starting from commercial ethyl (*R*)-4-cyano-3-hy-

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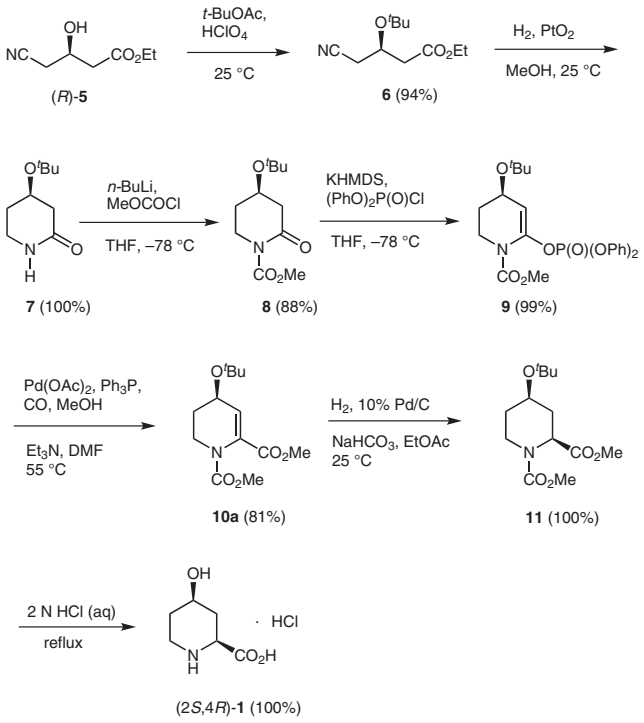
droxybutanoate [(*R*)-**5**] (96% ee) in which these drawbacks were overcome allowing for a facile synthesis.

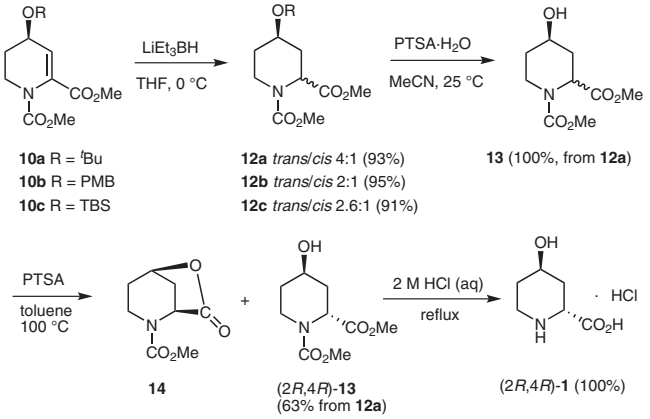
To avoid the use of nickel(II) chloride hexahydrate (and the tedious procedure of nitrile reduction) in the ring-closure step, we had first to revise the protection protocol in order to convert the nitrile into the corresponding lactam by simple hydrogenation. We therefore chose *tert*-butyl protection as this is an easily removable O-protecting group, compatible with the hydrogenation conditions and strong bases, and it has the advantage that a sterically hindered group would be already installed for the stereocontrolled reduction of the enamine double bond.



Scheme 2 Preparation of (2*S*,4*R*)-**1**

To protect (*R*)-**5** as *tert*-butyl ether **6** we stirred a solution of the alcohol in *tert*-butyl acetate at 25 °C for 24 hours, in the presence of perchloric acid (0.1 equiv), a procedure usually employed for the esterification of carboxylic acids1,[14] which provided **6** in 94% yield after chromatography (Scheme 2).[15] The subsequent hydrogenation was carried out over platinum(IV) oxide in methanol at room temperature for 48 hours (or in abs EtOH for 24 h), to give lactam **7** in quantitative yield. Following N-protection, vinyl phosphate **9** was prepared by treatment with potassium hexamethyldisilazanide (0.5 M in toluene) at –78 °C in tetrahydrofuran, followed by addition of diphenyl chlorophosphate. Lactam-derived vinyl phosphates are reported to be generally much more stable than the corresponding triflates,[16] and so we were pleased to observe that after an appropriate work-up, phosphate **9** proved stable for days as a crude reaction mixture and it could be purified by chromatography on silica gel (99%). We found also that if the phosphate was immediately used after chromatography, the yields of the subsequent carbonylative step were much higher. Moreover diphenyl chlorophosphate is much cheaper than the triflimides generally employed for trapping the enolates. The carbonylation was carried out according to standard conditions,[13,17] affording ester **10a** in 81% yield after chromatography.[18] Hydrogenation of **10a** was carried out over 10% palladium on carbon (50% wet) in ethyl acetate at 25 °C and afforded **11** as a 19:1 mixture together with its *trans*-diastereomer. The presence of sodium hydrogen carbonate in the reaction mixture was necessary to avoid loss of the protecting group due to the hydrogen chloride generated by reduction of the traces of palladium(II) chloride present in the catalyst.[19] We were glad to observe that the facial selectivity in the hydrogenation was comparable to that obtained with the *O*-silyl protecting group.[13] Hydrolysis of **11** (96% ee, 90% de) eventually furnished (2*S*,4*R*)-**1** as its hydrochloride salt in 66% overall yield over seven steps.

For the synthesis of *trans*-isomer (2*R*,4*R*)-**1**, after some failed attempts at reducing allylic alcohol **2**[13] by hydrogenation in the presence of Crabtree's catalyst,[20] we opted for the conjugate reduction of the α,β-unsaturated ester moiety of intermediate **10a** (Scheme 3) which would lead, after equilibration during the workup, to the prevailing formation of the thermodynamically more stable *trans*-isomers. For this attempt we employed also differently O-protected compounds **10b** and **10c**, which were prepared as reported.[13]



Scheme 3 Synthesis of (2*R*,4*R*)-**1**

We first treated compound **10b** with 1.2 equivalents of Super-Hydride ($LiEt_3BH$) in tetrahydrofuran at 0 °C, followed by quenching with saturated sodium hydrogen carbonate solution at –15 °C. The ^1H NMR analysis of the crude reaction mixture revealed that hydride conjugate addition occurred without any concurrent reduction of the ester and the substrate was quantitatively converted into a 2:1 mixture of the *trans*- and *cis*-isomers **12b**.[21] A slightly higher ratio in favor of the *trans*-isomer was obtained by applying the same procedure to the *O*-silyl-protected compound **10c**. In this case, the ratio between the *trans*- and *cis*-isomers was 2.6:1.[21] Eventually, with *O*-*tert*-butyl-protected compound **10a** the ratio between the two iso-

mers after reduction was 4:1. The chromatographic separation of the *cis*- and *trans*-isomers of **12a–c** was difficult and so, after deprotection of the 4-OH group, we applied the procedure described by Herdeis for a lactonization that should involve only the *cis*-isomer, leaving therefore the *trans*-isomer unaltered.[22] Thus, the diastereomeric mixtures of alcohol **13** obtained by deprotection of **12a–c** were treated with 4-toluenesulfonic acid in anhydrous toluene at 100 °C for 30 minutes and, after workup and removal of the solvent, the corresponding mixtures of **14** and (2*R*,4*R*)-**13** were obtained. These were easily separated by chromatography,[23] which provided pure *trans*-compound (2*R*,4*R*)-**13** in 44% (from **12b**), 50% (from **10c**), and 63% (from 1**2a**) yield over three steps.[24] Usual exhaustive hydrolysis of (2*R*,4*R*)-**13** quantitatively provided target (2*R*,4*R*)-**1** as its hydrochloride salt. Although the selectivity in the conjugate reduction was not higher than 4:1, however, this reaction is one of the last steps of the synthesis and the effective loss of material as the undesired *cis*-isomer is low, especially as the *O-tert*-butyl protection-based strategy allows us to obtain in a very few steps compound **10a** in excellent yield.

In conclusion we have developed a short and convenient synthesis of (2*S*,4*R*)- and (2*R*,4*R*)-4-hydroxypipecolic acid starting from commercial ethyl (*R*)-4-cyano-3-hydroxybutanoate. Key steps were the palladium-catalyzed methoxycarbonylation of an *O-tert*-butyl-protected 4-hydroxy-substituted lactam-derived vinyl phosphate and the stereocontrolled reduction of the enamine double bond. The *cis*-(2*S*,4*R*)-product was obtained in 66% overall yield over seven steps, the *trans*-(2*R*,4*R*)-product in 42% over eight steps. As ethyl (*S*)-4-cyano-3-hydroxybutanoate is easily prepared by standard procedures from commercial ethyl (*R*)-4-chloro-3-hydroxybutanoate, the synthesis of the two enantiomers (2*R*,4*S*)- and (2*S*,4*S*)-4-hydroxypipecolic acid is an obvious extension.

Chromatographic separations were performed under pressure on silica gel 60 (Merck, 70–230 mesh) using flash-column techniques, PE = petroleum ether; R_f values refer to TLC carried out on 0.25-mm silica gel plates with the same eluant indicated for column chromatography. THF was distilled from Na/benzophenone. CH_2Cl_2 and heptane were distilled from CaH_2. Commercial anhyd DMF and cyclohexane were used. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C. MS spectra were carried out by EI at 70 eV. Compounds **2**, **10b**, and **10c** were prepared as reported.[13,25]

Ethyl (*R*)-3-*tert*-Butoxy-4-cyanobutanoate (6)

To a soln of (*R*)-**5** (1.257 g, 8.0 mmol) in *t*-BuOAc (100 mL) was added dropwise $HClO_4$ (48 μL, 0.8 mmol) and the mixture was stirred at 25 °C for 24 h. Then sat. aq Na_2CO_3 soln (50 mL) was added, the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (50 mL) and dried (K_2CO_3). After filtration and evaporation of the solvent, **6** (1.65 g, 97%) was obtained as a pale yellow liquid, which can directly be used in the next step. Chromatography (EtOAc–*n*-hexane, 1:3, R_f = 0.3), gave **6** (1.602 g, 94%) as a pale yellow oil.

$[\alpha]_D^{20}$ –9.0 (*c* 2.00, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.15–4.03 (m, 1 H + 2 H), 2.62–2.54 (m, 4 H), 1.26–1.15 (m, 9 H + 3 H).

^{13}C NMR (50.33 MHz, $CDCl_3$): δ = 170.4 (s), 117.5 (s), 75.1 (s), 64.3 (d), 60.7 (t), 41.2 (t), 28.1 (q, 3 C), 25.4 (t), 14.1 (q).

MS (EI, 70 eV): *m*/*z* (%) = 198 ([M$^+$ – 15], 15), 140 (35), 112 (28), 57 (100).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.98; H, 8.77; N, 6.28.

(*R*)-4-*tert*-Butoxypiperidin-2-one (7)

To a stirred soln of **6** (506 mg, 2.38 mmol) in MeOH (10 mL) was added PtO_2 (54 mg, 0.2 mmol) under N_2. The mixture was flushed with H_2 and then left under static pressure of H_2 (balloon) at 25 °C. After 48 h the reaction was complete (TLC). The catalyst was filtered, washed with MeOH, and the soln was concentrated under vacuum, to give pure **7** (408 mg, 100%) as a white solid. The same reaction can be carried out in abs EtOH, in which case it was complete in 24 h; mp 102.5–103.5 °C.

$[\alpha]_D^{20}$ +17.4 (*c* 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (br s, 1 H), 3.96–3.89 (m, 1 H), 3.50–3.43 (m, 1 H), 3.34–3.20 (m, 1 H), 2.55 (dd, *J* = 17.6, 5.0 Hz, 1 H), 2.34 (dd, *J* = 17.6, 6.4 Hz, 1 H), 1.91–1.83 (m, 1 H), 1.79–1.71 (m, 1 H), 1.12 (s, 9 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 171.6 (s), 74.0 (s), 64.0 (d), 40.7 (t), 38.4 (t), 30.2 (t), 28.3 (q, 3 C).

MS (EI, 70 eV): *m*/*z* (%) = 156 ([M$^+$ – 15], 3), 115 (48), 98 (28), 87 (18), 72 (21), 59 (100).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.03; H, 10.00; N, 8.09.

Methyl (*R*)-4-*tert*-Butoxy-2-oxopiperidine-1-carboxylate (8)

To a cooled (–78 °C) soln of **7** (372 mg, 2.17 mmol) in anhyd THF (9 mL) under N_2, was added dropwise 1.6 M BuLi in hexane (1.49 mL, 2.39 mmol, 1.1 equiv). After 40 min, methyl chloroformate (185 μL, 2.39 mmol, 1.1 equiv) was added dropwise, the cooling bath was removed, and the mixture was allowed to warm to 0 °C and the mixture was stirred for a further 2 h. Then sat. aq $NaHCO_3$ soln (6 mL) was slowly added, followed by H_2O (15 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtered and the solvent was evaporated to give **8** as a yellowish solid that was chromatographed (CH_2Cl_2–MeOH, 40:1 + 0.1% Et_3N, R_f = 0.32) to give pure **8** (438 mg, 88%) as a white solid; mp 55–56 °C.

$[\alpha]_D^{20}$ +15.5 (*c* 0.47, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99–3.93 (m, 1 H), 3.89 (ddd, *J* = 12.8, 8.2, 4.7 Hz, 1 H), 3.86 (s, 3 H), 3.67 (ddd, *J* = 12.8, 7.3, 4.7 Hz, 1 H), 2.69 (dd, *J* = 16.8, 5.1 Hz, 1 H), 2.53 (dd, *J* = 16.8, 6.6 Hz, 1 H), 2.06–1.93 (m, 1 H), 1.86–1.76 (m, 1 H), 1.18 (s, 9 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 169.9 (s), 154.8 (s), 74.2 (s), 63.7 (d), 53.9 (q), 43.8 (t), 42.7 (t), 31.2 (t), 28.2 (q, 3 C).

MS (EI, 70 eV): *m*/*z* (%) = 229 ([M$^+$], 3), 173 (30), 156 (25), 102 (22), 88 (20), 57(100).

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.41; H, 8.13; N, 6.02.

Methyl (*R*)-4-*tert*-Butoxy-6-[(diphenoxyphosphoryl)oxy]-3,4-dihydropyridine-1(2*H*)-carboxylate (9)

To a 0.5 M soln of KHMDS in toluene (4.7 mL, 2.35 mmol) in THF (12.5 mL), cooled to –78 °C and under N_2, was added a soln of **8** (430 mg, 1.88 mmol) in THF (5 mL) and the resulting mixture was stirred for 1.5 h. Then a soln of $(PhO)_2P(O)Cl$ (487 μL, 2.35 mmol) in THF (4 mL) was added and the mixture was stirred at –78 °C for 1 h; the temperature was allowed to rise to 0 °C. Then, 10% aq NaOH soln (38 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined extracts were washed with 10%

NaOH (24 mL) and dried (anhyd K_2CO_3 for 30 min). After filtration and evaporation of the solvent (without heating and leaving a small volume of solvent), the crude phosphate was chromatographed (silica gel 3.5 cm in a column with i.d. of 3 cm, EtOAc–*n*-hexane, 30:70 + 1% Et_3N, R_f = 0.27) to give **9** (856 mg, 99%) as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 10 H), 4.92 (br s, 1 H), 3.65–3.60 (m, 1 H), 3.52 (s, 3 H), 3.49–3.21 (m, 2 H), 1.82–1.64 (m, 2 H), 1.14 (s, 9 H).

^{13}C NMR (50.33 MHz, $CDCl_3$): δ = 154.1 (s), 150.4 (s), 141.1 (s), 129.7 (d, 4 C), 125.3 (d, 2 C), 120.1 (d, 4 C), 102.2 (d), 74.1 (s), 61.9 (d), 53.1 (q), 42.9 (t), 32.7 (t), 28.1 (q, 3 C).

Dimethyl (*R*)-4-*tert*-Butoxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (10a)

Phosphate **9** (856 mg, 1.86 mmol) was immediately dissolved in DMF (4.8 mL), $Pd(OAc)_2$ (42 mg, 0.186 mmol), and Ph_3P (97 mg, 0.372 mmol) were added and the soln was stirred for 10 min under a CO atmosphere (balloon). Then Et_3N (516 μL, 3.72 mmol) and MeOH (3 mL, 74.4 mmol) were added and stirring was continued at 55 °C (external bath) for 3 h under static CO pressure. The soln was filtered through Celite and the MeOH was evaporated. The residue was diluted with H_2O (40 mL) and extracted with Et_2O (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and filtered and the solvent was evaporated to give an oily residue that was chromatographed (EtOAc–*n*-hexane, 1:2 + 1% Et_3N, R_f = 0.33) to give **10a** (408 mg, 81%) as a thick pale yellow oil.

$[\alpha]_D^{23}$ +157 (*c* 0.54, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (d, *J* = 3.9 Hz, 1 H), 4.07–4.16 (m, 1 H), 3.97 (dt, *J* = 12.9, 4.3 Hz, 1 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.28 (ddd, *J* = 12.9, 8.9, 4.7 Hz, 1 H), 1.89–1.81 (m, 2 H), 1.21 (s, 9 H).

^{13}C NMR (50.33 MHz, $CDCl_3$): δ = 164.7 (s), 153.8 (s), 132.3 (s), 122.5 (d), 74.1 (s), 60.6 (d), 52.8 (q), 51.8 (q), 40.5 (t), 32.4 (t), 27.8 (q, 3 C).

MS (EI, 70 eV): *m*/*z* (%) = 271 ([M$^+$], 18), 198 (87), 183 (100), 94 (82), 80 (42), 57 (79).

Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.41; H, 7.67; N, 5.01.

Dimethyl (2*S*,4*R*)-4-*tert*-Butoxypiperidine-1,2-dicarboxylate (11)

To a stirred suspension of $NaHCO_3$ (86 mg) in EtOAc (11 mL) was added 10% Pd/C (50% wet, 142.5 mg) under N_2. The mixture was flushed with H_2 and then stirring was continued for 30 min. The soln of **10a** (114 mg, 0.42 mmol) in EtOAc (1 mL) was added via microsyringe and the suspension was stirred at r.t. for 4 h under static H_2 pressure. After filtration through a Celite layer, and evaporation of the solvent, the crude reaction was purified by chromatography (EtOAc–*n*-hexane, 1:4, R_f = 0.15), to give **11** (115 mg, 100%) as a colorless oil; 19:1 diastereomeric mixture.

$[\alpha]_D^{25}$ –14.3 (*c* 2.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (br d, *J* = 5.9 Hz, major rotamer, 1 H) and 4.64 (br d, *J* = 5.5 Hz, minor rotamer, 1 H), 3.93 (br d, *J* = 13.3 Hz, minor rotamer, 1 H) and 3.78 (br d, *J* = 13.1 Hz, major rotamer, 1 H), 3.86–3.76 (m, 1 H), 3.71 (s, 3 H + 3 H of the major rotamer), 3.67 (s, 3 H, minor rotamer), 3.56–3.38 (m, 1 H), 2.36–2.26 (m, 1 H), 1.83–1.75 (m, 1 H), 1.60–1.50 (m, 2 H), 1.11 (s, 9 H).

^{13}C NMR (50.33 MHz, $CDCl_3$): δ = 172.4 (s), 158.6 (s) and 158.5 (s), 73.5 (s), 61.9 (d), 52.8 (q), 51.7 (q) and 51.4 (q), 36.6 (t), 33.7 (t), 31.7 (t), 27.9 (q, 3 C).

MS (EI, 70 eV): *m*/*z* (%) = 273 ([M$^+$], 3]), 214 (52), 199 (13), 158 (100), 140 (32), 114 (39), 57 (42).

Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.11; H, 8.37; N, 5.07.

(2*S*,4*R*)-4-Hydroxypiperidine-2-carboxylic Acid Hydrochloride Salt [(2*S*,4*R*)-1·HCl][7c,13,22b]

A suspension of **11** (38.7 mg, 0.14 mmol) in aq 2 M HCl (6 mL) was refluxed under stirring for 18 h. After cooling, the mixture was washed with Et_2O (2 × 8 mL) and concentrated. The residue was triturated with acetone and dried under vacuum for 24 h. Salt (2*S*,4*R*)-**1**·HCl (25 mg, 100%) was obtained as a white foamy solid. Spectroscopic data as reported.[13,22b]

$[\alpha]_D^{25}$ +9.5 (*c* 0.53 MeOH) [Lit.[7c] $[\alpha]_D^{25}$ +9.9 (*c* 1.01 MeOH, 95.8% ee)].

Dimethyl (2*R*/*S*,4*R*)-4-*tert*-Butoxypiperidine-1,2-dicarboxylate (12a) and Dimethyl (2*R*,4*R*)-4-Hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

Dimethyl (2*R*/*S*,4*R*)-4-*tert*-Butoxypiperidine-1,2-dicarboxylate (12a); Typical Procedure from 10a

To a soln of **10a** (135.6 mg, 0.5 mmol) in anhyd THF (1.7 mL), cooled at 0 °C and under N_2, was added dropwise 1 M $LiEt_3BH$ in THF (600 μL, 0.60 mmol). The mixture was stirred at 0 °C for 1 h, then it was cooled to –15 °C and quenched with sat. aq $NaHCO_3$ soln (5 mL). The mixture was extracted with CH_2Cl_2 (5 × 15 mL) and the combined extracts were washed with H_2O (15 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvent, MeOH (5 mL) was added and the solvent evaporated again. This operation was repeated two times providing *trans*-**12a** with its *cis*-isomer; yield: 127 mg (93%); ratio *trans*/*cis* 4:1 (by ^{1}H NMR).[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (br s, major rotamer, 1 H) and 4.86 (br s, minor rotamer, 1 H), 4.16 (br d, *J* = 12.9 Hz, minor rotamer, 1 H) and 4.02 (br d, *J* = 13.7 Hz, major rotamer, 1 H), 3.76 (s, 3 H), 3.74–3.65 (m, 3 H + 1 H), 3.13–2.91 (m, 1 H), 2.38–2.25 (br m, 1 H), 1.83–1.67 (m, 1 H), 1.66–1.54 (m, 1 H), 1.51–1.36 (m, 1 H), 1.18 (s, 9 H).

Dimethyl (2*R*,4*R*)-4-Hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

The above 4:1 mixture of **12a** was then dissolved in MeCN (6 mL) and PTSA·H_2O (105 mg, 0.55 mmol) was added, and the mixture was stirred vigorously at 25 °C for 24 h [TLC monitoring (EtOAc–*n*-hexane, 1:1)]. The soln was filtered through a short pad of Celite–$NaHCO_3$ (1:1) and concentrated. The residue (91 mg) was dissolved in anhyd toluene (3.0 mL) and PTSA (43 mg, 0.25 mmol) was added. The mixture was then heated at 100 °C (external bath) with stirring under N_2. After 30 min the soln was cooled to r.t. and concentrated. The residue was chromatographed (EtOAc–PE, 1:1, R_f = 0.13) to give (2*R*,4*R*)-**13** (68 mg, 63% from **12a**) as a colorless oil.

$[\alpha]_D^{25}$ +21.5 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (br s, 1 H) and 4.90 (br s, minor rotamer, 1 H), 4.18 (br d, *J* = 12.1 Hz, minor rotamer, 1 H) and 4.06 (br d, *J* = 12.0 Hz, major rotamer, 1 H), 3.75–3.61 (m, 3 H + 3 H + 1 H), 3.15–2.95 (m, 1 H), 2.47 (br d, *J* = 11.7 Hz, 1 H), 1.96–1.84 (m, 1 H), 1.66–1.56 (m, 1 H), 1.47–1.37 (m, 1 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 171.5 (s), 156.4 (s), 65.9 (d), 54.2 (d), 53.1 (q), 52.4 (q), 40.3 (t), 35.4 (t), 33.9 (t).

MS (EI, 70 eV): *m*/*z* (%) = 217 ([M$^+$], 1), 158 (100), 140 (14), 114 (62).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.58; H, 6.85; N, 6.37.

Dimethyl (2*R*/*S*,4*R*)-4-(4-Methoxybenzyloxy)piperidine-1,2-dicarboxylate (12b) and Dimethyl (2*R*,4*R*)-4-hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

Dimethyl (2*R*/*S*,4*R*)-4-(4-Methoxybenzyloxy)piperidine-1,2-dicarboxylate (12b)

Following the typical procedure for **12a** using **10b** (193 mg, 0.58 mmol) in anhyd THF (2 mL) and 1 M $LiEt_3BH$ in THF (690 μL, 0.69 mmol) gave *trans*-**12b** with its *cis*-isomer; yield: 186 mg (95%); ratio *trans*/*cis* 2:1 (by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ (attributable signals) = 5.06 (br s, 1 H) and 4.91 (br s, minor rotamer, 1 H), 4.48 (s, 2 H), 4.20 (br d, *J* = 11.1 Hz, minor rotamer, 1 H) and 4.06 (br d, *J* = 11.2 Hz, major rotamer, 1 H), 3.80–3.60 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.72 and 3.70 (s, 3 H, two rotamers), 3.11–2.94 (m, 1 H), 2.61–2.50 (br m, 1 H), 2.02–1.94 (m, 1 H), 1.67–1.56 (m, 1 H), 1.50–1.37(m, 1 H).

Dimethyl (2*R*,4*R*)-4-hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

The above 2:1 mixture of **12b** was dissolved in EtOAc (6.5 mL) and 10% Pd/C (58 mg) was added under N_2. The mixture was flushed with H_2 and then left under static pressure of H_2 (balloon) at 25 °C. After 48 h the catalyst was filtered, washed with EtOAc, and the soln concentrated. The residue (116 mg) was dissolved in anhyd toluene (4 mL) and PTSA (55 mg, 0.32 mmol) was added. The mixture was then heated at 100 °C (external bath) with stirring and under N_2. After 30 min the soln was cooled to r.t. and concentrated. The residue was chromatographed (EtOAc–PE, 1:1, R_f = 0.13) to give (2*R*,4*R*)-**13** (55 mg, 44% from **10b**) as a colorless oil. Spectroscopic and analytical data as reported above.

Dimethyl (2*R*/*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)piperidine-1,2-dicarboxylate (12c) and Dimethyl (2*R*,4*R*)-4-Hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

Dimethyl (2*R*/*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)piperidine-1,2-dicarboxylate (12c)

Following the typical procedure for **12a** using **10c** (170 mg, 0.52 mmol) in anhyd THF (1.8 mL) and $LiEt_3BH$ in THF (620 μL, 0.62 mmol) gave *trans*-**12c** with its *cis*-isomer; yield: 157 mg (91%); ratio *trans*/*cis* 2.6:1 (by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ (attributable signals) = 4.98 (br s, major rotamer, 1 H) and 4.83 (br s, minor rotamer, 1 H), 4.13 (br d, *J* = 13.1 Hz, minor rotamer, 1 H) and 3.98 (br d, *J* = 12.9 Hz, major rotamer, 1 H), 3.80–3.60 (m, 1 H), 3.72 (s, 3 H), 3.70 and 3.68 (s, 3 H, two rotamers), 3.10–2.89 (m, 1 H), 2.37–2.27 (br m, 1 H), 1.88–1.70 (m, 1 H), 1.66–1.50 (m, 1 H), 1.48–1.35 (m, 1 H), 0.85 (s, 9 H), 0.02 (s, 6 H).

Dimethyl (2*R*,4*R*)-4-Hydroxypiperidine-1,2-dicarboxylate [(2*R*,4*R*)-13]

The above 2.6:1 mixture of **12c** was then dissolved in MeCN (18 mL) and 3 M HCl soln was added (18 mL), and the mixture was stirred vigorously at 25 °C for 4 h [TLC monitoring (EtOAc–PE, 1:1)]. The soln was transferred into a separatory funnel, neutralized with sat. $NaHCO_3$, and extracted with EtOAc (4 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue (102 mg) was dissolved in anhyd toluene (3.5 mL) and PTSA (48 mg, 0.28 mmol) was added. The mixture was then heated at 100 °C (external bath) with stirring and under N_2. After 30 min the soln was cooled to r.t., and concentrated. The residue was chromatographed (EtOAc–PE, 1:1, R_f = 0.13) to give (2*R*,4*R*)-**13** (56 mg, 50% from **12c**) as a colorless oil. Spectroscopic and analytical data as reported above.

(2*R*,4*R*)-4-Hydroxypiperidine-2-carboxylic Acid Hydrochloride Salt [(2*R*,4*R*)-1·HCl][26]

A suspension of (2*R*,4*R*)-**13** (30 mg, 0.14 mmol) in aq 2 M HCl (17 mL) was refluxed with stirring for 18 h. The mixture was cooled, washed with Et_2O (2 × 8 mL), and concentrated. The residue was triturated with acetone and dried under vacuum for 24 h. Salt (2*R*,4*R*)-**1**·HCl (25 mg, 100%) was obtained as a white foamy solid.

$[\alpha]_D^{20}$ –2.6 (*c* 0.95, 6 M HCl) [Lit.[26a] $[\alpha]_D^{20}$ –2.7 (*c* 1.0, 6 M HCl)].

^{1}H NMR (400 MHz, D_2O): δ = 4.32–4.26 (br m, 1 H), 4.26 (dd, *J* = 12.3, 3.5 Hz, 1 H), 3.43–3.34 (m, 2 H), 2.31 (dt, *J* = 14.6, 3.2 Hz, 1 H), 2.06 (t, *J* = 12.6 Hz, 1 H), 1.96–1.89 (m, 2 H) [Lit.[26a] ^{1}H NMR (D_2O): δ = 4.40–4.20 (m, 2 H), 3.50–3.35 (m, 2 H), 2.33 (td, *J* = 14.8, 3.8 Hz, 1 H), 2.20–2.10 (m, 1 H), 2.05–1.90 (m, 2 H)].

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References

(1) (a) Romeo, J. T.; Swain, L. A.; Bleecker, A. B. *Phytochemistry* **1983**, *22*, 1615. (b) Schenk, V. W.; Schutte, H. F. *Flora* **1963**, *153*, 426.
(2) (a) Cocito, C. *Microbiol. Rev.* **1979**, *43*, 145. (b) Vanderhaeghe, H.; Janssen, G.; Compernolle, F. *Tetrahedron Lett.* **1971**, *12*, 2687.
(3) Clark-Lewis, J. W.; Mortimer, P. I. *Nature* **1959**, *184*, 1234.
(4) Aiello, A.; Fattorusso, E.; Giordano, A.; Menna, M.; Müller, W. E. G.; Perović-Ottstadt, S.; Schröder, H. C. *Bioorg. Med. Chem.* **2007**, *15*, 5877.
(5) Gupta, R. K.; Krishnamurti, M. *Phytochemistry* **1979**, *18*, 2021.
(6) Evans, S. V.; Shing, T. K.; Aplin, R. T.; Fellows, L. E.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 2593.
(7) (a) Copeland, T. D.; Wondrak, E. M.; Toszer, J.; Roberts, M. M.; Oroszlan, S. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 310. (b) Dragovich, P. S.; Parker, J. E.; French, J.; Inbacuan, M.; Kalish, V. J.; Kissinger, C. R.; Knighton, D. R.; Lewis, C. T.; Moomaw, E. W.; Parge, H. E.; Pelletier, L. A. K.; Prins, T. J.; Showalter, R. E.; Tatlock, J. H.; Tucker, K. D.; Villafranca, J. E. *J. Med. Chem.* **1996**, *39*, 1872. (c) Gillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, Y.; Lavellée, P. *J. Org. Chem.* **1996**, *61*, 2226. (d) Ho, B.; Zabriskie, T. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 739. (e) Skiles, J. W.; Giannousis, P. P.; Fales, K. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 963.
(8) (a) Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Leander, J. D.; Lodge, D.; Paschal, J. W.; Elzey, T. *J. Med. Chem.* **1991**, *34*, 90. (b) Hays, S. J.; Malone, T. C.; Johnson, G. *J. Org. Chem.* **1991**, *56*, 4084.
(9) (a) Anderson, P. C.; Soucy, F.; Yoakim, C.; Lavallée, P.; Beaulieu, P. L. US 5,545, **640**. (b) Lamarre, D.; Croteau, G.; Wardrop, E.; Bourgon, L.; Thibeault, D.; Clouette, C.; Vaillancourt, M.; Cohen, E.; Pargellis, C.; Yoakim, C.; Anderson, P. C. *Antimicrob. Agents Chemother.* **1997**, *41*, 965.
(10) Bellier, B.; Da Nascimiento, S.; Meudal, H.; Gincel, E.; Roques, B. P.; Garbay, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1419.
(11) For a recent review on the asymmetric synthesis of pipecolic acids and derivatives see: (a) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101. (b) Cordero, F. M.; Bonollo, S.; Machetti, F.; Brandi, A. *Eur. J. Org. Chem.* **2006**, 3235.

(12) (a) Sun, C.-S.; Lin, Y.-S.; Hou, D.-R. *J. Org. Chem.* **2008**, *73*, 6877. (b) Lloyd, R. C.; Lloyd, M. C.; Smith, M. E. B.; Holt, K. E.; Swift, J. P.; Keene, P. A.; Taylor, S. J. C.; McCague, R. *Tetrahedron* **2004**, *60*, 717. (c) Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J.-R.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2004**, *69*, 130. (d) Celestini, P.; Danieli, B.; Lesma, G.; Sacchetti, A.; Silvani, A.; Passarella, D.; Virdis, A. *Org. Lett.* **2002**, *4*, 1367. (e) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 754. (f) Agami, C.; Bisaro, F.; Comesse, S.; Guesné, S.; Kadouri-Puchot, C.; Morgentin, R. *Eur. J. Org. Chem.* **2001**, 2385. (g) Sabat, M.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1209. (h) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106. (i) Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551. (j) Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4231. (k) Di Nardo, C.; Varela, O. *J. Org. Chem.* **1999**, *64*, 6119. (l) Golubev, A.; Sewald, N.; Burger, K. *Tetrahedron Lett.* **1995**, *36*, 2037.

(13) Occhiato, E. G.; Scarpi, D.; Guarna, A. *Eur. J. Org. Chem.* **2008**, 524.

(14) (a) Anelli, P. L.; Fedeli, F.; Gazzotti, O.; Lattuada, L.; Lux, G.; Rebasti, F. *Bioconjugate Chem.* **1999**, *10*, 137. (b) Chen, H.; Feng, Y.; Xu, Z.; Ye, T. *Tetrahedron* **2005**, *61*, 11132.

(15) Purification is not necessary, but a much cleaner lactam is obtained if the protected nitrile is purified by chromatography.

(16) For a review see: (a) Occhiato, E. G. *Mini-Rev. Org. Chem.* **2004**, *1*, 149. Recent progresses in the use of heterocyclic-derived vinyl phosphates: (b) Claveau, E.; Gillaizeau, I.; Blu, J.; Bruel, A.; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832; and references therein. (c) Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360.

(17) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(18) Elimination of ROH to give an α,β,γ,δ-unsaturated ester has been sometime observed by us in the presence of acids, even when compound **10** was stored in fridge and traces of acids were present. The same elimination occurs with phosphate **9**.

(19) Kaisalo, L. H.; Hase, T. A. *Tetrahedron Lett.* **2001**, *42*, 7699.

(20) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655; The reaction was carried out in CH_2Cl_2 under H_2 at 1 atm (no conversion after 24 h) and 50 atm. In the latter case we observed a certain degree of conversion after 24 h (40%) but the facial selectivity was poor (ratio *trans*/*cis* ~3:2).

(21) Compounds *trans*-**12a**, *trans*-**12b**, and *trans*-**12c**[13] are easily differentiated from the corresponding *cis*-compounds by ^{1}H NMR analysis. In *trans*-compounds, the H2 is shifted downfield [*trans*-**12a**: δ = 5.02 and 4.86 (two rotamers); *trans*-**12b**: δ = 5.06 and 4.91 (two rotamers); *trans*-**12c**: δ = 4.98 and 4.83 (two rotamers)] and $H6_{axial}$ is upfield shifted (~3.00 ppm in *trans*-**12a**,**b**,**c**) compared to the corresponding protons in the *cis*-isomers: H2 resonates at *cis*-**12a**: δ = 4.80 and 4.64, *cis*-**12b**: δ = 4.77 and 4.62, *cis*-**12c**: δ = 4.78 and 4.63; $H6_{axial}$ resonates for *cis*-**12a**–**c** at ca. δ = 3.45. The same applies to the corresponding alcohols: in *trans*-compound **13** H2 resonates at δ = 5.04 and 4.90 (two rotamers) and $H6_{axial}$ at ca. δ = 3.0. In the corresponding *cis*-isomer,[13] H2 resonates at δ = 4.85 and 4.70 (two rotamers) and $H6_{axial}$ is shifted downfield to δ = 3.4.

(22) (a) Herdeis, C.; Engel, W. *Arch. Pharm. (Weinheim)* **1993**, *326*, 297. (b) Herdeis, C.; Engel, W. *Arch. Pharm. (Weinheim)* **1992**, *325*, 419.

(23) Compound **14** was recovered only in traces after chromatography as it probably decomposed in part. Compound **14** has a diagnostic downfield shifted H4 proton to δ = 4.97, in accordance with the value (δ = 4.90–5.00) reported for the analogous *N*-tosyl and *N*-Cbz compounds (see ref. 22). **14**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.97 (m, 1 H), 4.90–4.70 (br m, 1 H), 4.30–4.00 (br m, 1 H), 3.74 (s, 3 H), 3.35–3.15 (br m, 1 H), 2.55–2.40 (m, 1 H), 2.40–2.37 (m, 1 H), 2.14–2.05 (m, 1 H), 1.98–1.85 (m, 1 H).

(24) Compound (2*R*,4*R*)-**13**, possessing *trans*-stereochemistry, is easily differentiated by ^{1}H NMR from its *cis*-isomer especially as the axially oriented proton on C4 is now shielded from δ = 4.15 to 3.70. Moreover in the *trans*-compound there is an NOE enhancement between H4 and $H6_{axial}$. Enantiopure *cis*-isomer (2*S*,4*R*)-**13** has been already prepared by us (see ref. 13) and, in its racemic form, by Hiemstra and Speckamp. See: (a) Esch, P. M.; de Boer, R. F.; Hiemstra, H.; Boska, I. M.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4063. (b) Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039.

(25) Bartali, L.; Scarpi, D.; Guarna, A.; Prandi, C.; Occhiato, E. G. *Synlett* **2009**, 913.

(26) (a) Agami, C.; Couty, F.; Poursoulis, M.; Vaissermann, J. *Tetrahedron* **1992**, *48*, 431. (b) Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron* **1996**, *52*, 14757.