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Stereoselective Synthesis of (2*S*,4*R*)-4-Hydroxypipecolic Acid

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A new synthetic route to enantiopure (2*S*,4*R*)-4-hydroxypipecolic acid from commercial ethyl (3*S*)-4-chloro-3-hydroxybutanoate is reported. The synthesis is based on the Pd-catalyzed methoxycarbonylation of a 4-alkoxy-substituted δ-valerolactam-derived vinyl triflate followed by the stereocontrolled hydrogenation of the enamine double bond. The final product was obtained after exhaustive hydrolysis in 20 % yield over 10 steps.

Introduction

Pipecolic acids and their derivatives are useful building blocks for the preparation of biologically active compounds.[1] In particular, the naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid (**1**) (Figure 1), isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*[2] and a constituent of cyclodepsipeptide antibiotics such as virginiamycin S_2,[3] has been embedded in the structure of NMDA receptor antagonists[4] and HIV-protease inhibitors such as palinavir (Figure 1).[5] Because of its importance in medicinal chemistry, much effort has been directed towards the enantioselective synthesis of **1** by the resolution of key racemic intermediates and by using chiral auxiliaries or starting materials from the chiral pool.[1c,1e,6]

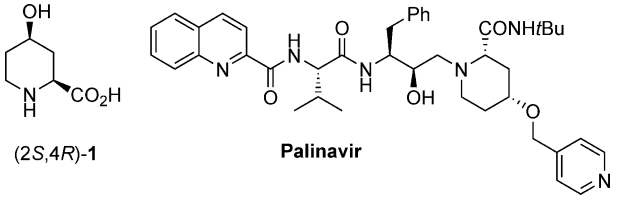
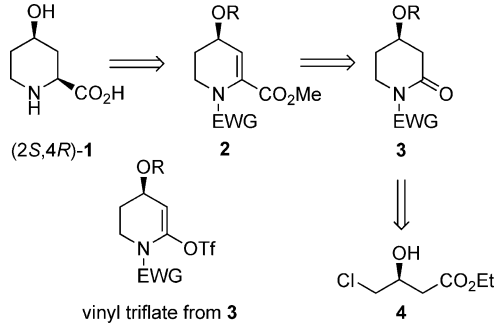


Figure 1. Structure of (2*S*,4*R*)-4-hydroxypipecolic acid (left) and palinavir (right).

As a part of our study on the use of lactam-derived vinyl triflates in organic synthesis,[7] we have envisaged a new synthetic route to enantiopure (2*S*,4*R*)-4-hydroxypipecolic acid (**1**) (Scheme 1) from commercial ethyl (3*S*)-4-chloro-3-hydroxybutanoate (**4**).[8] The key step in the synthesis is the stereocontrolled hydrogenation of the double bond in tetrahydropyridine-2-carboxylate **2**, which in turn could be obtained by Pd^0-catalyzed methoxycarbonylation of the vinyl triflate prepared from enantiopure lactam **3**. Two issues had to be addressed in the course of this synthesis, the first being the actual feasibility of the requisite 4-alkoxy- (or silyloxy-)substituted lactam-derived vinyl triflate. It is in fact known that the stability of vinyl triflates of this type is strongly affected by both the size and the electronic nature of the substituents on the lactam ring such that they cannot in many cases be conveniently used in coupling reactions.[9] The second issue was the facial selectivity possibly exerted by the C-4 stereocenter in the catalytic hydrogenation of the enamine double bond in **2**. In the heterogeneous hydrogenation of similar carbocyclic compounds a poor bias on the stereochemical outcome has always been shown by the allylic OH group.[10,11] So, if such is the case, the use of a bulky substituent (TBDPS or TBDMS group) on the hydroxy group of **2** could help in directing the reduction towards the less hindered face of the double bond to furnish the target *cis* product.[12]



Scheme 1.

Results and Discussion

To address the first point we focused our attention on racemic ethyl 4-chloro-3-hydroxybutanoate (**4**) (Scheme 2). This was converted into the corresponding nitrile **5** which

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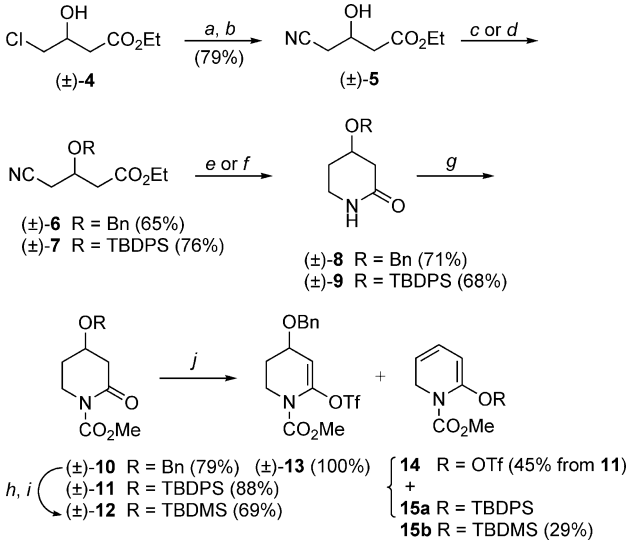
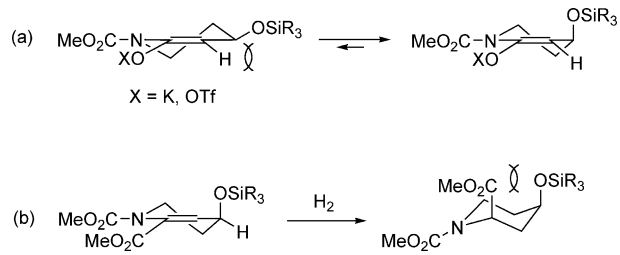
was transformed into differently protected lactams according to a reported methodology.[13] However, we found it more convenient to protect nitrile **5** as the corresponding TBDPS ether prior to hydrogenation, thus obtaining piperidinone **9** with the protection already installed on the 4-hydroxy group. After protection of the N atom, we attempted to convert lactam **11** into the corresponding vinyl triflate by treatment with KHMDS in THF at –78 °C and then by quenching the enolate with *N*-phenyl triflimide. However, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed that complete elimination had occurred to give **14** (45% after chromatography). Moreover, the signals of the 2-*O*-silylated compound **15a** (1:2 ratio with **14**) were observed in the ^{1}H NMR spectrum.[14] Hoping that a less bulky 4-substituent would be more compatible with the conditions for the formation of the triflate, we repeated the experiment with the TBDMS-protected lactam **12**, prepared from the benzyloxy derivative **10** we already had in hand. However, in this case elimination was again the major pathway accompanied by the formation of a greater amount (by ^{1}H NMR analysis of the crude reaction mixture) of the silyl enol ether **15b** (29% after chromatography).[14]



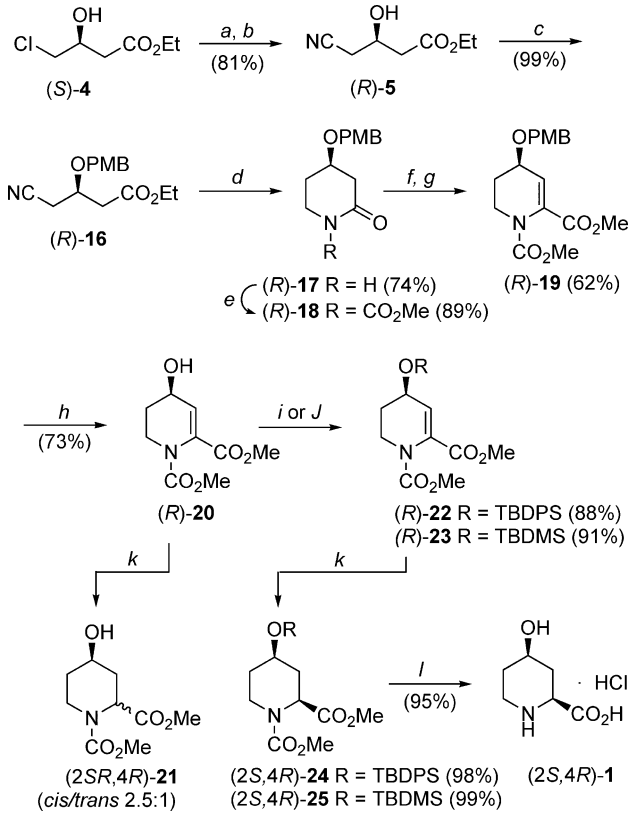
Scheme 2. Reagents and conditions: (a) NaI, acetone, reflux, 3 d; (b) NaCN, EtOH/H_2O, 4:1, 45 °C, 3 h; (c) $BnOC(=NH)CCl_3$, TfOH (cat), DCM/cyclohexane, 1:2, 0→25 °C, 22 h; (d) TBDPSCl, imidazole, DMF, 40 °C, 12 h; (e) $NaBH_4$, $NiCl_2·6H_2O$, EtOH, 0 °C, 3 h; then 25 °C, 2.5 h; (f) H_2, PtO_2, MeOH, 30 °C, 24 h; (g) *n*BuLi, MeOCOCl, THF, –78 °C, 4 h; (h) H_2, 10% Pd/C, EtOAc, 25 °C, 16 h; (i) TBDMSCl, imidazole, DMF, 30 °C, 5 h; (j) KHMDS, THF, –78 °C, 1.5 h; then $PhNTf_2$, –78 °C, 1 h.

The low recovery of organic material after chromatography suggests in any case that degradation of the substrates had occurred in both experiments. Thus, 4-silyloxy-substituted lactams appear unsuitable for the preparation of the corresponding vinyl triflates. Instead, the 4-benzyloxy group of compound **10** was stable under basic conditions so that **10** could be quantitatively converted into the corresponding vinyl triflate **13**. A possible reason for the particular tendency of enolates (or triflates) of **11** and **12** to exclusively give the elimination products is the strong A$^{(1,2)}$ strain generated between the olefinic proton on C-3 and the bulky equatorial silyloxy group after formation of the enolate (Scheme 3, a). To reduce the strain, the 4-silyloxy group should adopt an axial orientation,[15] but this could be prone to elimination under the reaction conditions.



Scheme 3.

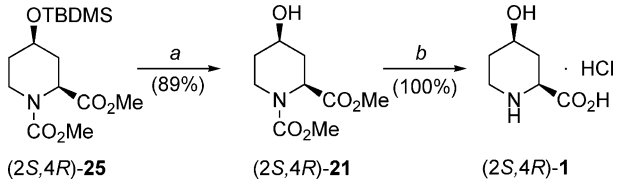
It was clear at this point that the required bulky silyl protection of the 4-hydroxy had to be installed at a later stage, that is, after the formation of the triflate and subsequent Pd-catalyzed carbonylation. This approach was applied to the synthesis of enantiopure (2*S*,4*R*)-4-hydroxypipecolic acid (**1**), as reported in Scheme 4.



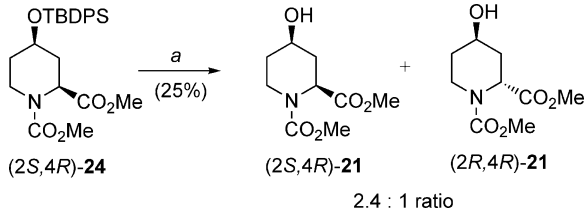
Scheme 4. Reagents and conditions: (a) NaI, acetone, reflux, 3 d; (b) NaCN, EtOH/H_2O, 4:1, 45 °C, 3 h; (c) $PMBOC(=NH)CCl_3$, $BF_3·Et_2O$ (cat), DCM/cyclohexane, 1:2, –5→25 °C, 3 h; (d) $NaBH_4$, $NiCl_2·6H_2O$, EtOH, 0 °C, 3 h; then 25 °C, 2.5 h; (e) *n*BuLi, MeOCOCl, THF, –78 °C, 4 h; (f) KHMDS, THF, –78 °C, 1.5 h; then $PhNTf_2$, –78 °C, 1 h; (g) $Pd(OAc)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 40–45 °C, 3 h; (h) DDQ, CH_2Cl_2, H_2O, 25 °C, 24 h; (i) TBDPSCl, imidazole, DMF, 40 °C, 3.5 h; (j) TBDMSCl, imidazole, DMF, 40 °C, 3.5 h; (k) H_2, 10% Pd/C, EtOAc, 50 °C, 3 h; (l) 2 N HCl, reflux, 23 h.

In contrast to the reported procedure in which the bacterium *Rhodococcus erytropolis* was used to desymmetrize a dinitrile,[13] we prepared enantiopure nitrile (*R*)-**5** by starting from the commercial ethyl 4-chloro-3-hydroxybutanoate [(*S*)-**4**].[16] Compound **5** was protected as a *p*-methoxybenzyl (PMB) ether and then the nitrile group was chemoselectively reduced to afford lactam (*R*)-**17** in 74% yield. After protection of the N atom,[17] (*R*)-**18** was converted into the corresponding triflate and this was immediately subjected to methoxycarbonylation,[18] providing (*R*)-**19** in 62% yield over two steps. Deprotection eventually gave key intermediate (*R*)-**20** in 73% yield. Compound **20** was hydrogenated at room temperature over Pd/C in both MeOH and ethyl acetate as the solvent to provide, as expected, an approximately 2.5:1 mixture of the *cis* and *trans* diastereomers of **21**. Both TBDPS and TBDMS ethers **22** and **23**, respectively, were then prepared and subjected to the same hydrogenation conditions in ethyl acetate. The reactions did not occur at room temperature, however, by increasing the temperature to 50 °C hydrogenation was complete after a few hours giving (2*S*,4*R*)-**24** and (2*S*,4*R*)-**25** in quantitative yields. The *cis* compound (2*S*,4*R*)-**24** was obtained as a 17:1 mixture (by ^{1}H NMR) with its *trans* isomer. The diastereoselectivity was higher in the hydrogenation of the TBDMS-protected (*R*)-**23** as *cis*-(–)-**25** was obtained in a 23:1 mixture with the *trans* isomer. Hydrogenation of the double bond in compounds **22** and **23** does not take place at room temperature as it generates a strained diaxial 2,4-disubstituted final compound (Scheme 3, b). The silyloxy group is pseudoaxial to remove the aforementioned $A^{(1,2)}$ strain and hydrogenation of the double bond occurs on the opposite side to give the *cis* compound. At the same time the 2-methoxycarbonyl group is forced towards an axial orientation to relieve the $A^{(1,3)}$ strain with the *N*-protection,[19] thus providing a 2,4-diaxial derivative for the formation of compounds **24** and **25** for which higher temperatures are required.

The *cis* (and diaxial) stereochemistry of **24** and **25** is evident from the low values of the ^3J coupling constants of 2-H and 4-H (2.7–2.9 Hz for 4-H and 6.2–7.0 Hz for 2-H) which is consistent with an equatorial orientation of both protons. Moreover, the equatorial carbinolic proton is shifted downfield to 4.07 ppm in **24** (and to 4.08 ppm in **25**), whereas in the *trans* isomer of **24** the same proton resonates at higher fields (3.57–3.65 ppm) as it is axially oriented.[20] This assignment was confirmed by converting **24** and **25** into *cis*-**21** (Schemes 5 and 6), known in its racemic form, for which the axial orientation of the two substituents on the piperidine ring has been demonstrated.[21] Thus, selective deprotection of **25** (Scheme 5) quantitatively gave (2*S*,4*R*)-**21** possessing identical spectroscopic data to that of *cis*-(±)-**21**. TBAF-Mediated deprotection of **24** (Scheme 6) in THF was slow and provided mainly the *cis* product **21** together with a certain amount (2.4:1 ratio) of the *trans* diastereomer[22] which was formed because of partial epimerization under the basic deprotection conditions.[23,24]



Scheme 5. Reagents and conditions: (a) 3 N HCl, ACN, 25 °C, 4 h; (b) 2 N HCl, reflux, 18 h.



Scheme 6. Reagents and conditions: (a) TBAF, 3-Å molecular sieves, THF, 9 h.

Finally, exhaustive hydrolysis (2 N aqueous HCl, reflux for 18–24 h) of TBDMS-protected compound **25** (Scheme 4), as well as **21** (Scheme 5), provided diastereomerically pure (2*S*,4*R*)-**1** as the hydrochloride salt in 95–100% yield.

Conclusions

In conclusion, a stereoselective synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid (**1**) has been realized starting from commercial ethyl (3*S*)-4-chloro-3-hydroxybutanoate (**4**) in 10 steps and in 20% overall yield. The synthesis was possible as 4-benzyloxy-substituted lactam-derived vinyl triflates are sufficiently stable to allow the Pd-catalyzed methoxycarbonylation reaction and the synthesis was based on the stereoselective enamine double-bond hydrogenation of the methyl ester consequently obtained. As both enantiomers of ethyl 4-chloro-3-hydroxybutanoate are commercially available the methodology can also be used for the synthesis of the unnatural enantiomer (2*R*,4*S*)-**1**. Finally, the feasibility of 4-benzyloxy-substituted δ-valerolactam-derived vinyl triflates sets the stage for Pd-catalyzed cross-coupling reactions and therefore the synthesis of several natural products containing the 4-hydroxypiperidine nucleus.

Experimental Section

Chromatographic separations were performed under pressure on silica gel 60 (Merck, 70–230 mesh) using flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates with the same eluent as indicated for column chromatography. THF was distilled from Na/benzophenone. Dichloromethane, cyclohexane and heptane were distilled from CaH_2. Commercial anhydrous DMF was used. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C. Mass spectra were recorded at 70 eV by applying the EI technique. Racemic ethyl 4-chloro-3-hydroxybutanoate (**4**) was prepared as reported.[25] Racemic ethyl 3-hydroxy-4-iodobutanoate and ethyl (*R*)-3-hydroxy-4-iodobutanoate were prepared from (±)-**4** and commercial (*S*)-**4**, respectively, as reported.[16,26]

Ethyl 4-Cyano-3-hydroxybutanoate [(±)-5]:[27] Racemic ethyl 3-hydroxy-4-iodobutanoate[26] (1.024 g, 3.98 mmol) was dissolved in a vigorously stirred 4:1 ethanol/water mixture (1.6 mL). The solution was heated to 45 °C (external bath) and NaCN (273 mg, 5.57 mol) was added. Vigorous stirring was continued at this temperature for 3 h. The reaction mixture was then cooled, the solvent evaporated and the residue dissolved in ethyl acetate (6 mL). The solution was filtered through Celite mixed with silica gel, washed with EtOAc (3 × 6 mL), and the solvent was then removed. The orange liquid obtained was purified by chromatography (CH_2Cl_2/MeOH, 30:1, R_f = 0.33) to give (±)-**5** (500 mg, 79%) as a pale yellow liquid with ^1H and ^{13}C NMR spectra identical to those reported.[26,27]

Ethyl 3-(Benzyloxy)-4-cyanobutanoate [(±)-6]: Benzyl 2,2,2-trichloroacetimidate (1.42 mL, 7.65 mmol) was added to a solution of (±)-**5** (800 mg, 5.1 mmol) in anhydrous CH_2Cl_2 (2 mL) and cyclohexane (4 mL) and, after cooling to 0 °C, triflic acid (44 μL, 0.51 mmol) was added dropwise under N_2. Stirring was continued for 15 min at 0 °C before allowing the reaction mixture to warm to room temperature. After 4 h, the mixture was cooled again to 0 °C and further amounts of benzyl 2,2,2-trichloroacetimidate (470 μL) and triflic acid (22 μL) were added. The reaction mixture was left to stir overnight at room temperature. After 18 h the solution was filtered through a Celite layer, washing with cyclohexane. The filtrate was diluted with EtOAc (30 mL), washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL), then brine (50 mL), and finally dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:5, R_f = 0.29) to give (±)-**6** (818 mg, 65%) as pale-yellow thick oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.57–2.82 (m, 4 H, $NCCH_2$ and CH_2CO_2Et), 4.05–4.20 (m, 1 H, C*H*OBn), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.64 (s, 2 H, OCH_2Ph), 7.39–7.30 (m, 5 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 14.1 (q, OCH_2CH_3), 23.1 (t, C-4), 39.0 (t, C-2), 61.0 (t, OCH_2CH_3), 71.2 (t, OCH_2Ph), 72.3 (d, C-3), 116.9 (s, *C*N), 127.8 (d, 2 C_{arom}), 128.1 (d, C_{arom}), 128.4 (d, 2 C_{arom}), 136.9 (s, C_{arom}), 170.0 (s, C=O) ppm. MS: m/z (%) = 247 (1.9) $[M]^+$, 107 (74), 91 (100). $C_{14}H_{17}NO_3$ (247.29): calcd. C 68.00, H 6.93, N 5.66; found C 67.89, H 7.08, N 5.45.

Ethyl 3-(*tert*-Butyldiphenylsilyloxy)-4-cyanobutanoate [(±)-7]: Imidazole (355 mg, 5.21 mmol) and TBDPSCl (947 μL, 3.70 mmol) were added to a solution of (±)-**5** (270 mg, 1.72 mmol) in anhydrous DMF (2.5 mL) under nitrogen and the resulting solution was left stirring at 40 °C (external bath). After 12 h the mixture was diluted with water (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:8, R_f = 0.27) to give (±)-**7** (518 mg, 76%) as a thick colorless oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.08 [s, 9 H, $SiC(CH_3)_3$], 1.21 (t, J = 7.3 Hz, 3 H, OCH_2CH_3), 2.53 (d, J = 4.4 Hz, 2 H, $NCCH_2$), 2.67 (d, J = 6.2 Hz, 2 H, CH_2CO_2Et), 4.06 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 4.26–4.40 (m, 1 H, C*H*OSi), 7.37–7.44 (m, 6 H, CH_{arom}), 7.64–7.36 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 14.0 (q, OCH_2CH_3), 19.2 [s, $SiC(CH_3)_3$], 25.6 (t, C-4), 26.7 [q, 3 C, $SiC(CH_3)_3$], 40.8 (t, C-2), 60.7 (t, OCH_2CH_3), 65.7 (d, C-3), 116.9 (s, *C*N), 127.7 (d, 2 C_{arom}), 127.8 (d, 2 C_{arom}), 130.0 (d, C_{arom}), 130.1 (d, C_{arom}), 132.5 (s, 2 C_{arom}), 135.6 (d, 2 C_{arom}), 135.7 (d, 2 C_{arom}), 169.9 (s, C=O) ppm. MS: m/z (%) = 395 (0.1) $[M]^+$, 338 (100), 232 (80), 199 (98), 188 (73), 183 (70). $C_{23}H_{29}NO_3Si$ (395.57): calcd. C 69.84, H 7.39, N 3.54; found C 69.48, H 7.30, N 3.40.

4-(Benzyloxy)piperidin-2-one [(±)-8]: $NaBH_4$ (113 mg, 3 mmol) in small portions (H_2 develops) was added to a stirred solution of $NiCl_2 \cdot 6H_2O$ (694 mg, 2.92 mmol) in EtOH (5.5 mL), cooled to 0 °C. After 15 min a solution of nitrile (±)-**6** (360 mg, 1.46 mmol) in EtOH (6 mL) was added dropwise, followed by the remaining $NaBH_4$ (1.103 g, 29.2 mmol) which was added in small portions in 3 h [during the addition of $NaBH_4$, further EtOH (8 mL) was added in small volumes to maintain the fluidity of the black suspension]. After that time, the suspension was stirred for 2.5 h at room temperature and then water (8 mL) was carefully added and the mixture was filtered through a Celite layer washing with EtOH (3 × 15 mL). The solution was concentrated under vacuum, the residue was dissolved in EtOAc (50 mL) and washed with 10% NH_4OH (aq.) (2 × 15 mL), brine (15 mL), and finally dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (CH_2Cl_2/MeOH, 25:1, R_f = 0.21) to give (±)-**8** (212 mg, 71%) as a white solid. M.p. 95–96 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.89–2.00 (m, 2 H, 5-H and 5-H′), 2.43–2.69 (m, 2 H, 3-H and 3-H′), 3.15–3.29 (m, 1 H, 6-H), 3.43–3.55 (m, 1 H, 6-H′), 3.80–3.95 (m, 1 H, 4-H), 4.56 (s, 2 H, OCH_2Ph), 6.73 (br. s, 1 H, N*H*), 7.20–7.40 (m, 5 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 27.2 (t, C-5), 37.6 (t, C-3), 38.0 (t, C-6), 70.2 (t, OCH_2Ph), 70.8 (d, C-4), 127.3 (d, 2 C_{arom}), 127.6 (d, 1 C_{arom}), 128.3 (d, 2 C_{arom}), 137.9 (s, 1 C_{arom}), 170.7 (C=O) ppm. MS: m/z (%) = 205 (0.4) $[M]^+$, 99 (86), 91 (100). $C_{12}H_{15}NO_2$ (205.25): calcd. C 70.22, H 7.37, N 6.82; found C 70.41, H 7.62, N 6.85.

4-(*tert*-Butyldiphenylsilyloxy)piperidin-2-one [(±)-9]: PtO_2 (50 mg) was added to a stirred solution of (±)-**7** (480 mg, 1.21 mmol) in MeOH (6 mL) under N_2. The mixture was flushed with H_2 and then left under a static pressure of H_2 (balloon) at 30 °C. After 24 h the catalyst was filtered, washing with MeOH (4 mL), and Et_3N (335 μL, 2.42 mmol) was added to the solution which was stirred for 2 h at room temperature. Then it was concentrated under vacuum, the residue was diluted with water (20 mL), extracted with EtOAc (3 × 15 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (EtOAc, R_f = 0.31) to give (±)-**9** (290 mg, 68%) as a gummy white solid. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.06 [s, 9 H, $SiC(CH_3)_3$], 1.70–1.79 (m, 2 H, 5-H and 5-H′), 2.42 (d, J = 5.1 Hz, 2 H, 3-H and 3-H′), 3.07–3.20 (m, 1 H, 6-H), 3.49–3.61 (m, 1 H, 6-H′), 4.06–4.21 (m, 1 H, 4-H), 6.20 (br. s, 1 H, N*H*), 7.31–7.59 (m, 6 H, CH_{arom}), 7.60–7.71 (m, 4 H, CH_{arom}) ppm. Spectroscopic and analytical data are identical to those reported.[13]

Methyl 4-(Benzyloxy)-2-oxopiperidine-1-carboxylate [(±)-10]: A 1.6 M solution of *n*BuLi (1.47 mL, 2.34 mmol) in hexane was added dropwise to a cooled (–78 °C) solution of lactam (±)-**8** (480 mg, 2.34 mmol) in anhydrous THF (8 mL) under N_2. After 30 min a solution of methyl chloroformate (181 μL, 2.34 mmol) in THF (3 mL) was added dropwise and the reaction mixture was left stirring for 4 h at –78 °C. Water (4 mL) was then added and the mixture warmed to room temperature. Further water was added (20 mL) and the mixture extracted with Et_2O (3 × 15 mL), washed with brine, and dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (CH_2Cl_2/MeOH, 40:1, R_f = 0.32) to give (±)-**10** (488 mg, 79%) as a pale-yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.00–2.09 (m, 2 H, 5-H and 5-H′), 2.76 (d, J = 5.1 Hz, 2 H, 3-H and 3-H′), 3.64–3.77 (m, 1 H, 6-H), 3.86 (s, 3 H, OCH_3), 3.86–4.00 (m, 2 H, 4-H and 6-H′), 4.55 (s, 2 H, OCH_2Ph), 7.31–7.40 (s, 5 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 28.2 (t, C-5), 40.9 (t, C-3), 42.3 (t, C-6), 54.0 (q, OCH_3), 70.3 (t, OCH_2Ph), 70.4 (d, C-4), 127.4 (d, 2 C_{arom}), 127.7 (d, 1 C_{arom}), 128.4 (d, 2 C_{arom}), 137.5 (s, 1 C_{arom}),

151.8 (s, N–CO), 168.9 (C=O) ppm. MS: *m*/*z* (%) = 263 (0.4) $[M]^+$, 157 (46), 125 (36), 91 (100). $C_{14}H_{17}NO_4$ (263.29): calcd. C 63.87, H 6.51, N 5.32; found C 63.66, H 6.91, N 5.02.

Methyl 4-(*tert*-Butyldiphenylsilyloxy)-2-oxopiperidine-1-carboxylate [(±)-11]: Prepared as reported above for (±)-**10**. Starting from (±)-**9** (461 mg, 1.29 mmol), the title compound (±)-**11** (469 mg, 88%) was obtained as a thick pale-yellow oil after chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.33). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.05 [s, 9 H, SiC(CH_3)$_3$], 1.77–1.86 (m, 2 H, 5-H and 5-H′), 2.58 (d, *J* = 4.4 Hz, 2 H, 3-H and 3-H′), 3.57–3.69 (m, 1 H, 6-H), 3.87 (s, 3 H, OCH_3), 3.86–4.01 (m, 1 H, 6-H′), 4.13–4.22 (m, 1 H, 4-H), 7.33–7.46 (m, 6 H, CH_{arom}), 7.59–7.68 (m, 4 H, CH_{arom}) ppm. Spectroscopic and analytical data are identical to those reported.[13]

Methyl 4-(*tert*-Butyldimethylsilyloxy)-2-oxopiperidine-1-carboxylate [(±)-12]: 10% Pd/C (97 mg, 0.091 mmol) was added to a stirred solution of (±)-**10** (239 mg, 0.91 mmol) in EtOAc (9 mL) under N_2. The mixture was flushed with H_2 and then left under a static pressure of H_2 (balloon) at room temperature. After 16 h the catalyst was filtered and the solution concentrated to give the methyl 4-hydroxy-2-oxopiperidine-1-carboxylate intermediate as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.80–2.09 (m, 2 H, 5-H and 5-H′), 2.59 (dd, *J* = 17.2, 5.5 Hz, 1 H, 3-H), 2.80 (dd, *J* = 17.2, 4.8 Hz, 1 H, 3-H′), 3.61–3.72 (m, 1 H, 6-H), 3.86 (s, 3 H, OCH_3), 3.86–4.02 (m, 1 H, 6-H′), 4.13–4.33 (m, 1 H, 4-H) ppm.

This was directly dissolved in anhydrous DMF (1.2 mL) under nitrogen and imidazole (178 mg, 2.60 mmol) and TBDMSCl (156 mg, 1.03 mmol) were added. The resulting solution was left stirring at 30 °C (external bath). After 5 h the mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.27) to give (±)-**12** (171 mg, 69%) as a thick colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.07 [s, 6 H, Si(CH_3)$_2$], 0.87 [s, 9 H, SiC(CH_3)$_3$], 1.81–1.90 (m, 1 H, 5-H), 1.92–2.00 (m, 1 H, 5-H′), 2.55 (dd, *J* = 17.0, 4.9 Hz, 1 H, 3-H), 2.68 (dd, *J* = 17.0, 4.3 Hz, 1 H, 3-H′), 3.72 (dt, *J* = 12.7, 5.3 Hz, 1 H, 6-H), 3.86 (s, 3 H, OCH_3), 3.84–3.91 (m, 1 H, 6-H′), 4.17–4.23 (m, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$) δ = –4.8 [q, 2 C, Si(CH_3)$_2$], 18.0 (s, Si*C*), 25.7 [q, 3 C, SiC(CH_3)$_3$], 31.3 (t, C-5), 42.2 (t, C-3), 44.2 (t, C-6), 53.9 (q, OCH_3), 64.8 (d, C-4), 154.9 (s, N–C=O), 169.5 (C=O) ppm. MS: *m*/*z* (%) = 287 (0.3) $[M]^+$, 230 (100), 188 (68), 89 (84). $C_{13}H_{25}NO_4Si$ (287.43): calcd. C 54.32, H 8.77, N 4.87; found C 54.01, H 8.73, N 4.61.

Methyl 4-(Benzyloxy)-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,4-tetrahydropyridine-1-carboxylate [(±)-13]: A solution of (±)-**10** (249 mg, 0.950 mmol) in THF (2 mL) was added to a solution of KHMDS (2.37 mL of a 0.5 M solution in toluene, 1.18 mmol) in THF (5.5 mL), cooled to –78 °C under nitrogen, and the resulting mixture was stirred for 1.5 h. Afterwards a solution of $PhNTf_2$ (423 mg, 1.18 mmol) in THF (1 mL) was added and left to stir for 1 h at –78 °C before allowing the temperature to rise to 0 °C. Then a 10% NaOH aqueous solution (10 mL) was added, the mixture was extracted with Et_2O (3 × 10 mL), washed with 10% NaOH (10 mL) and water (3 × 10 mL), and dried with anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent (without heating), triflate (±)-**13** (375 mg, 100%) was obtained as a yellow oil of sufficient purity to allow characterized as such. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.71–1.88 (m, 1 H, 5-H), 1.99–2.13 (m, 1 H, 5-H′), 3.40 (ddd, *J* = 15.2, 11.7, 2.6 Hz, 1 H, 6-H), 3.81 (s, 3 H, OCH_3), 4.06–4.20 (m, 2 H, 6-H′ and 4-H), 4.57 (s, 2 H, OCH_2Ph) 5.38 (d, *J* = 4.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 29.4 (t, C-5), 43.1 (t, C-6), 53.7 (q, OCH_3), 68.6 (t, OCH_2Ph), 70.5 (d, C-4), 104.9 (d, C-3), 118.3 (q, $J_{C,F}$ = 319 Hz, CF_3), 127.7 (d, 2 C_{arom}), 127.9 (d, 1 C_{arom}), 128.5 (d, 2 C_{arom}), 137.6 (s, 1 C_{arom}), 141.7 (s, C-2), 153.2 (s, N–CO) ppm. MS: *m*/*z* (%) = 304 (0.9) $[M - 91]^+$, 181 (28), 156 (44), 91 (100).

Ethyl (*R*)-4-Cyano-3-hydroxybutanoate [(–)-5]:[27] Prepared as reported above for (±)-**5**. Starting from ethyl (*R*)-3-hydroxy-4-iodobutanoate (2.80 g, 10.88 mmol), (*R*)-**5** (1.384 g) was obtained in 81% yield after chromatography as a light-yellow liquid with ^{1}H and ^{13}C NMR spectra identical to those reported.[27,28] $[\alpha]_D^{25}$ = –31.1 (*c* = 0.64, $CHCl_3$) {lit.: $[\alpha]_D$ = –31.3 (*c* = 1.0, $CHCl_3$);[27] $[\alpha]_D$ = –33.1 (*c* = 1.2, $CHCl_3$)[28]}.

Ethyl (*R*)-4-Cyano-3-[(4-methoxybenzyl)oxy]butanoate [(–)-16]: A solution of (–)-**5** (1.092 g, 6.96 mmol) in dichloromethane (7.5 mL) was added to a stirred solution of freshly prepared *p*-methoxybenzyl 2,2,2-trichloroacetimidate[29] (3.01 g, 10.65 mmol) in cyclohexane (15 mL) under N_2. The solution was cooled to –5 °C and BF_3·Et_2O (30 μL) was added dropwise. After 10 min the reaction mixture was warmed to room temperature and after 2 h a further amount of trichloroacetimidate (980 mg) was added. After 1 h, the mixture was filtered through a Celite layer, washing with a 1:2 mixture of CH_2Cl_2 and hexane (150 mL). The solution was then washed with $NaHCO_3$(sat) (3 × 50 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.29) to give (–)-**16** (1.921 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ = –7.1 (*c* = 0.57, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (t, *J* = 7.3 Hz, 3 H, OCH$_2$CH_3), 2.55–2.81 (m, 4 H, NCCH_2 and CH_2CO$_2$Et), 3.80 (s, 3 H, OCH_3), 4.05–4.20 (m, 1 H, C*H*OPMB), 4.16 (q, *J* = 7.3 Hz, 2 H, OCH_2CH$_3$), 4.57 (s, 2 H, OCH_2Ar), 6.88 (d, *J* = 8.8 Hz, 2 H, CH_{arom}), 7.27 (d, *J* = 8.8 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 14.2 (q, OCH$_2$*C*H$_3$), 23.2 (t, C-4), 39.0 (t, C-2), 55.3 (q, OCH_3), 60.9 (t, OCH_2CH$_3$), 70.9 (t, OCH_2Ar), 71.9 (d, C-3), 113.8 (d, 2 C_{arom}), 116.8 (s, *C*N), 129.4 (d, 2 C_{arom}), 129.6 (s, C_{arom}), 159.3 (s, C_{arom}), 169.8 (s, C=O) ppm. MS: *m*/*z* (%) = 277 (7) $[M]^+$, 137 (100), 121 (87). $C_{15}H_{19}NO_4$·$^1/_3H_2O$ (283.33): calcd. C 63.59, H 7.00, N 4.94; found C 63.54, H 6.87, N 4.64.

(*R*)-4-[(4-Methoxybenzyl)oxy]piperidin-2-one [(+)-17]: Prepared as described above for compound (±)-**8**. Starting from (–)-**16** (950 mg, 3.43 mmol), title compound (+)-**17** (600 mg) was obtained in 74% yield after chromatography (CH_2Cl_2/MeOH, 20:1, R_f = 0.29) as a white solid, m.p. 101–102 °C. $[\alpha]_D^{25}$ = +7.0 (*c* = 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.89–2.00 (m, 2 H, 5-H and 5-H′), 2.44–2.69 (m, 2 H, 3-H and 3-H′), 3.16–3.29 (m, 1 H, 6-H), 3.43–3.56 (m, 1 H, 6-H′), 3.81 (s, 3 H, OCH_3), 3.80–3.92 (m, 1 H, 4-H), 4.50 (s, 2 H, OCH_2Ar), 5.90 (br. s, 1 H, N*H*), 6.88 (d, *J* = 8.8 Hz, 2 H, CH_{arom}), 7.26 (d, *J* = 8.8 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 27.2 (t, C-5), 35.0 (t, C-3), 38.0 (t, C-6), 55.3 (q, OCH_3), 69.9 (t, OCH_2Ph), 70.6 (d, C-4), 113.7 (d, 2 C_{arom}), 128.9 (d, 2 C_{arom}), 129.9 (s, C_{arom}), 159.0 (s, 1 C_{arom}), 170.8 (C=O) ppm. MS: *m*/*z* (%) = 235 (2) $[M]^+$, 121 (74), 99 (100). $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 66.10, H 7.31, N 5.40.

Methyl (*R*)-4-[(4-Methoxybenzyl)oxy]-2-oxopiperidine-1-carboxylate [(+)-18]: Prepared as reported above for (±)-**10**. Starting from (+)-**17** (750 mg, 3.19 mmol), the title compound (+)-**18** (832 mg, 89%) was obtained after chromatography (CH_2Cl_2/MeOH, 40:1, R_f = 0.27) as a thick pale-yellow oil. $[\alpha]_D^{25}$ = +9.2 (*c* = 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.97–2.07 (m, 2 H, 5-H and 5-H′), 2.73 (d, *J* = 5.1 Hz, 2 H, 3-H and 3-H′), 3.63–4.00 (m, 3 H,

4-H, 6-H and 6-H′), 3.80 (s, 3 H, ArOCH_3), 3.86 (s, 3 H, OCH_3), 4.47 (s, 2 H, OCH_2Ar), 6.87 (d, J = 8.8 Hz, 2 H, CH_{arom}), 7.26 (d, J = 8.8 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 28.3 (t, C-5), 40.9 (t, C-3), 42.3 (t, C-6), 53.9 (q, ArO*C*H$_3$), 55.3 (q, O*C*H$_3$), 70.0 (t, O*C*H$_2$Ar), 70.1 (d, C-4), 113.8 (d, 2 C_{arom}), 129.0 (d, 2 C_{arom}), 129.4 (s, C_{arom}), 154.4 (s, N–C=O), 159.1 (s, 1 C_{arom}), 168.9 (C=O) ppm. MS: *m*/*z* (%) = 293 (0.1) [M]$^+$, 240 (57), 121 (100). $C_{15}H_{19}NO_5$ (293.32): calcd. C 61.42, H 6.53, N 4.78; found C 61.50, H 6.41, N 4.57.

Dimethyl 4-[(4-Methoxybenzyl)oxy]-1,4,5,6-tetrahydropyridine-1,2-dicarboxylate [(+)-19]: A solution of (+)-**18** (520 mg, 1.77 mmol) in THF (4 mL) was added to a solution of KHMDS (4.38 mL of a 0.5 M solution in toluene, 2.19 mmol) in THF (10 mL), cooled to –78 °C and under nitrogen, and the resulting mixture was stirred for 1.5 h. Afterwards a solution of $PhNTf_2$ (784 mg, 2.19 mmol) in THF (3 mL) was added and left to stir for 1 h at –78 °C before allowing the temperature to rise to 0 °C. Then a 10% NaOH aqueous solution (20 mL) was added, the mixture was extracted with Et_2O (3 × 20 mL), washed with 10% NaOH (20 mL) and water (3 × 20 mL), and dried with anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent (without heating), the crude triflate (780 mg) was directly used in the next step without purification. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.71–1.90 (m, 1 H, 5-H), 1.93–2.11 (m, 1 H, 5-H′), 3.40 (ddd, J = 15.3, 11.6, 2.5 Hz, 1 H, 6-H), 3.81 (s, 3 H + 3 H, ArOCH_3 and OCH_3), 4.00–4.18 (m, 2 H, 6-H′ and 4-H), 4.50 (s, 2 H, OCH_2Ar), 5.39 (d, J = 3.8 Hz, 1 H, 3-H), 6.88 (d, J = 8.7 Hz, 2 H, CH_{arom}), 7.25 (d, J = 8.7 Hz, 2 H, CH_{arom}) ppm.

The triflate was dissolved in DMF (8 mL), Ph_3P (47 mg, 0.177 mmol) and $Pd(OAc)_2$ (19.8 mg, 0.0885 mmol) were added, and the solution was stirred for 10 min under a CO atmosphere (balloon). Then Et_3N (494 μL, 3.54 mmol) and MeOH (2.9 mL, 70.8 mmol) were added and stirring was continued at 40–45 °C (external bath) for 3 h under a static CO pressure. The solution was diluted with water (40 mL) and extracted with Et_2O (4 × 20 mL), washed with brine (20 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:2, R_f = 0.34) to give (+)-**19** (368 mg, 62%) as a thick pale-yellow oil. $[\alpha]_D^{25}$ = +134.0 (c = 1.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.78–1.90 (m, 1 H, 5-H), 2.00–2.12 (m, 1 H, 5-H′), 3.31 (td, J = 12.1, 3.3 Hz, 1 H, 6-H), 3.72 (s, 3 H, OCH_3), 3.79 (s, 3 H, ArOCH_3), 3.80 (s, 3 H, OCH_3), 3.92–4.08 (m, 2 H, 6-H′ and 4-H), 4.52 (s, 2 H, OCH_2Ar), 6.04 (d, J = 4.0 Hz, 1 H, 3-H), 6.88 (d, J = 8.8 Hz, 2 H, CH_{arom}), 7.25 (d, J = 8.8 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 29.4 (t, C-5), 40.6 (t, C-6), 52.4 (q, O*C*H$_3$), 53.3 (q, ArO*C*H$_3$), 55.3 (q, O*C*H$_3$), 67.3 (t, O*C*H$_2$Ar), 70.0 (d, C-4), 113.9 (d, 2 C_{arom}), 119.2 (d, C-3), 129.3 (d, 2 C_{arom}), 129.5 (s, C_{arom}), 133.8 (s, C-2), 154.1 (s, N–C=O), 159.3 (s, 1 C_{arom}), 165.0 (C=O) ppm. MS: *m*/*z* (%) = 335 (3) [M]$^+$, 199 (34), 167 (36), 140 (36), 121 (100). $C_{17}H_{21}NO_6$ (335.35): calcd. C 60.89, H 6.31, N 4.18; found C 60.57, H 6.01, N 4.43.

Dimethyl (*R*)-4-Hydroxy-1,4,5,6-tetrahydropyridine-1,2-dicarboxylate [(+)-20]: H_2O (666 μL), followed by DDQ (236 mg, 1.039 mmol) in small portions, was added to a stirred solution of (+)-**19** (290 mg, 0.866 mmol) in CH_2Cl_2 (12 mL). After 24 h, $NaHCO_3$ (sat) (15 mL) and then CH_2Cl_2 (30 mL) were added. The phases were separated, the organic layer was washed with $NaHCO_3$ (sat) (20 mL), and the aqueous layer extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:1, R_f = 0.17) to give (+)-**20** (136 mg, 73%) as a thick colorless oil. $[\alpha]_D^{25}$ = +127.7 (c = 0.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.87–1.96 (m, 2 H, 5-H and 5-H′), 2.79 (br. s, 1 H, O*H*), 3.30 (ddd, J = 13.2, 9.2, 5.5 Hz, 1 H, 6-H), 3.74 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.04 (dt, J = 13.2, 4.4 Hz, 1 H, 6-H′), 4.24–4.35 (m, 1 H, 4-H), 5.96 (d, J = 4.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 32.1 (t, C-5), 40.2 (t, C-6), 52.4 (q, O*C*H$_3$), 53.4 (q, O*C*H$_3$), 61.1 (d, C-4), 121.0 (d, C-3), 133.0 (s, C-2), 153.9 (s, N–C=O), 164.9 (C=O) ppm. MS: *m*/*z* (%) = 215 (38) [M]$^+$, 183 (79), 155 (59), 127 (47), 114 (49), 97 (74), 59 (100). $C_9H_{13}NO_5$ (215.20): calcd. C 50.23, H 6.09, N 6.51; found C 49.91, H 6.27, N 6.18.

Dimethyl (*R*)-4-(*tert*-Butyldiphenylsilyloxy)-1,4,5,6-tetrahydropyridine-1,2-dicarboxylate [(+)-22]: Imidazole (62 mg, 0.9 mmol) and TBDPSCl (92 μL, 0.36 mmol) were added to a stirred solution of (+)-**20** (65 mg, 0.3 mmol) in anhydrous DMF (0.5 mL) and the mixture was stirred for 3.5 h at 40 °C (external bath) under N_2. After cooling to room temperature, water (5 mL) was added and the solution extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.33) to give (+)-**22** (120 mg, 88%) as a thick colorless oil. $[\alpha]_D^{25}$ = +107.7 (c = 1.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.07 [s, 9 H, SiC(CH_3)$_3$], 1.60–1.78 (m, 1 H, 5-H), 1.81–1.97 (m, 1 H, 5-H′), 3.43 (td, J = 13.2, 2.6 Hz, 1 H, 6-H), 3.70 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.95 (dt, J = 13.2, 4.8 Hz, 1 H, 6-H′), 4.22–4.29 (m, 1 H, 4-H), 5.77 (d, J = 3.7 Hz, 1 H, 3-H), 7.30–7.49 (m, 6 H, CH_{arom}), 7.57–7.73 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz): δ = 19.1 (s, Si*C*), 26.8 [q, 3 C, SiC(*C*H$_3$)$_3$], 32.5 (t, C-5), 40.4 (t, C-6), 52.2 (q, O*C*H$_3$), 53.2 (q, O*C*H$_3$), 62.7 (d, C-4), 121.6 (d, C-3), 127.6 (d, 4 C_{arom}), 129.7 (d, 2 C_{arom}), 132.5 (s, C-2), 133.4 (s, 2 C_{arom}), 135.6 (d, 4 C_{arom}), 154.0 (s, N–C=O), 165.0 (C=O) ppm. MS: *m*/*z* (%) = 453 (4) [M]$^+$, 396 (59), 213 (100), 199 (93). $C_{25}H_{31}NO_5Si$ (453.60): calcd. C 66.20, H 6.89, N 3.09; found C 66.54, H 6.53, N 3.02.

Dimethyl (*R*)-4-(*tert*-Butyldimethylsilyloxy)-1,4,5,6-tetrahydropyridine-1,2-dicarboxylate [(+)-23]: Prepared as reported above for (+)-**22**, starting from (+)-**20** (78 mg, 0.36 mmol) and TBDMSCl (64 mg, 0.42 mmol). Chromatography (EtOAc/petroleum ether, 1:5, R_f = 0.27) provided (+)-**23** (108 mg, 91%) as a thick colorless oil. $[\alpha]_D^{25}$ = +154.0 (c = 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 [q, 6 H, Si(CH_3)$_2$], 0.87 [s, 9 H, SiC(CH_3)$_3$], 1.81–1.87 (m, 1 H, 5-H and 5-H′), 3.30 (dt, J = 13.1, 7.0 Hz, 1 H, 6-H), 3.71 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.96 (dt, J = 13.1, 4.3 Hz, 1 H, 6-H′), 4.22 (q, J = 3.9 Hz, 1 H, 4-H), 5.85 (d, J = 3.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = –4.76 (q, Si*C*H$_3$), –4.60 (q, Si*C*H$_3$), 18.0 (s, Si*C*), 25.7 [q, 3 C, SiC(*C*H$_3$)$_3$], 33.0 (t, C-5), 40.3 (t, C-6), 52.3 (q, O*C*H$_3$), 53.2 (q, O*C*H$_3$), 61.9 (d, C-4), 122.3 (d, C-3), 132.5 (s, C-2), 154.2 (s, N–C=O), 165.2 (s, C=O) ppm. MS: *m*/*z* (%) = 329 (0.1) [M]$^+$, 272 (100), 198 (46). $C_{15}H_{27}NO_5Si$ (329.46): calcd. C 54.68, H 8.26, N 4.25; found C 54.71, H 7.87, N 3.93.

Dimethyl (2*S*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)piperidine-1,2-dicarboxylate [(–)-24]: 10% Pd/C (50% wet, 70 mg) was added to a stirred solution of (+)-**22** (100 mg, 0.22 mmol) in EtOAc (6 mL) and the mixture was flushed first with N_2 and then with H_2 before being left under a static H_2 pressure (balloon) at 50 °C (external bath) for 3 h. After filtration through a Celite layer, the solution was concentrated to give an oil which was purified by chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.33) to give (–)-**24** (98 mg, 98%) as thick colorless oil. $[\alpha]_D^{25}$ = –17.1 (c = 0.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 [s, 9 H, SiC(CH_3)$_3$], 1.26–1.45

(m, 2 H, 5_{ax}-H and 5_{eq}-H), 1.80 (br. dd, J = 14.1, 6.8 Hz, 1 H, 3_{ax}-H), 2.51 (br. d, J = 14.1 Hz, 1 H, 3_{eq}-H), 3.52–3.66 (m, 1 H, 6_{ax}-H), 3.66 (s, 3 H, C–CO_2CH_3), 3.69 and 3.72 (s, 3 H, two rotamers, N–CO_2CH_3), 3.80 (br. d, J = 13.5 Hz, major rotamer, 6_{eq}-H), 3.94 (br. d, J = 12.2 Hz, minor rotamer, 6_{eq}-H), 4.08 (br. quint, J = 2.7 Hz, 1 H, 4_{eq}-H), 4.68 (br. d, J = 6.2 Hz, minor rotamer, 2_{eq}-H), 4.84 (br. d, J = 6.8 Hz, major rotamer, 2_{eq}-H), 7.34–7.46 (m, 6 H, CH_{arom}), 7.61–7.69 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 19.2 (s, Si*C*), 26.9 [q, 3 C, SiC(CH_3)$_3$], 31.2 and 31.5 (t, two rotamers, C-5), 33.4 (t, C-3), 35.8 and 36.0 (t, two rotamers, C-6), 50.9 and 51.2 (q, two rotamers, N–CO_2CH_3), 52.1 (q, C–CO_2CH_3), 52.8 (d, C-2), 64.8 (d, C-4), 127.5 and 127.6 (d, two rotamers, 4 C_{arom}), 129.7 and 129.8 (d, two rotamers, 2 C_{arom}), 135.4 (s, 2 C_{arom}), 135.7 and 135.8 (d, two rotamers, 4 C_{arom}), 157.0 and 157.6 (s, two rotamers, N–C=O), 172.0 (s, C=O) ppm. MS: *m*/*z* (%) = 455 (0.1) $[M]^+$, 398 (65), 140 (100). $C_{25}H_{33}NO_5Si$ (455.62): calcd. C 65.90, H 7.30, N 3.07; found C 66.81, H 7.51, N 2.88.

Dimethyl (2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)piperidine-1,2-dicarboxylate [(–)-25]: Prepared as reported above for (–)-**24**. Starting from (+)-**23** (74 mg, 0.22 mmol), (–)-**25** (72 mg, 99%) was obtained after chromatography (EtOAc/petroleum ether, 1:4, R_f = 0.35) as a thick colorless oil. $[\alpha]_D^{25}$ = –16.6 (c = 0.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.01 [s, 6 H, Si(CH_3)$_2$], 0.84 [s, 9 H, SiC(CH_3)$_3$], 1.55–1.63 (m, 2 H, 5_{ax}-H and 5_{eq}-H), 1.84 (br. dd, J = 14.2, 7.0 Hz, 1 H, 3_{ax}-H), 2.30–2.39 (br. m, 1 H, 3_{eq}-H), 3.35–3.55 (m, 1 H, 6_{ax}-H), 3.69 (s, 3 H, C–CO_2CH_3), 3.69 and 3.71 (s, 3 H, two rotamers, N–CO_2CH_3), 3.80 (br. d, J = 12.2 Hz, major rotamer, 6_{eq}-H), 3.94 (br. d, J = 12.3 Hz, minor rotamer, 6_{eq}-H), 4.07 (br. quint, J = 2.9 Hz, 1 H, 4_{eq}-H), 4.63 (br. d, J = 6.6 Hz, minor rotamer, 2_{eq}-H), 4.78 (br. d, J = 7.0 Hz, major rotamer, 2_{eq}-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = –5.2 (q, SiCH_3), –5.0 (q, SiCH_3), 18.1 (s, Si*C*), 25.7 [q, 3 C, SiC(CH_3)$_3$], 31.9 and 32.1 (t, two rotamers, C-5), 33.8 and 33.9 (t, two rotamers, C-3), 35.7 and 35.9 (t, two rotamers, C-6), 50.9 and 51.2 (q, two rotamers, N–CO_2CH_3), 51.9 (q, C–CO_2CH_3), 52.7 (d, C-2), 63.8 (d, C-4), 156.6 and 157.0 (s, two rotamers, N–C=O), 171.9 (s, C=O) ppm. MS: *m*/*z* (%) = 331 (0.1) $[M]^+$, 274 (100). $C_{15}H_{29}NO_5Si$ (331.48): calcd. C 54.35, H 8.82, N 4.23; found C 54.02, H 9.11, N 3.99.

Dimethyl (2*S*,4*R*)-4-Hydroxypiperidine-1,2-dicarboxylate [(–)-21]: A 3 N HCl solution (5 mL) was added to a solution of (–)-**25** (70 mg, 0.21 mmol) in acetonitrile (5 mL) and the mixture was vigorously stirred at room temperature. After 4 h, the mixture was neutralized with $NaHCO_3$ (sat), extracted with EtOAc (3 × 15 mL), and the combined organic layers dried with Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was purified by chromatography (EtOAc/petroleum ether, 1:1, R_f = 0.17) to give (–)-**21** (41 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ = –34.4 (c = 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.59–1.80 (m, 2 H, 5_{ax}-H and 5_{eq}-H), 1.90 (br. dd, J = 13.6, 6.0 Hz, 1 H, 3_{ax}-H), 2.43 (br. d, J = 13.6 Hz, 1 H, 3_{eq}-H), 3.32–3.51 (m, 1 H, 6_{ax}-H), 3.69 and 3.73 (s, 3 H, two rotamers, N–CO_2CH_3), 3.73 (s, 3 H, C–CO_2CH_3), 3.84 (br. d, J = 12.1 Hz, major rotamer, 6_{eq}-H), 3.97 (br. d, J = 8.6 Hz, minor rotamer, 6_{eq}-H), 4.15 (br. s, 1 H, 4_{eq}-H), 4.70 (br. s, minor rotamer, 2_{eq}-H), 4.85 (br. s, major rotamer, 2_{eq}-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ = 31.2 (t, C-5), 33.3 (t, C-3), 35.5 and 35.8 (t, two rotamers, C-6), 50.8 and 51.1 (q, two rotamers, N–CO_2CH_3), 52.3 (q, C–CO_2CH_3), 52.9 (d, C-2), 63.2 (d, C-4), 156.9 and 157.2 (s, two rotamers, N–C=O), 172.9 (s, C=O) ppm. MS: *m*/*z* (%) = 185 (1) $[M - 32]^+$, 158 (100) $[M - 59]^+$, 114 (66). $C_9H_{15}NO_5$ (217.22): calcd. C 49.76, H 6.96, N 6.45; found C 49.73, H 7.26, N 6.22.

(2*S*,4*R*)-4-Hydroxypiperidine-2-carboxylic Acid Hydrochloride (1·HCl):[30] A vigorously stirred dispersion of (–)-**25** (70 mg, 0.21 mmol) in a 2 N HCl aqueous solution (12 mL) was refluxed for 23 h. The mixture was then cooled to room temperature, extracted with Et_2O (2 × 20 mL), and the aqueous layer concentrated under vacuum. The solid residue was triturated with CH_2Cl_2 (2 × 4 mL), discarding the organic phase, and then dissolved in hot EtOH (2 mL). The solution was filtered, concentrated, and the white foamy solid was dried under vacuum (0.1 Torr) at 70 °C for 3 h to give **1**·HCl (36 mg) in 95% yield. M.p. 202–204 °C (decomp.). $[\alpha]_D^{25}$ = +7.11 (c = 0.46, MeOH). ^{1}H NMR (D_2O, 400 MHz): δ = 1.63–1.73 (m, 1 H, 3_{ax}-H), 1.74–1.83 (m, 1 H, 5_{ax}-H), 2.18 (br. d, J = 14.2, 1 H, 5_{eq}-H), 2.56 (br. d, J = 13.8 Hz, 1 H, 3_{eq}-H), 3.12 (td, J = 12.7, 3.3 Hz, 1 H, 6_{ax}-H), 3.59 (td, J = 12.7, 4.1 Hz, 1 H, 6_{eq}-H), 4.00–4.06 (m 1 H, 4_{ax}-H), 4.07 (dd, J = 9.4, 3.9 Hz, 1 H, 2_{ax}-H) ppm. ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.58–1.73 (m, 2 H, 3_{ax}-H and 5_{ax}-H), 2.10 (br. d, J = 14.0, 1 H, 5_{eq}-H), 2.49 (br. d, J = 13.4 Hz, 1 H, 3_{eq}-H), 3.08 (td, J = 12.9, 3.3 Hz, 1 H, 6_{ax}-H), 3.49 (td, J = 12.9, 3.9 Hz, 1 H, 6_{eq}-H), 3.87–3.95 (m, 1 H, 4_{ax}-H), 4.06 (dd, J = 11.9, 3.5 Hz, 1 H, 2_{ax}-H) ppm. ^{13}C NMR (D_2O, 100.4 MHz): δ = 30.2 (t, C-5), 34.0 (t, C-3), 41.8 (t, C-6), 56.0 (d, C-2), 65.1 (d, C-4), 171.4 (s, C=O) ppm.

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[14] Compound **14** has the following ^{1}H NMR ($CDCl_3$, 200 MHz) data: δ = 3.82 (s, 3 H, OCH_3), 4.38 (dd, J = 4.1, 1.5 Hz, 2 H, CH_2N), 5.74 (d, J = 5.5 Hz, 1 H, 3-H), 5.77–5.83 (m, 1 H, 4-H), 5.99–6.04 (m, 1 H, 5-H) ppm. In compounds **15a** and **15b** 3-H is strongly shielded (4.60 and 4.93 ppm, respectively) as a silyloxy group is at C-2 in place of the electron-withdrawing OTf group. Accordingly, in the ^{13}C NMR spectrum of **15b**, C-3 is shifted upfield and resonates at δ = 94.0 ppm. Compound **15b** has the following ^{1}H NMR ($CDCl_3$, 200 MHz) data: δ = 0.20 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 3.74 (s, 3 H, OCH_3), 4.23 (dd, J = 4.4, 1.0 Hz, 2 H, CH_2N), 4.93 (d, J = 5.5 Hz, 1 H, 3-H), 5.39–5.47 (m, 1 H, 4-H), 5.88–5.97 (m, 1 H, 5-H) ppm. The formation of **15a** and **15b** represents quite an anomalous migration of the silyl-protecting group which could have occurred intermolecularly.

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[23] This was demonstrated by treating the diastereomeric 2.4:1 mixture of *cis*- and *trans*-**21** with TBAF in THF at room temperature. After 24 h the *trans* isomer was the major component of the mixture (the *cis*/*trans* ratio was 1:1.5). Deprotection of **24** with HF–pyridine in THF left the starting material unaltered after 24 h at room temperature.

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