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A Short, Chemo-Enzymatic Synthesis of Both Enantiomers of *trans*-3-Hydroxypipecolic Acid

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Dedicated to C.I.N.M.P.I.S. on the occasion of its 20th anniversary

Keywords: Synthetic methods / Cross-coupling / Enzyme catalysis / Amino acids / Lactams

A short synthesis of both enantiomers of *trans*-3-hydroxypipecolic acid was based on the Suzuki–Miyaura reaction of a lactam-derived enol phosphate and the lipase-catalyzed kinetic resolution of the alcohol obtained by hydroboration/oxidation of the coupling product. The $RuCl_3$-catalyzed oxidation of the heteroaryl group introduced by the Suzuki–Miyaura coupling eventually afforded, in six or seven steps, the target compounds in 15–17 % overall yield.

Introduction

Many natural compounds that display significant biological activity incorporate a pipecolic acid fragment as an essential structural feature. Immunosuppressive agents rapamycin[1] and FK506,[1a,2] antitumor antibiotics sandramycin[3] and quinaldopeptin,[4] and cytotoxic apratoxin H[5] contain simple pipecolic acid units. Cyclodepsipeptide antibiotic virginiamycin S2,[6] and serotonin-receptor antagonist damipipecoline[7] embody a 4-hydroxypipecolic acid, whereas *cis* 3-hydroxypipecolic acid is embedded in the natural antitumor antibiotic tetrazomine (Figure 1).[8] Besides, pipecolic acids play an important role in medicinal chemistry as either templates or α-amino acid analogues for the preparation of conformationally restricted peptides[9] and various pharmaceutically active compounds, such as local-anesthetic analogue ropivacaine,[10] HIV protease inhibitor Palinavir,[11] and one of the most potent and selective *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, CGS20281.[12]

Owing to their widespread presence in nature and their significant medicinal potential, there has been much interest in the development of new methods for the asymmetric synthesis of pipecolic acids.[13] In this context, *trans*- and *cis*-3-hydroxypipecolic acids **1** and **2** are no exceptions because a number of syntheses of both compounds have been reported, also owing to the fact that 3-hydroxypiperidine is a privileged scaffold in nature.[14a] As recently reviewed, methods based on the use of starting material from the chiral pool or that involve enantiomerically enriched reagents or catalysts have been mainly exploited, with a few additional tactics centered on the enzymatic resolution of racemic compounds.[14]

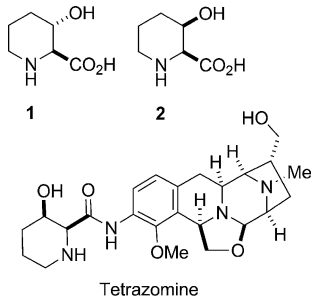

Figure 1. Natural 3-hydroxypipecolic acids and tetrazomine.

We have recently demonstrated that enantiopure 4-hydroxy-, 5-hydroxy- and 4,5-dihydroxypipecolic acids can be efficiently prepared by Pd-catalyzed methoxycarbonylation reaction of suitably functionalized lactam-derived enol phosphates (Scheme 1, a).[15] By this strategy, racemic or enantiopure lactams **3** are converted into enecarbamate esters **4**, which are then reduced to give target compounds **5**. As a consequence of this interest in pipecolic acids, we decided to investigate if an analogous approach, but which entails a Suzuki–Miyaura reaction instead of a carbonylative process to form the C–C bond at C2 (Scheme 1, b), could efficiently provide *trans*-3-hydroxypipecolic acid **1**. After hydroboration/oxidation of coupling product **6**, an enzymatic kinetic resolution should provide enantiopure intermediate **7,** which is finally oxidized to target compound **1**. Lipase-catalyzed resolutions have successfully been exploited for the synthesis of 3-hydroxypipecolic acids (both

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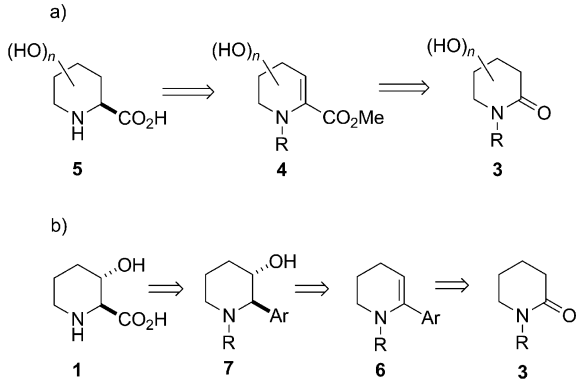
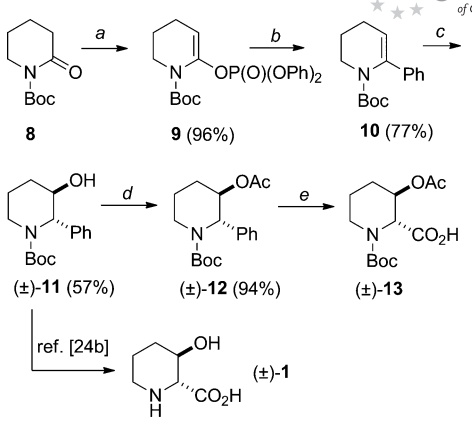
cis and *trans*) on only a few occasions, which involved piperidin-3-ols with the 2-carboxyxlic group already installed on the piperidine ring.[16] In our case, the resolution will be attempted on a 2-aryl- or heteroaryl-substituted piperidin-3-ol, with the advantage of obtaining enantiopure intermediates potentially useful for preparing biologically relevant 2-aryl-substituted piperidines.[17]



Scheme 1. Retrosynthetic analyses.-.

Results and Discussion

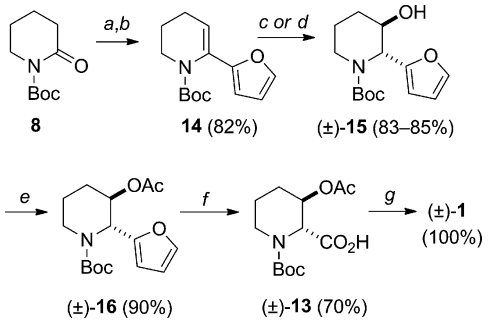
The Suzuki–Miyaura coupling of lactam-derived enol phosphates and triflates has been extensively surveyed in the past mainly by the group of Coudert and Gillaizeau[18] and by our own group,[19] and has found many applications in the synthesis of natural and biologically active heterocyclic compounds.[20] We decided to use this reaction to install a masked carboxylic group at C2 mainly because the carbonylative approach requires the availability and the manipulation of a toxic and expensive gas. Moreover, α,β-unsaturated esters such as **4** are not suitable to install the 3-OH group by hydroboration. Of course, this strategy involves a further oxidative step not required previously. To evaluate the feasibility of our approach, we first coupled enol phosphate **9** (Scheme 2), obtained in 96% yield from commercial *N*-*tert*-butoxycarbonyl(Boc)-protected δ-valerolactam, with phenylboronic acid under conditions that worked best for the corresponding enol triflate.[19b] The reaction was carried at 40 °C in the presence of $(Ph_3P)_2PdCl_2$ (5 mol-%) in a tetrahydrofuran (THF) and Na_2CO_3 (2 M) mixture and it was complete in 24 h to provide known dehydropiperidine **10** in 77% after chromatography. Hydroboration of **10** was carried out with BH_3·DMS at room temperature followed by oxidation with H_2O_2 in alkaline medium,[21] which provided racemic alcohol **11** in moderate yield (57%). The expected *trans* stereochemistry in **11** (and similarly in **15**, see later) is easily assigned on the basis of very low coupling constant values for protons at C2 and C3, which appear as broad singlets at δ = 4.5 and 5.4 ppm, respectively, in the ^{1}H NMR spectrum because of their equatorial orientation. Both the aryl and OH groups are thus axially oriented, the former to remove the $A^{(1,3)}$ strain with the *N*-protecting group.[22]



Scheme 2. *Reagents and conditions:* (a) $(PhO)_2POCl$, KHMDS, THF, –78 °C; (b) phenylboronic acid, $(Ph_3P)_2PdCl_2$, Na_2CO_3 (2 M), THF, 40 °C; (c) BH_3·DMS, THF; then H_2O_2 (35%), EtOH, NaOH (3 N), room temp.; (d) Et_3N, DMAP, Ac_2O, CH_2Cl_2, room temp.; (e) $NaIO_4$, $RuCl_3$·xH_2O, CCl_4/MeCN/H_2O, 0 °C.

Before attempting the enzymatic kinetic resolution of this alcohol we wanted to test the $RuCl_3$ catalyzed oxidation reaction of the phenyl group and so, after acetylation reaction of the OH group, we treated compound **12** under standard oxidative conditions.[23] To our disappointment, the reaction carried out with a catalytic amount of $RuCl_3$·xH_2O and in the presence of $NaIO_4$ (4 equiv.) in a CCl_4/acetonitrile/water mixture was sluggish, required the addition of further oxidant, and yielded carboxylic acid **13** in a very low yield and in mixture with byproducts derived from over-oxidation at position 6. The oxidative degradation of unsubstituted phenyl rings on similar systems has been reported for *N*-trifluoroacetyl-protected piperidines only,[17b,24] and never with *N*-Boc-protected analogues, which are probably not compatible with the reaction conditions. Although pipecolic acid **1** could formally be obtained from **11** after N deprotection and trifluoroacetylation,[24b] to keep our synthesis as short as possible we decided to introduce a more easily oxidized substituent at C2 from the beginning. So, we opted for a more electron-rich furan, which was established by the Pd-catalyzed coupling of *N*-Boc protected valerolactam derivative **9** with 2-furanylboronic acid (Scheme 3).

Also in this case the coupling was successful and provided **14** in 82% yield over two steps, after chromatography. Hydroboration of **14** was carried out both as reported above and with BH_3·THF at 0 °C for 22 h, followed by oxidation with trimethylamine *N*-oxide.[25] In both cases (±)-**15** was obtained in good yield (83 and 85%, respectively), although with the latter method purity of the crude reaction mixture was higher. After acetylation, we tested the oxidative conditions on compound (±)-**16** and were pleased to obtain acid (±)-**13** in good yield (70% after chromatography) after 10 min at room temperature. Although analysis of the ^{1}H NMR spectrum of (±)-**13** showed the presence of some unidentified impurities [this was true also for compound (–)-**13** and (+)-**18**, see later], after exhaustive hydrolysis in HCl (6 N) at reflux temperatures, an appropriate



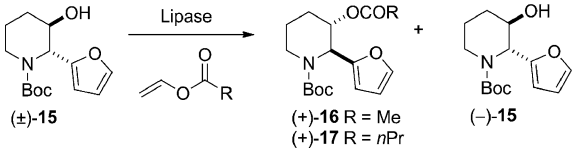
Scheme 3. *Reagents and conditions:* (a) $(PhO)_2POCl$, KHMDS, THF, –78 °C; (b) furanylboronic acid, $(Ph_3P)_2PdCl_2$, Na_2CO_3 (2 M, THF, 40 °C; (c) BH_3·THF, 0 °C, THF; then Me_3NO, THF, 65 °C; (d) BH_3·DMS, THF; then H_2O_2 (35%), NaOH (3 N), EtOH, r.t; (e) Et_3N, DMAP, Ac_2O, CH_2Cl_2, room temp.; (f) $NaIO_4$, $RuCl_3$·xH_2O, EtOAc/MeCN/H_2O, 0 °C; (g) HCl (6 N), reflux, 3 h.

work-up allowed us to obtain racemic 3-hydroxypipecolic acid **1** in quantitative yield and excellent purity.

For the enzymatic kinetic resolution of racemic **15** we opted to test three commercially available immobilized lipases, which we have successfully employed in the past for the enantioselective acylation reaction of 4-hydroxypipecolic acid precursors,[15b] CAL-B (*Candida antarctica* lipase B, supported on acrylic resin, trade name Novozym 435),[26] CAL-A (*C. antarctica* lipase A on Immobead 150),[27] and PS-AMANO-IM (*Burkholderia cepacia* lipase, immobilized diatomaceous earth).[28] As reported in Table 1, only CAL-B proved useful that gave an *E* value[29] around 50 when the resolution was carried out in THF and with vinyl butyrate as the acylant (Table 1, Entry 3). CAL-A proved less efficient but immobilized *B. cepacia* lipase did not appreciably convert **15** into any of the products even with an excess of acylant. This enzyme was the best in the kinetic resolution of 4-hydroxypipecolic acid derivatives[15b] and the same enzyme (lipase PS-C, but immobilized on ceramic particles)[28] provided the best results in the transesterification reaction of a methyl 3-hydroxypipecolate.[16b,16e] So, although the different immobilization forms resulted in differences, the 2-heteroaryl group could play a role in the inefficacy of this enzyme.

The absolute configuration of residual substrate (–)-**15** was determined by converting it, on a small scale, into corresponding pipecolic acid (–)-**1** (see later) and, by comparison of the optical rotation of its HCl salt ($[\alpha]_D^{21}$ = –14.9, *c* = 1.4 in water),[30] we found that CAL-B catalyzes the acylation of the (2*S*,3*S*) substrate. Interestingly, CAL-B is known to preferentially catalyze the acylation of the *R* alcohol in compounds like simple secondary and cyclic allylic alcohols,[26,31] but clearly this general rule cannot be extended to our case owing to the presence of a second vicinal stereocenter. CAL-A similarly has a stereopreference for the (2*S*,3*S*) enantiomer, whereas for the PS-AMANO-IM-catalyzed resolution, owing to the low conversions, the *ee* values nor the absolute configuration of the resolution products were calculated.

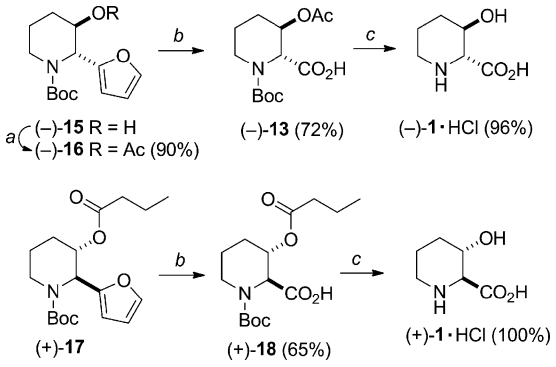
Table 1. Lipase-catalyzed kinetic resolution of (±)-**15**.



Entry	Acylant[a]	Solvent[b]	*t* [h]	*c*[c] [%]	(*S*,*S*)-**16**/**17** *ee* [%][d]	(*R*,*R*)-**15** *ee* [%][e]	*E*[f]
		CAL-B[g]					
1	VA	DIPE	19	58	50	75	6
2	VB	DIPE	17	60	42	99	11
3	VB	THF	25	45	91	81	53
4[h]	VB	THF	19	46	89	75	39
5	VB	TBME	17	57	50	98	12
		CAL-A[g]					
6	VB	THF	24[i]	31	89	37	25
7	VA	THF	43	45	83	63	21
		PS "Amano" IM[g]					
8[h]	VA	DIPE	39[i]	10	–	–	–
9	VB	THF	96[i]	25	–	–	–
10	VB	TBME	52[i]	18	–	–	–

[a] VA: vinyl acetate, VB: vinyl butyrate. [b] Anhydrous solvents were used. [c] Reaction monitored by GLC and conversion determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis, after hydrolysis to (+)-**15**, on a HPLC Lux 5µ Cellulose-4 column (250 × 4.60 mm). [e] Determined by HPLC analysis on a HPLC Lux 5µ Cellulose-4 column (250 × 4.60 mm). [f] *E* = enantiomeric ratio calculated as reported in ref.[29]. [g] Reaction carried out on 0.4 mmol of substrate at 30 °C; substrate concentration: 0.8 M; enzyme (mg)/substrate (mmol) ratio: 200 mg/mmol; 3.5 equiv. of acylant. [h] The reaction was carried out at 40 °C. [i] The reaction did not proceed further and it was stopped.

For the synthesis of (2*R*,3*R*)-3-hydroxypipecolic acid (–)-**1**, resolution of (±)-**15** was carried out on 200 mg of substrate and was stopped at a 57% of conversion to obtain required (–)-(2*R*,3*R*)-**15** in enantiopure form (99% *ee*) in an acceptable yield (38% after chromatography). After the lipase-catalyzed resolution, compound (–)-**15** was acetylated to give (–)-**16** (90%) (Scheme 4) and then oxidized as usual to afford (–)-**13** in 72% yield after chromatography. Exhaustive deprotection was attained by treatment with HCl (6 N) at reflux temperatures to give (–)-(2*R*,3*R*)-**1** as the HCl salt in quantitative yield.



Scheme 4. *Reagents and conditions:* (a) Et_3N, DMAP, Ac_2O, CH_2Cl_2, room temp.; (b) $NaIO_4$, $RuCl_3{\cdot}xH_2O$, EtOAc/MeCN/H_2O, 0 °C; (c) HCl (6 N), reflux, 3 h.

Its enantiomer was instead prepared by stopping the resolution at a 45% conversion, thus obtaining (+)-(2*S*,3*S*)-**17** in 91% *ee* (37% yield) and with a suitable protection already installed on 3-OH group. After usual oxidation and exhaustive deprotection (Scheme 4), (+)-(2*S*,3*S*)-**1** was obtained in quantitative yield as the HCl salt and with optical rotation consistent to that reported for this enantiomer.[32] By treating the residual substrate of the enzymatic kinetic resolution with further CAL-B and vinyl butyrate, and by stopping the reaction at a 18% conversion, enantiopure (–)-(2*R*,3*R*)-**15** (32% yield) was provided, which was converted into pipecolic acid (–)-**1** as described above.

Conclusions

In conclusion, we have reported a very short (six or seven steps) and facile synthesis of both enantiomers of *trans* 3-hydroxypipecolic acid based on the Suzuki–Miyaura reaction of a lactam-derived enol phosphate and the lipase-catalyzed kinetic resolution of the alcohol obtained by hydroboration/oxidation of the coupling product. The best enzyme for the racemate resolution was supported *Candida antarctica* lipase, which preferentially catalyzed the acylation of the alcohol with 3*S* absolute configuration. Then, the $RuCl_3$-catalyzed oxidation of the heteroaryl group introduced by Suzuki–Miyaura coupling afforded the target compounds, which are obtained in 15–17% overall yield. Despite a further oxidative step being required, the Suzuki–Miyara coupling strategy proved an excellent alternative to the alkoxycarbonylative process on lactam-derived enol phosphates for the introduction of a C-2 substituent in the synthesis of pipecolic acids and the extension of this approach to other piperidine derivatives is underway.

Experimental Section

General: Chromatographic separations were performed under pressure with silica gel 60 (Merck,70–230 mesh) by using flash column techniques; R_f values refer to TLC carried out on 0.25 mm silica gel plates with the same eluent indicated for column chromatography. ^{1}H NMR (400 and 200 MHz) and ppm. ^{13}C NMR (50.33 and 100.4 MHz) spectra were recorded at 25 °C. Mass spectra were carried out by direct inlet on a LCQ Fleet™ Ion Trap LC/MS system (Thermo Fisher Scientific) with an ESI interface in positive mode. HPLC analyses were carried out with a Dionex Ultimate 3000 instrument. Compounds **10** and **14** are known.[19b]

***tert*-Butyl 6-[(Diphenoxyphosphoryl)oxy]-3,4-dihydropyridine-1(2*H*)-carboxylate (9):** A solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.5 M, 15.8 mL, 7.89 mmol) was diluted in anhydrous THF (36 mL) and cooled to –78 °C. A solution of **8** (1.26 g, 6.31 mmol) in anhydrous THF (15 mL) was then added dropwise, keeping the temperature below –70 °C, and the resulting mixture was stirred for 1.5 h. A solution of diphenylchlorophosphate (1.63 mL, 7.89 mmol) in anhydrous THF (9 mL) was then added dropwise and, after 1 h, the mixture was warmed to 0 °C. Aqueous NaOH (10%, 150 mL) was slowly added and the product extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with NaOH (10%, 50 mL) and dried with K_2CO_3 for 40 min. After filtration and evaporation of the solvent, the crude was purified with a short pad of silica gel (eluent: *n*-hexane/EtOAc, 3:1, 1% Et_3N, R_f 0.30) to afford pure **9** in 96% yield as a pale yellow oil (2.61 g, 6.05 mmol). ^{1}H NMR (200 MHz): δ = 7.38–7.15 (m, 10 H, *Ph*), 5.10 (q, *J* = 3.3 Hz, 1 H, 3-H), 3.60–3.55 (m, 2 H, 6-H), 2.35–2.04 (m, 2 H, 4-H), 1.75–1.69 (m, 2 H, 5-H), 1.43 [s, 9 H, C(CH_3)$_3$] ppm.

***tert*-Butyl 6-Phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (10):**[19b] Aqueous Na_2CO_3 (2 M, 14.7 mL, 29.4 mmol), $(Ph_3P)_2PdCl_2$ (77.9 mg, 0.11 mmol) and phenylboronic acid (406 mg, 3.33 mmol) were added to a solution of **9** (958 mg, 2.22 mmol) in THF (30 mL). The reaction was stirred and heated at 40 °C for 24 h. The reaction was diluted with H_2O (35 mL) and the product extracted with Et_2O (3 × 35 mL). The combined organic layers were dried with K_2CO_3. After filtration and evaporation of the solvent, crude **10** was purified by flash chromatography (eluent: *n*-hexane, then *n*-hexane/EtOAc, 20:1, R_f 0.30) to afford pure **10** (445 mg, 1.72 mmol) in 77% yield. ^{1}H NMR (200 MHz): δ = 7.70–7.16 (m, 5 H, *Ph*), 5.31 (t, *J* = 3.7 Hz, 1 H, 5-H), 3.73–3.68 (m, 2 H, 2-H), 2.26 (dt, *J* = 6.6, 3.7 Hz, 2 H, 4-H), 1.91–1.78 (m, 2 H, 3-H), 1.05 [s, 9 H, C(CH_3)$_3$] ppm.

***tert*-Butyl 3-Hydroxy-2-phenylpiperidine-1-carboxylate [(±)-11]:** A solution of $(CH_3)_2S{\cdot}BH_3$ in THF (2 M, 375 μL, 0.75 mmol) was added to a solution of **10** (129 mg, 0.5 mmol) in anhydrous THF (1 mL) at 0 °C and under N_2 atmosphere. The cooling bath was removed and the mixture was stirred at room temperature for 5 h. The reaction was cooled to 0 °C and EtOH (550 μL), NaOH (3 M, 440 μL) and H_2O_2 (35%, 200 μL) were added. The resulting mixture was heated to reflux for 1 h and, after cooling, it was transferred into a flask that contained ice. The product was extract with Et_2O (4 × 4 mL) and the combined organic extracts were dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (*n*-hexane/EtOAc, 2:1, R_f 0.26) to

give (±)-**11** (79 mg, 0.28 mmol) in 57% yield as a white solid. ^{1}H NMR (400 MHz): δ = 7.37–7.34 (m, 2 H, *Ph*), 7.27–7.25 (m, 1 H, *Ph*), 7.25–7.19 (m, 2 H, *Ph*), 5.37 (br. s, 1 H, 2-H), 4.52 (br. m, 1 H, 3-H), 4.12–4.07 (br. d, J = 13.3 Hz, 1 H, 6-H_{eq}), 2.87 (td, J = 13.3, 3.3 Hz, 1 H, 6-H_{ax}), 1.98–1.87 (m, 2 H, 5-H and O*H*), 1.78–1.73 (m, 1 H, 4-H), 1.66–1.58 (m, 1 H, 4-H′), 1.48 [s, 9 H, C(CH_3)$_3$], 1.43–1.39 (m, 1 H, 5-H′) ppm. ^{13}C NMR (100.32 MHz): δ = 156.3 (C=O), 137.8 (C$_{ipso}$, *Ph*), 128.4 (2 C, *Ph*), 126.5 (C, *Ph*), 126.0 (2 C, *Ph*), 79.8 [*C*(CH$_3$)$_3$], 67.2 (*C*H-OH), 60.0 (*C*H-Ph), 39.6 (C-6), 28.1 [C(*C*H$_3$)$_3$], 25.7 (C-4), 18.6 (C-5) ppm. MS (ESI): *m*/*z* (%) = 577 (100) [2M + Na]$^+$, 300 (20) [M + Na]$^+$. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.31, H 8.25, N 5.26.

***tert*-Butyl 3-(Acetyloxy)-2-phenylpiperidine-1-carboxylate [(±)-12]:** Et$_3$N (70 μL, 0.5 mmol) and 4-dimethylaminopyridine (DMAP; 6.5 mg, 0.053 mmol) were added to a solution of alcohol (±)-**11** (70 mg, 0.25 mmol) in CH_2Cl_2 dry (1 mL) under an N_2 atmosphere. The mixture was cooled to 0 °C and acetic anhydride (43 μL, 0.46 mmol) was slowly added. The cooling bath was removed and the reaction was stirred at room temperature for 18 h. After dilution with CH_2Cl_2 (5 mL), $NaHCO_3$ satd. (5 mL) was added and the aqueous phase was extract with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (*n*-hexane/EtOAc, 8:1, R_f = 0.24) to give (±)-**12** (75 mg, 0.24 mmol) in 94% yield as a pale yellow oil. ^{1}H NMR (400 MHz): δ = 7.38–7.34 (m, 2 H, *Ph*), 7.27–7.24 (m, 2 H, *Ph*), 5.53–5.51 (br. m, 1 H, 3-H), 5.49 (s, 1 H, 2-H), 4.17–4.11 (br. d, J = 13.3 Hz, 1 H, 6-H_{eq}), 2.88 (td, J = 13.3, 3.3 Hz, 1 H, 6-H_{ax}), 2.12 (s, 3 H, O=CCH_3), 1.93–1.87 (m, 1 H, 5-H), 1.85–1.80 (m, 1 H, 4-H), 1.69–1.60 (m, 1 H, 4-H′), 1.45 [s, 9 H, C(CH_3)$_3$], 1.43–1.39 (m, 1 H, 5-H′) ppm. ^{13}C NMR (100.32 MHz): δ = 170.5 (O=*C*CH$_3$), 156.0 (N-*C*=O), 137.6 (C$_{ipso}$, *Ph*), 128.7 (2 C, *Ph*), 127 (C, *Ph*), 126.3 (2 C, *Ph*), 79.8 [*C*(CH$_3$)$_3$], 70.1 (C-3), 57 (C-2), 39.7 (C-6), 28.4 [C(*C*H$_3$)$_3$], 23.9 (C-4), 21.3 (*C*H$_3$C=O), 19.5 (C-5) ppm. MS (ESI): *m*/*z* (%) = 661 (100) [2M + Na]$^+$, 342 (27) [M + Na]$^+$. MS/MS (ESI of [M + Na]$^+$): *m*/*z* (%) = 342 (3) [M + Na]$^+$, 286 (100), 242 (9), 182 (11). $C_{18}H_{25}NO_4$ (319.40): calcd. C 67.69, H 7.89, N 4.39; found C 67.63, H 7.66, N 4.69.

***tert*-Butyl 6-(Furan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (14):**[19b] Aqueous Na_2CO_3 (2 M, 24.4 mL, 48.8 mmol), $(Ph_3P)_2PdCl_2$ (130 mg, 0.185 mmol) and 2-furanylboronic acid (621 mg, 5.55 mmol) were added to a solution of **9** (1.6 g, 3.73 mmol) in THF (48 mL). The mixture was heated at 40 °C for 2 h, then was diluted with H_2O (68 mL) and the product extracted with Et_2O (3 × 68 mL). The combined organic layers were dried with K_2CO_3. After filtration and evaporation of the solvent, crude **14** was purified by flash chromatography (eluent: *n*-hexane/EtOAc, 20:1, then *n*-hexane/EtOAc, 10:1, R_f 0.48) to afford pure **14** (755 mg, 3.03 mmol) in 82% yield. ^{1}H NMR (200 MHz): δ = 7.32 (dd, J = 1.8, 0.7 Hz, 1 H, 5′-H), 6.35 (dd, J = 3.3, 1.8 Hz, 1 H,4′-H), 6.22 (d, J = 3.3 Hz, 1 H, 3′-H), 5.52 (t, J = 4.0 Hz, 1 H,5-H), 3.68–3.63 (m, 2 H, 2-H), 2.26 (td, J = 7.0, 4.0 Hz, 2 H, 4-H), 1.91–1.82 (m, 2 H, 3-H), 1.26 [s, 9 H, C(CH_3)$_3$] ppm.

***tert*-Butyl 2-(Furan-2-yl)-3-hydroxypiperidine-1-carboxylate [(±)-15]. Method A:** A solution of $(CH_3)_2S{\cdot}BH_3$ in THF (2 M, 1 mL, 2 mmol) was added to a solution of **14** (250 mg, 1 mmol) in anhydrous THF (2 mL) at 0 °C under N_2 atmosphere. The cooling bath was removed and the mixture was stirred at room temperature for 4 h. The reaction was cooled to 0 °C and EtOH (1.1 mL), NaOH (3 N, 900 μL) and H_2O_2 (35%, 390 μL) were added. The resulting mixture was heated to reflux for 1 h. The solution was transferred into a flask that contained ice and the product was extracted with Et_2O (4 × 18 mL). The combined organic extracts were dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography (*n*-hexane/EtOAc, 3:1, R_f = 0.20) to give (±)-**15** (222 mg, 0.83 mmol) in 83% yield as a pale yellow oil.

Method B: To a stirred solution of **14** (219 mg, 0.82 mmol) in anhydrous THF (40 mL), a solution of $BH_3{\cdot}$THF in THF (1 M, 2.87 mL, 2.87 mmol) was added at –78 °C under nitrogen atmosphere. After 15 min, the temperature was raised to 0 °C and the reaction was stirred for 20 h. Then the mixture was warmed to room temperature and Me_3NO was added. The reaction was heated at 65 °C for 2 h. After cooling, EtOAc (80 mL) was added and the organic layer was washed with brine (2 × 40 mL) and dried with anhydrous Na_2SO_4. Chromatography (*n*-hexane/EtOAc, 3:1, R_f = 0.20) afforded pure (±)-**15** (187 mg, 0.7 mmol) in 85% yield as a colorless oil. ^{1}H NMR (400 MHz): δ = 7.35 (dd, J = 1.8, 0.6 Hz, 1 H, 5′-H), 6.33 (dd, J = 3.3, 1.8 Hz, 1 H, 4′-H), 6.11 (d, J = 3.3 Hz, 1 H, 3′-H), 5.34 (br. s, 1 H, 2-H), 4.34 (br. m, 1 H, 3-H), 4.04–4.00 (br. d, J = 13.1 Hz, 1 H, 6-H_{eq}), 2.87 (td, J = 13.1, 3.1 Hz, 1 H, 6-H_{ax}), 2.01 (br. s, 1 H, O*H*), 1.93–1.73 (m, 3 H, 5-H, 4-H, 4-H′), 1.47 [s, 9 H, C(CH_3)$_3$], 1.45–1.42 (m, 1 H, 5-H′) ppm. ^{13}C NMR (100.32 MHz): δ = 156.1 (N-*C*O), 151.9 (C-2′), 141. 7 (C-5′), 110.2 (C-4′), 107.0 (C-3′), 80.2 [*C*(CH$_3$)$_3$], 66.1 (C-3), 56.2 (C-2), 40.0 (C-6), 28.4 [C(*C*H$_3$)$_3$], 26.8 (C-4), 18.8 (C-5) ppm. MS (ESI): *m*/*z* (%) = 557 (48) [2M + Na]$^+$, 290 (100) [M + Na]$^+$. $C_{14}H_{21}NO_4$ (267.32): calcd. C 62.90, H 7.92, N 5.24; found C 62.64, H 7.89, N 5.37.

***tert*-Butyl 3-(Acetyloxy)-2-(furan-2-yl)piperidine-1-carboxylate [(±)-16]:** Prepared as reported above for (±)-**12**. Starting from alcohol (±)-**15** (178 mg, 0.67 mmol), (±)-**16** (160 mg, 0.6 mmol) was obtained in 90% yield after chromatography (*n*-hexane/EtOAc, 6:1, R_f = 0.21) as a colorless oil. ^{1}H NMR (400 MHz): δ = 7.36 (dd, J = 1.8, 1.0 Hz, 1 H, 5′-H), 6.33 (dd, J = 3.3, 1.8 Hz, 1 H, 4′-H), 6.15 (dd, J = 3.3, 1.0 Hz, 1 H, 3′-H), 5.44 (br. s, 1 H, 3-H), 5.32 (br. s, 1 H, 2-H), 4.07 (br. d, J = 12.7 Hz, 1 H, 6-H_{eq}), 2.88 (br. t, J = 12.7 Hz, 1 H, 6-H_{ax}), 2.08 (s, 3 H, O=CCH_3), 1.86–1.73 (m, 3 H, 5-H, 4-H and 4-H′), 1.48–1.42 [s, 9 H, C(CH_3)$_3$ and m, 1 H, 5-H′] ppm. ^{13}C NMR (100.32 MHz): δ = 170.3 (O=*C*CH$_3$), 155.4 (N-*C*=O), 151.1 (C-2′), 141.9 (C-5′), 110.3 (C-4′), 107.4 (C-3′), 80.0 [*C*(CH$_3$)$_3$], 68.4 (C-3), 53.1 (C-2), 39.7 (C-6), 28.4 [C(*C*H$_3$)$_3$], 24.7 (C-4), 21.2 (O=C*C*H$_3$), 19.5 (C-5) ppm. MS (ESI): *m*/*z* (%) = 641 (100) [2M + Na]$^+$, 332 (69) [M + Na]$^+$. MS/MS (ESI of [M + Na]$^+$): *m*/*z* (%) = 332 (10) [M + Na]$^+$, 276 (100), 232 (15), 172 (11). $C_{16}H_{23}NO_5$ (309.36): calcd. C 62.12, H 7.49, N 4.53; found C 61.93, H 7.22, N 4.69.

3-(Acetyloxy)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic Acid [(±)-13]: To a solution of $NaIO_4$ (734 mg, 3.43 mmol) in EtOAc (3.5 mL)/CH_3CN (5.7 mL)/H_2O (2.8 mL) cooled to 0 °C, $RuCl_3{\cdot}xH_2O$ (2 mg, 0.01 mmol) was added. The reaction was left stirred at 0 °C for 15 min, then a solution of (±)-**16** (153 mg, 0.49 mmol) in EtOAc (2.8 mL) was slowly added. After 5 min at 0 °C, H_2O (12 mL) was added and the product was extract with EtOAc (2 × 16 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the crude product was purified by chromatography (CH_2Cl_2/MeOH, 40:1 + 0.1% AcOH, R_f = 0.50) to give (±)-**13** (98 mg, 0.34 mmol) in 70% yield as a yellow gummy solid. ^{1}H NMR (400 MHz): δ = (1:1 mixture of rotamers) = 10.78 (br. s, 1 H, COO*H*), 5.43 (br. s, 1 H, 3-H, rotamer A), 5.34 (br. s, 1 H, 3-H, rotamer B), 5.07 (br. s, 2-H, rotamer A), 4.99 (br. s, 2-H, rotamer B), 4.11 (br. d, J = 12.5 Hz, 1 H, 6-H_{eq}, rotamer A), 3.97 (br. d, J = 12.5 Hz, 1 H, 6-H_{eq}, rotamer B), 2.97 (br. t, J = 12.5 Hz, 1 H, 6-H_{ax}, rotamer A), 2.85 (br. t, J = 12.5 Hz, 1 H, 6-

H_{ax}, rotamer B), 2.06 (s, 3 H, O=CH_3, rotamer A), 2.04 (s, 3 H, O=CH_3, rotamer B), 1.94–1.20 (m, 4 H, 4-H and 5-H, both rotamers) 1.45 [s, 9 H, C(CH_3)$_3$, rotamer A], 1.41 [s, 9 H, C(CH_3)$_3$, rotamer B] ppm. ^{13}C NMR (100.32 MHz): δ = (1:1 mixture of rotamers) = 177.3, 173.8 and 170.4 (*C*OOH and O=*C*CH$_3$, both rotamers), 156.3 (N-*C*=O, rotamer A), 155.3 (N-*C*=O, rotamer B), 80.7 [*C*(CH$_3$)$_3$], 67.9 (C-3, rotamer A), 67.3 (C-3, rotamer B), 57.9 (C-2, rotamer A), 57.1 (C-2, rotamer B), 41.7 (C-6, rotamer A), 40.5 (C-6, rotamer B), 28.3 [C(*C*H$_3$)$_3$], 25.4 (C-4), 21.1 (O=CCH$_3$, rotamer A), 20.8 (O=CCH$_3$, rotamer B), 18.9 (C-5, rotamer A), 18.8 (C-5, rotamer B) ppm. MS (ESI): *m*/*z* (%) = 597 (100) [2M + Na]$^+$, 310 (96) [M + Na]$^+$. MS/MS (ESI of [M + Na]$^+$): *m*/*z* (%) = 310 (3) [M + Na]$^+$, 254 (100), 210 (49). $C_{13}H_{21}NO_6$ (287.31): calcd. C 54.35, H 7.37, N 4.88; found C 54.11, H 7.19, N 4.95.

3-Hydroxypiperidine-2-carboxylic Acid Hydrochloride [(±)-1·HCl]: A solution of (±)-**13** (93 mg, 0.32 mmol) in HCl (6 N, 9 mL) was heated to reflux for 2 h. The reaction was then cooled to room temperature and the solvent was evaporated under vacuum. The residue was triturated with Et$_2$O (2 × 5 mL), and the organic phase was discarded to obtain (±)-**1·HCl** (100%) as a pale yellow solid. ^{1}H NMR (400 MHz): δ = 3.95–3.91 (m, 1 H, 3-H), 3.66 (d, *J* = 8.2 Hz, 2-H), 3.20–3.15 (m, 1 H, 6-H), 2.91–2.85 (m, 1 H, 6-H′), 1.86–1.78 (m, 2 H, 4-H and 5-H), 1.59–1.44 (m, 2 H, 4-H′ and 5-H′) ppm. ^{13}C NMR (100.32 MHz): δ = 169.6 (*C*OOH), 65.5 (C-3), 60.7 (C-2), 42.6 (C-6), 28.9 (C-4), 18.6 (C-5) ppm.

Kinetic Resolution of (±)-15 with CAL-B

***tert*-Butyl (*R*,*R*)-2-(Furan-2-yl)-3-hydroxypiperidine-1-carboxylate [(–)-15]:** To a solution of (±)-**15** (200 mg, 0.74 mmol) in diisopropyl ether (940 μL) at 30 °C was added CAL-B (148 mg). After 10 min, vinyl butyrate (330 μL, 2.6 mmol) was added and the reaction was left to stir and monitored by GLC. After 17 h, the conversion reached 57% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was purified by chromatography (*n*-hexane/EtOAc, 6:1, then *n*-hexane/EtOAc, 3:1, R_f 0.26) to give (–)-**15** (75 mg, 0.28 mmol) in 38% yield (99% *ee*).

(–)-15: $[\alpha]_D^{18}$ = –77.3 (*c* = 1.1, CHCl$_3$). Spectroscopic data identical to those reported above for (±)-**15**.

***tert*-Butyl (*R*,*R*)-3-(Acetyloxy)-2-(furan-2-yl)piperidine-1-carboxylate [(–)-16]:** Prepared as reported above for (±)-**16**. Starting from (–)-**15** (70 mg, 0.26 mmol), (–)-**16** (72 mg, 0.23 mmol) was obtained after chromatography (*n*-hexane/EtOAc, 6:1, R_f 0.21) in 90% yield as a colorless oil. $[\alpha]_D^{21}$ = –45.9 (*c* = 1.0, CHCl$_3$). Spectroscopic data identical to those reported above for (±)-**16**.

(*R*,*R*)-3-(Acetyloxy)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic Acid [(–)-13]: Prepared as reported above for (±)-**13**. Starting from (–)-**16** (70 mg, 0.23 mmol), (–)-**13** (49 mg, 0.17 mmol) was obtained after chromatography (CH$_2$Cl$_2$/MeOH, 20:1 with 0.1% AcOH, R_f 0.19) in 72% yield. $[\alpha]_D^{22}$ = –15.7 (*c* = 1.0, CHCl$_3$). Spectroscopic data identical to those reported above for (±)-**13**.

(*R*,*R*)-3-Hydroxypiperidine-2-carboxylic Acid Hydrochloride [(–)-1·HCl]:[30] Prepared as reported above for (±)-**1**·HCl. Starting from (–)-**13** (49 mg, 0.17 mmol), (–)-**1**·HCl (31 mg, 0.17 mmol) was obtained as a light yellow solid in quantitative yield. $[\alpha]_D^{21}$ = –14.9 (*c* = 1.4, water). Spectroscopic data identical to those reported above for (±)-**1**·HCl.

Two-Step Lipase-Catalyzed Kinetic Resolution of (±)-15

***tert*-Butyl (*R*,*R*)-2-(Furan-2-yl)-3-hydroxypiperidine-1-carboxylate [(–)-15] and *tert*-Butyl (*S*,*S*)-3-(Butyryloxy)-2-(furan-2-yl)piperidine-1-carboxylate [(+)-17]:** To a solution of (±)-**15** (540 mg, 2 mmol) in THF (2.6 mL) at 30 °C was added CAL-B (400 mg). After 10 min, vinyl butyrate (889 μL, 7 mmol) was added and the reaction was left to stir and monitored by GLC. After 25 h, the conversion reached 45% and the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was purified by chromatography (*n*-hexane/EtOAc, 6:1 then *n*-hexane/EtOAc, 3:1) to give (+)-**17** (250 mg, 0.74 mmol, R_f 0.21) in 37% yield (*ee* 91%), and (–)-**15** (259 mg, 0.97 mmol, R_f 0.26). To a solution of (–)-**15** (259 mg, 0.97 mmol) in THF (1.5 mL) at 30 °C was added CAL-B (236 mg). After 10 min, vinyl butyrate (524 μL, 4.13 mmol) was added and the reaction was left to stir vigorously and monitored by GLC. When the conversion reached 18% the reaction was stopped by filtration through a thin layer of Celite. After evaporation, the crude product was purified by chromatography (*n*-hexane/EtOAc, 3:1, R_f 0.26) to give enantiopure (–)-**15** (171 mg, 0.64 mmol) in 32% yield as a colorless oil.

(+)-17: $[\alpha]_D^{23}$ = +31.7 (*c* = 0.82, CHCl$_3$). ^{1}H NMR (400 MHz): δ = 7.36 (d, *J* = 1.2 Hz, 1 H, 5′-H), 6.33 (dd, *J* = 3.1, 2.0 Hz, 1 H, 4′-H), 6.15 (dd, *J* = 2.0, 1.2 Hz, 1 H, 3′-H), 5.42 (br. s, 1 H, 3-H), 5.34 (br. s, 1 H, 2-H), 4.08 (br. d, *J* = 12.5 Hz, 1 H, 6-H$_{eq}$), 2.88 (br. t, *J* = 12.5 Hz, 1 H, 6-H$_{ax}$), 2.32 (t, *J* = 7.4 Hz, 2 H, OCOCH_2CH$_2$), 1.86–1.76 (m, 3 H, 5-H, 4-H and 4-H′), 1.72–1.60 (m, 2 H, -CH$_2$CH_2CH$_3$), 1.47–1.44 [s, 9 H, C(CH_3)$_3$ and m, 1 H, 5-H′] ppm. ^{13}C NMR (100.32 MHz): δ = 173.0 (O=*C*CH$_2$), 155.4 (N-*C*=O), 151.2 (C-2′), 142.1 (C-5′), 110.4 (C-4′), 107.4 (C-3′), 80.0 [*C*(CH$_3$)$_3$], 68.2 (C-3), 53.3 (C-2), 39.8 (C-6), 36.5 (O=C*C*H$_2$CH$_2$), 28.5 [C(*C*H$_3$)$_3$], 24.8 (C-4), 19.7 (C-5), 18.6 (-CH$_2$*C*H$_2$CH$_3$), 13.8 (-CH$_2$*C*H$_3$) ppm. MS (ESI): *m*/*z* (%) = 697 (100) [2M + Na]$^+$, 360 (28) [M + Na]$^+$. $C_{18}H_{27}NO_5$ (337.41): calcd. C 64.07, H 8.07, N 4.15; found C 63.78, H 7.93, N 4.22.

(*S*,*S*)-3-(Butyryloxy)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic Acid [(+)-18]: Prepared as reported above for (±)-**13**. Starting from (+)-**17** (190 mg, 0.56 mmol), product (+)-**18** (114 mg, 65%) was obtained as a yellow gummy solid. $[\alpha]_D^{20}$ = +12.4 (*c* = 1.1, CHCl$_3$). ^{1}H NMR (400 MHz): δ = (1:1 mixture of rotamers) = 9.17 (br. s, 1 H, COOH), 5.45 (br. s, 1 H, 3-H, rotamer A), 5.36 (br. s, 1 H, 3-H, rotamer B), 5.09 (br. s, 2-H, rotamer A), 5.00 (br. s, 2-H, rotamer B), 4.14 (br. d, *J* = 12.3 Hz, 1 H, 6-H$_{eq}$, rotamer A), 3.99 (br. d, *J* = 12.3 Hz, 1 H, 6-H$_{eq}$, rotamer B), 3.00 (br. t, *J* = 12.3 Hz, 1 H, 6-H$_{ax}$, rotamer A), 2.86 (br. t, *J* = 12.3 Hz, 1 H, 6-H$_{ax}$, rotamer B), 2.31–2.30 (br. m, 2 H, O=CH_2CH$_3$, both rotamers), 1.67–1.60 (br. m, 2 H, CH$_2$CH_2CH$_3$), 1.47 [s, 9 H, C(CH_3)$_3$, rotamer A], 1.43 [s, 9 H, C(CH_3)$_3$, rotamer B], 1.94–1.20 (m, 4 H, 4-H and 5-H, both rotamers), 0.96–0.93 (br. m, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (100.32 MHz): δ = 173.8, 172.9 and 172.7 (*C*OOH and O=*C*CH$_2$, both rotamers), 156.1 (N-*C*=O, rotamer A), 155.3 (N-*C*=O, rotamer B), 80.7 [*C*(CH$_3$)$_3$], 67.4 (C-3, rotamer A), 67.3 (C-3, rotamer B), 57.9 (C-2, rotamer A), 57.1 (C-2, rotamer B), 41.6 (C-6, rotamer A), 40.3 (C-6, rotamer B), 36.3 (O=C*C*H$_2$CH$_2$), 28.2 [C(*C*H$_3$)$_3$], 25.4 (C-4), 18.9 (C-5, rotamer A), 18.8 (C-5, rotamer B), 18.5 (CH$_2$*C*H$_2$CH$_3$, rotamer A), 18.4 (CH$_2$*C*H$_2$CH$_3$, rotamer B), 13.6 (CH$_2$*C*H$_3$) ppm. MS (ESI): *m*/*z* (%) = 984 (100) [3M + K]$^+$, 669 (70) [2M + K]$^+$, 653 (59) [2M + Na]$^+$, 338 (19) [M + Na]$^+$. $C_{15}H_{25}NO_6$ (315.36): calcd. C 57.13, H 7.99, N 4.44; found C 57.45, H 7.81, N 4.28.

(*S*,*S*)-3-Hydroxypiperidine-2-carboxylic Acid Hydrochloride [(+)-1·HCl]:[32] Prepared as reported above for (±)-**1**·HCl. Starting from (+)-**18** (100 mg, 0.32 mmol), compound (+)-**1**·HCl (58 mg, 0.32 mmol) was obtained as a light yellow solid. $[\alpha]_D^{21}$ = +13.7 (*c* = 0.7, water). Spectroscopic data as reported above for (±)-**1**·HCl.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for all new

compounds; chiral HPLC chromatograms for racemic and enantiopure 3-hydroxypipecolic acid.

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