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PAPER

Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid: Application of an organocatalytic direct vinylogous aldol reaction†

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The γ-butenolide obtained from an organocatalyzed, direct vinylogous aldol reaction of γ-crotonolactone and benzaldehyde serves as the key starting material in the expedient synthesis of a 3-hydroxy-2-phenyl piperidine intermediate which is converted to the target 2,3-disubstituted piperidines.

Introduction

The piperidine motif is found in numerous biologically relevant natural products[1] as well as in medicinal and pharmaceutical agents,[2] and the synthesis of functionalized piperidines has therefore continued to engage synthetic chemists over the years.[3] Stereoselective routes to aryl substituted[4] and hydroxylated piperidines[5] have been extensively investigated. In particular, the biological activity and the synthesis of a variety of 2,3-disubstituted piperidines has attracted considerable interest. This is perhaps best exemplified by the synthetic efforts directed towards the neurokinin receptor antagonists (+)-L-733,060[6] and (+)-CP-99,994;[7] as well as (2*S*,3*R*)-3-hydroxypipecolic acid,[8] a constituent of the antibiotic tetrazomine (Fig. 1). Herein, we describe an organocatalysis based enantioselective synthesis of these three targets.

The 2-substituted 3-hydroxy piperidine motif is accessible by the rearrangement of 5-(1-aminoalkyl (or aminoaryl) butyrolactones (Fig. 2).[9] The aminobutyrolactones can, in turn, be obtained from the corresponding hydroxy precursors, which are typically obtained by stereoselective vinylogous Mukaiyama aldol reactions of 2-siloxyfurans and aldehydes.[10] However, a much simpler route to stereodefined 5-(1-hydroxyalkyl/aryl) butenolides involves the organocatalytic, direct vinylogous aldol reaction of γ-crotonolactone (2(5H)-furanone) with aldehydes, a reaction that has received attention only recently.[11] Given the structural similarities in the targets of the present study (Fig. 1), it appeared that a suitably functionalized butyrolactone could potentially be employed as a common synthetic precursor to achieve most of the objectives. In addition, this synthetic strategy would also highlight the utility of the organocatalytic direct vinylogous aldol (ODVA) reaction (Fig. 2).

Results and discussion

Our studies therefore began with the synthesis of **1** (Scheme 1) and its conversion to (5*S*,6*S*)-5-hydroxy-6-phenylpiperidin-2-one (**3**) which is an advanced precursor to (+)-L-733,060 and (+)-CP-99,994. Initially, the direct vinylogous aldol reaction of commercially available γ-crotonolactone and benzaldehyde was examined in the presence of selected aminothiourea and aminosquaramide catalysts derived from stilbenediamine, 1,2-cyclohexane diamine and amines obtained from cinchona alkaloids. Extensive optimization studies with these catalysts revealed the aminosquaramide **A**[12] as the most efficient catalyst in terms of the yield, diastereoselectivity and enantioselectivity for the aldol product.[11c] Thus, the direct vinylogous aldol reaction of γ-crotonolactone with benzaldehyde provided the butenolide **1** in good yield and diastereoselectivity (74%, anti/*syn* = 8/1) and excellent enantiomeric excess (>99% ee for the anti diastereomer) when the reaction was conducted in dichloromethane at ambient temperature (Scheme 1).

The aldol product **1** (as a diastereomeric mixture) was easily converted to the lactam **3** *via* a series of simple transformations. Hydrogenation of **1** to the butyrolactone **1a**, subsequent mesylation of the secondary alcohol to give **1b** and displacement of the

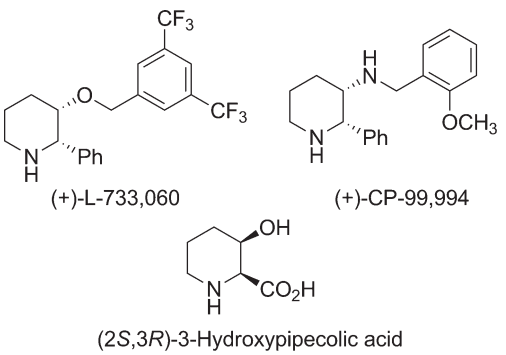

Fig. 1 Biologically active 2,3-disubstituted piperidines targeted in this study.

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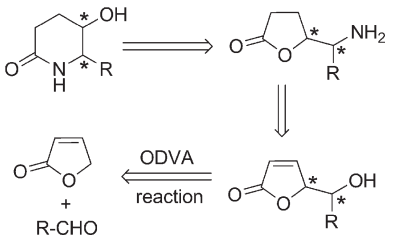
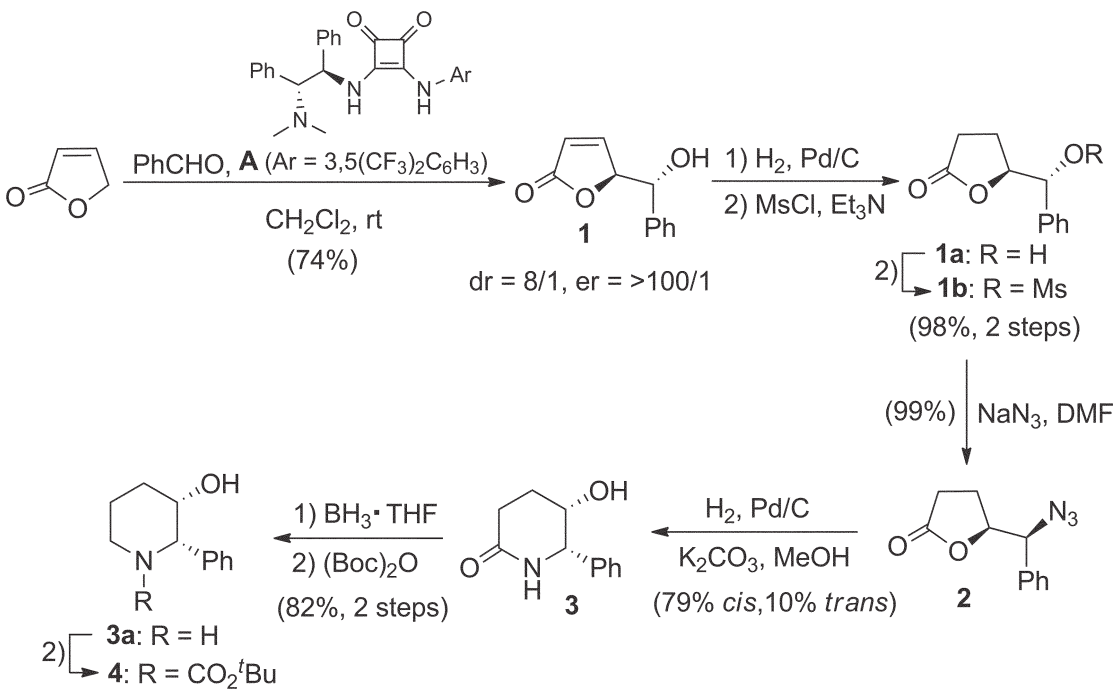


Fig. 2 The organocatalytic direct vinylogous aldol route to functionalized piperidines.

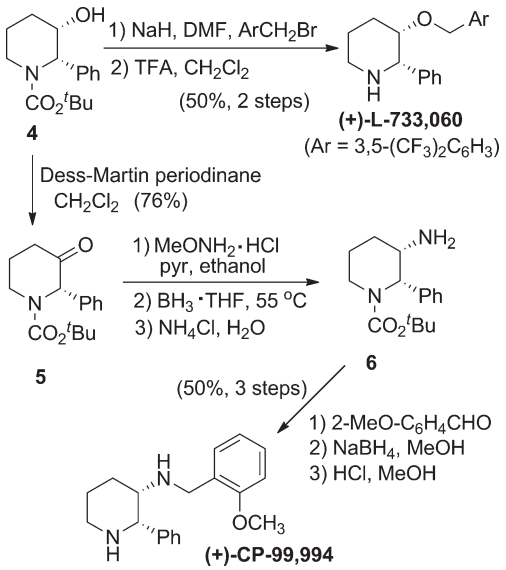
mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **2**. It should be mentioned that the attempted mesylation of **1** exclusively resulted in its dehydration. This unwanted side reaction is effectively prevented by prior reduction of the double bond in **1**. Reduction of the azide (H_2, Pd/C) generated a mixture of the corresponding amino butyrolactone and the required piperidone **3** resulting from an intramolecular *N*-acylation of the amino lactone. Notably, hydrogenation of the azide in the presence of a base (K_2CO_3) significantly facilitated this rearrangement to directly provide **3** without any residual amino lactone. At this stage, *cis* **3** was easily separated from the minor (*trans*) diastereomer by flash chromatography and all further transformations were carried out with diastereomerically pure *cis* **3**.[13] The overall conversion of **1** to **3** is quite efficient (76% yield over four steps) and can be conducted without purification of any of the intermediates. Reduction of the piperidone **3** with borane[6e] provided the corresponding piperidine (**3a**, 96%) which was converted to the *N*-Boc derivative **4**.

The conversion of **4** to the neurokinin receptor antagonist targets was achieved by adaptation and some modification of previously described methods (Scheme 2). *O*-Alkylation of **4** with 3,5-bistrifluoromethylbenzylbromide followed by deprotection provided (+)-L-733,060 (9 steps from benzaldehyde, 24.8% overall yield). The synthesis of (+)-CP-99,994 required the synthesis of ketone **5** and subsequent reductive amination, and both of these steps required detailed attention to the reaction conditions. Oxidation of **4** with Dess–Martin periodinane provided the 3-piperidinone **5** (77%, 94% ee). Notably, in our hands, the enantiomeric excess of **5** was dependent on the method of oxidation[14] and the DMP procedure[15] is by far the best for obtaining **5** in good yield and high enantiomeric excess. Subsequent oximation of **5** with methoxyamine by a significant modification[14] of the reported procedure[15] (ethanol instead of pyridine as the solvent) gave the corresponding oxime ether which was reduced stereoselectively to the amine **6**. Reductive amination of **6** with 2-methoxybenzaldehyde followed by deprotection provided CP-99,994.

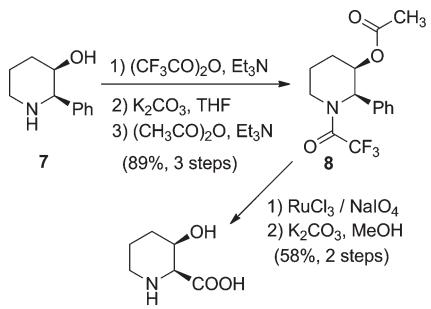
We next investigated the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid. This particular diastereomer of 3-hydroxypipecolic acid has been the subject of numerous investigations and it continues to attract interest from synthetic chemists.[8a–f] At the outset, it seemed reasonable that direct oxidation of the phenyl ring in the *O*-acetyl derivative of *N*-Boc-(2*R*,3*R*)-2-phenyl-3-hydroxy piperidine[16] (*ent*-**4**) would lead us to the pipecolic acid target. However, attempted oxidation ($RuCl_3/NaIO_4$) of this substrate invariably lead to a mixture of products, none of which corresponded to the required carboxylic acid. Interestingly, a change in the *N*-protecting group[8c,17] was beneficial. Accordingly, (2*R*,3*R*)-2-phenyl-3-hydroxy piperidine (**7**) was first converted to the *N*,*O*-bis trifluoroacetyl derivative and the trifluoroacetate ester was selectively replaced with an acetate to provide **8** (89%). Oxidation of the phenyl ring in **8**, with $RuCl_3/NaIO_4$, now proceeded smoothly to provide the corresponding carboxylic acid. Methanolysis of the trifluoroacetamide and the



Scheme 1



Scheme 2



Scheme 3

acetate in this intermediate gave (2*S*,3*R*)-3-hydroxypipecolic acid (58% from **8**, Scheme 3).[8c]

Conclusion

In conclusion, we have achieved the synthesis of three representative members of the 2,3-disubstituted class of bioactive piperidines from the butenolide **1**. The syntheses developed in this study are based on an organocatalytic vinylogous aldol reaction as the pivotal step and are particularly concise.[18] Notably, ketone **5** is also a starting material in the synthesis of spirocyclic NK-1 receptor antagonists.[19,20] The methodology presented here has potential relevance in the preparation of libraries of antagonists, related to the those described here, by variation of the aldehyde in the direct vinylogous aldol step. Current efforts focus on the application of this methodology to other biologically relevant piperidine-based natural products and their analogs.

Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. Compounds **1**, **4**, **4a** and **6a** were prepared by literature methods. The conversion of **4a** to (+)-L-733,060 and of **6a** to (+)-CP-99,994 was achieved by literature methods.

(*S*)-5-((*R*)-Hydroxy(phenyl)methyl)furan-2(5H)-one (1)[11c]

The literature procedure[11c] was adapted. To the catalyst **A** (20 mol%, 1.00 g) was added benzaldehyde (970 μL, 9.14 mmol) followed by 2-(5H)-furanone (1.28 mL, 18.3 mmol) and dichloromethane (5 mL). The mixture was stirred for 192 h at room temperature. The mixture was diluted with ethyl acetate (30 mL) and aqueous 2 M HCl (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10 : 1) to give **1** as a pale yellow solid (1.73 g, 74%). The diastereomeric composition (*anti* : *syn* = 8 : 1) was determined by ^{1}H NMR analysis of the crude product. The enantiomeric excess was determined by HPLC (Chiralpak AS-H, hexanes/2-propanol 90 : 10, 254 nm, t_1 = 32.6 min (minor *anti*), t_2 = 37.7 min (minor *syn*), t_3 = 53.1 min (major *syn*), t_4 = 70.5 min (major *anti*). ee: > 99% (anti)). In repeated experiments an ee range of 97 to >99% was observed. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **1** is in agreement with that reported in the literature.[11b,c]

(*S*)-Dihydro-5-((*R*)-(hydroxy(phenyl)methyl)furan-2(3H)-one (1a)[6e]

Pd/C (10%, 75 mg) was added to a stirred solution of **1** (750 mg, 3.94 mmol) in EtOAc (10 mL). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2. The mixture was filtered through Celite and the filter cake was washed with EtOAc (2 × 30 mL). The combined filtrates were concentrated *in vacuo* to provide 758 mg (99%) of **1a** as a white solid (*anti* : *syn* = 8 : 1). IR: 3391, 1753, 1453, 1370, 1182, 1042, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***anti* diastereomer**: δ 7.39–7.32 (m, 5H, Ar*H*), 5.13 (d, 1H, J = 2.7 Hz, C*H*OH), 4.72–4.65 (m, 1H, C*H*CH$_2$), 2.59–2.50 (m, 2H, C*H*$_2$C=O, C*H*CH$_2$), 2.5–2.4 (m, 1H, C*H*$_2$C=O), 2.32–2.24 (m, 1H, C*H*$_2$CH–O), 1.97–1.90 (m, 1H, C*H*$_2$CH–O); **Visible resonances for the *syn* diastereomer**: δ 4.65–4.60 (m, 1H, C*H*CH$_2$), 2.06–2.01 (m, 1H, C*H*$_2$CHO); ^{13}C NMR (75 MHz, $CDCl_3$): ***anti* diastereomer**: δ 177.6 (CH$_2$*C*O), 138.4 (Ar*C*), 128.7 (Ar*C*), 128.2 (Ar*C*), 126.0 (Ar*C*), 83.3 (CH$_2$*C*HO), 73.5 (*C*HOH), 28.6 (*C*H$_2$CO), 20.7 (*C*H$_2$CHO); **Visible resonances for the *syn* diastereomer**: δ 176.8 (CH$_2$*C*O), 138.3 (Ar*C*), 128.8 (Ar*C*), 128.2 (Ar*C*), 127.0 (Ar*C*), 83.4 (CH$_2$*C*HO), 77.2 (*C*HOH), 28.5 (*C*H$_2$CO), 24.0 (*C*H$_2$CHO); MS (EI pos): *m*/*z*: 193.1 (M + 1).

(*S*)-Dihydro-5-((*R*)-(methylsulfonyl)(phenyl)methyl)furan-2(3H)-one (1b)[6e]

Triethyl amine (626 μL, 4.5 mmol) was added slowly to an ice cold solution of **1a** (720 mg, 3.75 mmol) in CH_2Cl_2, followed by the addition of methane sulfonyl chloride (349 μL, 4.5 mmol). The reaction mixture was stirred for 1 h at 0 °C and water (20 mL) was added at 0 °C. The mixture extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to provide 1.1 g (>99%) of **1b** as a yellow oil (*anti* : *syn* = 8 : 1) This was shown to be pure by ^{1}H NMR and was used in the next step without purification.

IR: 3027, 2938, 1775, 1351, 1171, 1031, 944, 912, 874, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***anti* diastereomer (major)**: δ 7.35 (m, 5H), 5.73 (d, 1H, J = 3.9 Hz), 4.86–4.80 (m, 1H), 2.91 (s, 3H), 2.50–2.40 (m, 2H), 2.28–2.09 (m, 2H); **Visible resonances for the *syn* diastereomer (minor)**: δ 5.52 (d, 1H, J = 5.7 Hz), 2.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ***anti***: δ 176.1, 133.5, 129.6, 129.1, 126.9, 82.8, 80.4, 39.0, 27.7, 22.1; ***syn***: δ 176.0, 133.7, 130.0, 129.2, 127.5, 84.3, 80.3, 39.3, 27.9, 24.2; MS (API-ES) *m*/*z* 270.4 (M^+); HRMS (CI): 271.0640 (271.0640 calc. for $C_{12}H_{15}O_5S$, M + H).

(*S*)-5-((S)-Azido(phenyl)methyl)-dihydrofuran-2(3H)-one (2)[6e]

Sodium azide (1.22 g, 18.7 mmol) was added to the crude mesylate (1.1 g, 4.1 mmol) in DMF (5 mL) and the mixture was stirred at 80 °C for 4 h. The mixture was cooled to room temperature and EtOAc (30 mL) was added followed by water (30 mL). The resulting biphase was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 838 mg (>99%) of **2** as a yellow oil (*syn* : *anti* = 8 : 1). This was pure by ^{1}H NMR and was used in the next step without purification.

IR: 2101, 1774, 1455, 1250, 1175, 1148, 1066, 990, 913 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***syn* diastereomer**: δ 7.44–7.35 (m, 5H), 4.71–4.61 (m, 1H), 4.60 (d, 1H, J = 5.9 Hz), 2.48–2.34 (m, 2H), 2.15–2.05 (m, 1H), 2.05–1.95 (m, 1H); **Visible resonances for the *anti* diastereomer**: δ 4.90 (d, 1H, J = 4.2 Hz), 2.58–2.45 (m, 2H), 2.25–2.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): ***syn* diastereomer**: δ 176.2, 134.5, 129.2, 127.8, 127.2, 81.2, 68.5, 28.0, 24.6; **Visible resonances for the *anti* diastereomer**: δ 176.4, 134.6, 129.1, 129.0, 81.4, 67.8, 28.1, 22.3; MS (EI pos.): *m*/*z* 218.1 (M + 1); HRMS (APCI pos.): *m*/*z* 218.0972 (218.0930 calc. for $C_{11}H_{12}N_3O_2$ (M + H)).

(5*S*,6*S*)-5-Hydroxy-6-phenylpiperidin-2-one (3)[6b]

To a stirred solution of **2** (810 mg, 3.73 mmol) in methanol (5 mL) was added K_2CO_3 (160 mg, 1.16 mmol) followed by Pd/C (10%, 81 mg). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 × 30 mL) and the combined filtrates were concentrated *in vacuo* under reduced pressure to provide a yellow gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95 : 5 as the eluant) to provide 564 mg (79%) of **3** as a fluffy white solid and 70 mg (10%) of the 5*S*,6*R* isomer as a white solid.

***cis* Diastereomer.** Mp: 99 °C (lit.[6b] mp. 92 °C); IR: 3360, 3197, 2945, 1643, 1461, 1399, 1351, 1318, 1197, 1069, 986, 942 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.41 (m, 2H, Ar*H*), 7.37–7.33 (m, 3H, Ar*H*), 5.85 (br s, 1H, CON*H*), 4.67 (d, 1H, J = 2.7 Hz, C*H*Ar), 4.08 (br s, 1H, C*H*OH), 2.76–2.69 (m, 1H, CH_2C═O), 2.41–2.37 (m, 1H, CH_2C═O), 2.15–2.13 (m, 1H, CHCH_2), 2.04–2.01 (m, 1H, CHCH_2), 1.69 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (*C*═O), 137.9 (ArC_{ipso}), 129.2 (Ar*C*), 128.7 (Ar*C*), 127.0 (Ar*C*), 66.2 (*C*HOH), 61.9 (*C*HAr), 26.7 (CH*C*H_2), 26.07 (*C*H_2C═O); MS (APCI, pos.) *m*/*z* 192.1 (M + 1); HRMS (EI): 191.0950 (191.0946 calc. for $C_{11}H_{13}NO_2$ (M + H)); $[\alpha]_D^{23}$ = +55.3 (c 1.06, CH_2Cl_2), lit. $[\alpha]_D^{25}$ = +52.0 (c 1.1, CH_2Cl_2).[6b]

***trans* Diastereomer.** IR: 3237, 2364, 1631, 1581, 1485, 1446, 1349, 1333, 1175, 1076, 945, 801 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.40 (m, 2H, Ar*H*), 7.40–7.35 (m, 3H, Ar*H*), 5.70 (br s, 1H, CON*H*), 4.69 (d, J = 2.8 Hz, 1H, C*H*Ar), 4.10 (br s, 1H, C*H*OH), 2.72–2.82 (ddd, 1H, J = 18.0, 11.9, 6.5 Hz, CH_2CO), 2.40–2.45 (ddd, 1H, J = 18.0, 6.2, 2.8 Hz, CH_2CO), 2.19–2.15 (m, 1H, CHCH_2), 2.07–2.03 (m, 1H, CHCH_2), 1.47 (br t, 1H, J = 1.5 Hz, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (*C*═O), 137.8 (ArC_{ipso}), 129.2 (Ar*C*), 128.8 (Ar*C*), 127.0 (Ar*C*), 66.3 (*C*HOH), 61.9 (*C*HAr), 26.7 (CH*C*H_2), 26.1 (*C*H_2C═O); MS (APCI pos.): *m*/*z* 192.3 (M^+); $[\alpha]_D^{23}$ = +26.0 (c 1.0, MeOH); lit. $[\alpha]_D^{23}$ = +31.6 (c 0.75, MeOH).[21]

(2*S*,3*S*)-2-Phenylpiperidin-3-ol (3a)[6e]

Borane-THF complex (4.7 mL, 4.68 mmol) was added to **3** (300 mg, 1.56 mmol), and the mixture was heated to reflux for 5 h. The mixture was cooled to 0 °C, aqueous HCl (3 M, 12 mL) was added and the mixture was stirred for 30 min. at room temperature. The mixture was then concentrated *in vacuo* to dryness under reduced pressure and the residue was basified with 5% aqueous NaOH at 0 °C to pH ~10. The resulting mixture was extracted with EtOAc, dried (Na_2SO_4), and concentrated *in vacuo* to provide **3a** as a white solid (267 mg, 96%). This was shown to be pure by ^{1}H NMR and was used in the next step without purification.

Mp: 90–93 °C. IR: 3274, 2926, 2851, 1447, 1323, 1089, 1054, 1053, 989 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.32 (m, 3H), 7.32–7.24 (m, 2H), 3.86 (br s, 1H), 3.78 (br s, 1H), 3.22–3.19 (m, 1H), 2.83–2.78 (dt, 1H, J = 2.8, 12.1 Hz), 2.02–1.92 (m, 1H), 1.89–1.84 (m, 1H), 1.74–1.67 (m, 1H), 1.52–1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 128.5, 127.3, 126.6, 68.9, 65.0, 47.5, 32.0, 19.9; MS (APCI, pos.): *m*/*z* 178.1 (M + 1); HRMS (EI): 177.1153 (177.1154 calc. for $C_{11}H_{15}NO$); $[\alpha]_D^{23}$ = +66.4 (c 0.62, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (4)[6b]

Reaction of **3a** (500 mg, 2.82 mmol) and di-*tert*-butyl dicarbonate in the presence of triethylamine (431 μL, 3.1 mmol) and DMAP (25 mg, 0.20 mmol) in dichloromethane (5 mL) by

adaptation of the literature procedure[6b] followed by purification of the crude product by flash chromatography on silica gel (hexanes/ethylacetate, 7 : 3) provided 663 mg (85%) of **4** as a colorless oil. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **4** was in agreement with that reported in the literature.[6b]

(2*S*,3*S*)-*tert*-Butyl-3-(3,5-bis(trifluoromethyl)benzyloxy)-2-phenylpiperidine-1-carboxylate (4a)[6e]

Reaction of the sodium salt of **4** (prepared from 60 mg, 0.216 mmol of **4**) and sodium hydride (95%, 16 mg, 0.65 mmol) in DMF/THF (3 : 1, 1 mL) and bis(trifluoromethyl) benzylbromide (100 mg, 0.33 mmol) at 0 °C for 16 h, by adaptation of the literature procedure,[6e] provided after purification of the crude product by flash chromatography on silica gel (hexanes/ethylacetate, 9 : 1) 57 mg (52%) of **4a** as a colorless oil. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **4** was in agreement with that reported in the literature.[6g]

(2*S*,3*S*)-3-(3,5-Bis(trifluoromethyl)benzyloxy)-2-phenylpiperidine ((+)-L-733,060)[6b]

Deprotection of **4a** (46 mg, 0.09 mmol) with trifluoroacetic acid (70 μL, 0.91 mmol) in CH_2Cl_2 (1 mL) by adaptation of the literature procedure[6b] provided 34 mg (92%) of (+)-L-733,060 as a pale yellow liquid. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for (+)-L-733,060 was in agreement with that reported in the literature.[6b]

(*S*)-*tert*-Butyl-3-oxo-2-phenylpiperidine-1-carboxylate (5)[15]

This was prepared by a modification of the reported procedure.[15] Dess–Martin periodinane (642 mg, 1.5 mmoles) was added to a solution of the crude alcohol **4** (140 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with saturated brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc, 8 : 2) to give 106 mg (77%) of **5** as a pale yellow liquid. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **5** is in agreement with that reported in the literature.[20]

IR: 2974, 1690, 1401, 1361, 1247, 1154 (br), 1105, 1031, 967 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.20 (m, 5H, Ar*H*), 5.65 (br s, 1H, C*H*Ar), 4.08 (br s, 1H, CH_2N), 3.34–3.30 (br m, 1H, CH_2N), 2.51–2.40 (m, 2H, CH_2C═O), 1.98–1.88 (m, 2H, CH_2CH$_2$C═O), 1.43 (br s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (CH$_2$*C*═O), 155.0 (N–*C*═O), 135.6 (Ar*C*), 128.9 (Ar*C*), 127.6 (Ar*C*), 125.4 (Ar*C*), 80.7 (*C*(CH$_3$)$_3$), 65.9 (br, *C*HAr), 40.1 (br, NCH_2), 37.3 (*C*H$_2$C═O), 28.2 (C(*C*H$_3$)$_3$), 22.8 (*C*H$_2$CH$_2$N); HRMS (EI pos.): 275.1525 (275.1521 calc. for $C_{16}H_{21}NO_3$); HPLC: Chiralpak AD-H, hexanes/2-propanol 99 : 1, 254 nm, t_{major} = 33.9 min, t_{minor} = 35.7 min.; ee = 94% ee.

(2*S*,3*S*)-*tert*-Butyl 3-amino-2-phenylpiperidine-1-carboxylate (6)[15]

This was prepared by a modification of the reported procedure.[15] To a stirred solution of ketone **5** (60 mg, 0.22 mmol) in ethanol (0.5 mL) at room temperature, was added anhydrous pyridine (26 μL, 0.33 mmol) followed by methoxylamine hydrochloride (27 mg, 0.33 mmol) and the mixture was stirred at room temperature for 30 min. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was stirred for 30 min, and then extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo* to provide the crude oxime methyl ether of **5** as a pale yellow oil (70 mg). This was treated with BH_3-THF (1 M soln. in THF; 651 μL, 0.63 mmol) under N_2 and the solution was stirred at 50 °C for 4h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 9 : 1) to provide 40 mg (67%) of **6** as a pale yellow oil. IR: 2931, 1682, 1407, 1362, 1252, 1147, 868 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 7.3 Hz, Ar*H*), 7.31–7.28 (m, 2H, Ar*H*), 7.26–7.23 (m, 1H, Ar*H*), 5.20 (d, 1H, J = 6.0 Hz, C*H*Ar), 4.01 (br d, 1H, J = 10.9 Hz, C*H*NH$_2$), 3.20–3.11 (m, 2H, NCH_2), 1.88–1.65 (m, 4H, CH_2CH_2CH), 1.45 (br s, 2H, NH_2), 1.36 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4 (*C*O$_2$tBu), 139.1 (Ar*C*), 129.4 (2 × Ar*C*), 128.2 (2 × Ar*C*), 127.2 (Ar*C*), 79.7 (O*C*(CH$_3$)$_3$), 60.6 (N*C*H), 51.2 (*C*HNH$_2$), 39.8 (N*C*H$_2$), 29.2 (NH$_2$CH*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 24.4 (NCH$_2$*C*H$_2$); MS (EI pos.): m/z 277.2 (M + 1).

(2*S*,3*S*)-*tert*-Butyl 3-(2-methoxybenzylamino)-2-phenylpiperidine-1-carboxylate (6a)[15]

Reaction of **6** (16 mg, 0.06 mmol) and 2-methoxybenzaldehyde (21 μL) to provide the imine and reduction of the imine with sodium borohydride (13 mg, 0.35 mmol) by adaptation of the literature procedure[22] followed by purification of the crude product by flash column chromatography on silica gel (CH_2Cl_2/ethylacetate, 9 : 1) provided 18 mg (78%) of **6a** as a pale yellow oil. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **6a** is in agreement with that reported in the literature.[15]

HPLC (Chiralpak OD-H, hexanes/2-propanol 90 : 10, 210 nm, t_{minor} = 4.64 min, t_{major} = 5.20 min; ee = 93%.

(2*S*,3*S*)-*N*-(2-Methoxybenzyl)-2-phenylpiperidin-3-amine ((+)-CP-99,994)[15]

Reaction of **6a** (18 mg, 0.05 mmol) in conc. aqueous HCl/methanol (1 : 1 v/v, 1 mL) by adaptation of the literature procedure[15] provided 12 mg (92%) of (+)-CP-99,994 as a pale yellow oil. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) for **6a** is in agreement with that reported in the literature.[15]

HPLC (Chiralpak OD-H, hexanes/2-propanol 90 : 10, 210 nm, t_{major} = 6.27 min, t_{minor} = 9.75 min; ee = 94%

N-Trifluoroacetyl-(2*S*,3*R*)-3-acetoxy-2-phenylpiperidine (8)[8c]

To an ice cold solution of the aminoalcohol **7** (*ent*-**3a**, 500 mg, 2.82 mmol; prepared as described for **3a**, but with the

enantiomer of catalyst **A**) in CH_2Cl_2 (30 mL) containing Et_3N (2.3 mL, 16.9 mmol) and dimethylaminopyridine (17 mg, 0.14 mmol) was added triflouroacetic anhydride (1.6 mL, 11.3 mmol). The solution was stirred at room temperature for 12 h, water was added and the solution was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in THF (30 mL), K_2CO_3 (770 mg, 5.57 mmol) was added and the mixture was stirred for 36 h at room temperature. Water was added and the mixture was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc, 7 : 3) to provide 715 mg (93%) of the trifluoroacetamide derivative of **7** as a pale yellow oil. This was dissolved in CH_2Cl_2 (30 mL), Et_3N (1.57 mL, 11.29 mmol) and dimethylaminopyridine (15 mg, 0.12 mmol) were added and the solution was cooled to 0 °C. Acetic anhydride (0.53 mL, 5.19 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc, 8 : 2) to provide 795 mg (89%) of **8** as a pale yellow oil.

IR: 1743, 1687, 1451, 1370, 1235, 1193, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): **Major rotamer**: δ 7.49–7.26 (m, 5H), 5.99 (d, 1H, J = 5.7 Hz), 5.25–5.20 (m, 1H), 3.83 (br d, 1H, J = 14.0 Hz), 3.19–3.13 (m, 1H), 2.17–2.11 (m, 1H), 2.0 (s, 3H), 1.85–1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 135.4, 128.9, 128.7, 128.0, 128.0, 127.8, 116.6 (q, J = 288.0 Hz), 55.5, 41.2 (q, J = 3.4 Hz), 24.9, 23.9, 21.1; **Minor rotamer**: ^1H NMR (500 MHz, $CDCl_3$), visible resonances: 5.55 (d, J = 5.3 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 2.78–2.72 (dt, 1H, J = 4.1, 13.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), visible resonances: δ 169.7 ($COCH_3$), 156.5 (q, J = 36.1 Hz), 135.0, 72.4, 70.6, 57.7, 38.8, 23.5, 21.1; MS (APCI pos.): m/z 316.1 (M + 1); HRMS (CI+): m/z 316.1154 (316.1161 calc. for $C_{15}H_{17}NO_3F_3$ (M + H)).

(2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid[8e]

To a mixture of **8** (150 mg, 0.475 mmol) in carbon tetrachloride (0.75 mL), acetonitrile (0.75 mL) and water (1.1 mL), were added sodium periodate (1.53 g, 7.13 mmol) and ruthenium chloride (5 mg, 0.024 mmol) and the mixture was stirred vigourously at ambient temperature for 20 h. The mixture was filtered through a pad of Celite and the residue was rinsed several times with CH_2Cl_2. The black filtrates were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue obtained was dissolved in methanol (5 mL), K_2CO_3 (393 mg, 2.84 mmol) was added and the mixture was stirred at room temperature for 12 h. The resulting solution was concentrated *in vacuo* and the residue was dissolved in aqueous HCl (1 M, 1 mL). This solution was applied to a column of Dowex 50Wx8 resin (200–400 dry mesh) and the column was eluted with deionized water (250 mL) followed by aqueous ammonia (3 M). Fractions containing the product were concentrated *in vacuo* to provide 40 mg (58%) of (2*S*,3*R*)-3-hydroxypiperidine-2-carboxylic acid as a white solid. Spectroscopic data (IR, ^1H NMR, ^{13}C NMR and MS) is in agreement with that reported in the literature.[8e] Mp. 231–235 °C (lit.[8a] mp 233–238 °C) $[\alpha]_D^{23}$ −53.5 (*c* 0.6, H_2O); lit. $[\alpha]_D^{25}$ −53.8 (*c* 0.6, H_2O).[8a]

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provided CP-99,994 with 50% ee. Changing the solvent to ethanol and employing only the necessary amount of pyridine was found to be important for minimizing the racemization of **5**. Likewise, direct imination of **5** with the appropriate amine (ref. 6a), with or without Lewis acid catalysis, eventually provided racemic CP-99,994. These observations suggest that **5** is prone to racemization if it is heated or exposed to excess base and that the extent of racemization, under these conditions, may depend on variables that are difficult to regulate.

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