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Fast and Efficient Access to a Family of Multifunctional 1,3,5-Trisubstituted Piperidines

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Abstract: A collection of new 1,3,5-trisubstituted piperidines has been synthesized starting from the commercially available 5-bromonicotinic acid. A unified, diastereoselective strategy allows the controlled access to both *cis* and *trans* stereochemistries. The heterocyclic compounds thus prepared bear multiple functional groups suitable for structural diversification and combichem protocols.

Keywords: Piperidines, protecting groups, pyridines, scaffolds, stereoselective synthesis

INTRODUCTION

The potential for structural diversification offered by combinatorial methods may reach higher levels if new scaffolds are contemplated, especially when orthogonal protection and automated protocols are compatible with the chemical methodology. This is particularly important in medicinal chemistry, where the classical scaffolds have suffered almost exhaustive exploitation. On the other hand, the use of privileged structures[1] greatly increases the chances of finding bioactive compounds. In this context, we envisaged the practical access to a collection of 5-arylnipecotic acid derivatives as new scaffolds for combinatorial chemistry.

There is a limited number of approaches suitable for the preparation of 3,5-disubstituted piperidines.[2,3] We planned the synthesis of the

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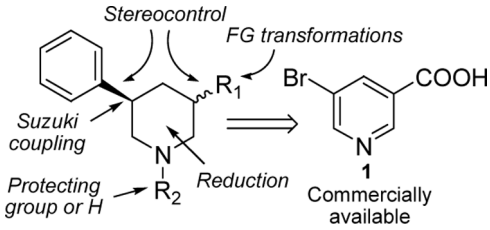


Figure 1. Retrosynthesis of the 1,3,5-trisubstituted piperidine targets.

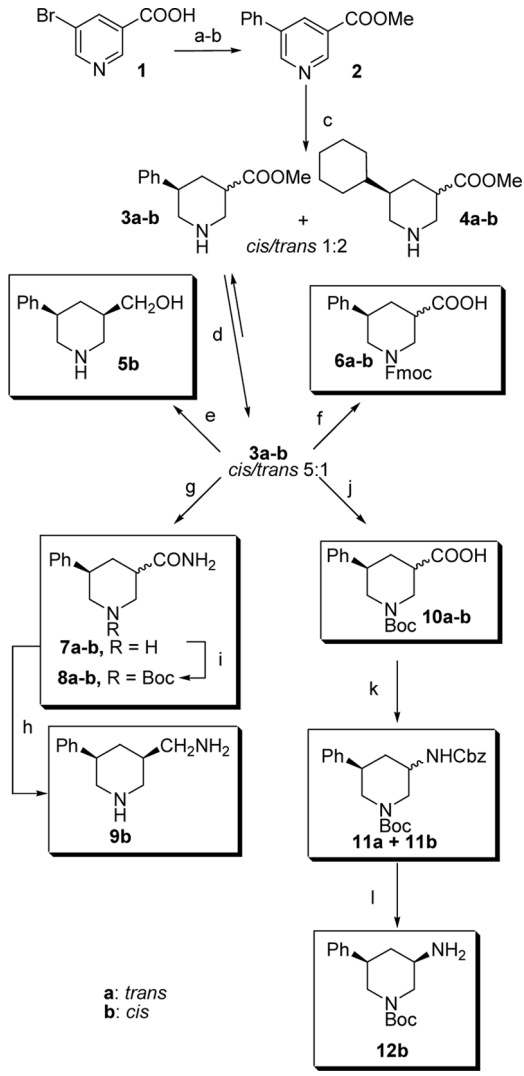
required compounds starting from the commercially available 5-bromonicotinic acid, **1**. The key reactions would involve the aryl moiety introduction (through a Pd-mediated coupling), reduction of the pyridine ring, functional group transformations (affecting the carboxylic acid), and protective group chemistry (NH and/or other functionalities) as outlined in Fig. 1. The stereochemical control would arise as the result of a thermodynamic epimerization at the carbonyl α-position.

RESULTS AND DISCUSSION

According to Scheme 1, the methyl 5-bromonicotinate was obtained from the acid **1** ($SOCl_2$ and then MeOH) in 96% yield. The Suzuki coupling [4] was achieved following a previously described procedure,[5] using $Pd(PPh_3)_4$ and $PhB(OH)_2$ in an aqueous Na_2CO_3 solution. The 5-arylnicotinate **2** can be conveniently obtained (89%). Using Jeffery (phosphine-free) conditions (K_3PO_4, $Bu_4N^+Br^-$, DMF),[6] **2** was isolated in 64% yield.

Reduction of the pyridine ring was achieved by hydrogenation over a mixture of catalysts consisting of Pd/C and PtO_2 in AcOH at room temperature and atmospheric pressure. In this way, a stereoisomeric mixture of piperidines **3a,b** (*cis*/*trans* 1:2) was obtained in 90% yield. Unexpectedly, overreduction on the aryl substituent was also observed in 5–10%. Attempts of reduction using only the Adam's catalyst in AcOH or aqueous HCl (in the absence of palladium) yielded the cyclohexyl-type products (**4a,b**, 90%) as the major components of the crude mixture.

Base-promoted epimerization of the **3a,b** mixture (tBuOK/MeOH) (**4c**) afforded a useful *cis*/*trans* 5:1 ratio of epimers. MMF94 and semiempirical AM1 calculations show the *cis* epimer being around 2 kcal/mol more stable than the *trans* epimer. Diequatorial disposition of the substituents on the former (confirmed by NMR spectroscopic analysis of related derivatives) seems to be in good agreement with the theoretical predictions. 5-Arylnipecotic acid is obtained sometimes as a minor by-product, but it can be recovered carrying out a Fischer esterification



Scheme 1. Reagents and conditions: (a) $SOCl_2$, 85 °C and then MeOH, CH_2Cl_2 60 °C (96%); (b) $Pd(PPh_3)_4$, $PhB(OH)_2$, toluene, MeOH, Na_2CO_3 2 M, 80 °C (89%); (c) H_2, Pd/C, PtO_2, AcOH, rt, 1 atm (90%); (d) KtBuO, MeOH, 60 °C; (e) $LiAlH_4$, THF, rt (85%); (f) H_2O reflux (96%) and then FmocCl, Na_2CO_3, dioxane, 0 °C to rt (85%); (g) NH_3-MeOH, KCN, sealed tube, 100 °C (79%); (h) $LiAlH_4$, THF (80%); (i) Boc_2O, THF, $NaHCO_3$, rt (99%); (j) Boc_2O, CH_2Cl_2, Et_3N, rt, and then NaOH 10%, MeOH, rt (90%, two steps); (k) DPPA, Et_3N, benzene, and then $PhCH_2OH$, 80 °C (65%); (l) H_2, Pd/C, MeOH, rt, 1 atm (90%).

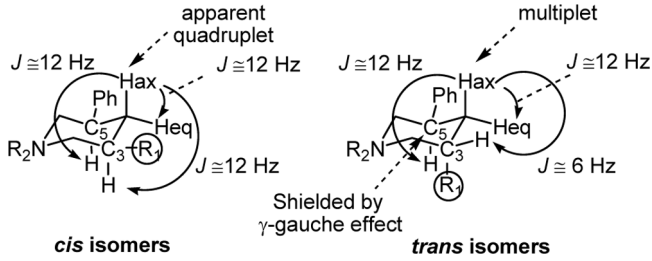


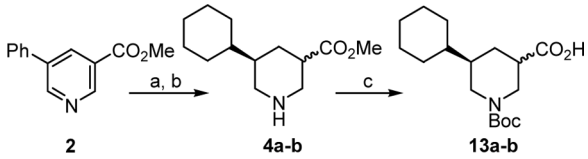
Figure 2. Diagnostic features for the stereochemical assignment.

(MeOH, H_2SO_4). The chromatographic separation of **3a** and **3b** was not practical, and the mixture was used throughout the scheme.

The first building block, the hydroxymethyl derivative **5b** (85%), was prepared by reduction of **3a,b** with $LiAlH_4$ in tetrahydrofuran (THF). In this case, the *trans* epimer was efficiently separated by flash chromatography. Spectral NMR analysis (^1H, ^{13}C, correlation spectroscopy (COSY), and heteronuclear single quantum coherence (HSQC) experiments) secured the *cis* stereochemistry. The stereochemical assignment is based on the following diagnostic features: the *cis* isomers display an apparent quadruplet for H-4ax in the ^1H NMR spectra, because of its three (almost equal) large coupling constants, whereas the *trans* isomers show for this hydrogen the expected broad and complex multiplet. On the other hand, the aryl substituted carbon atom, C-5, is considerably shielded (≈5 ppm) in the *trans* series, probably through a γ-gauche effect (Fig. 2).

The Fmoc-protected β-aminoacids **6a** and **6b** were obtained from the epimeric mixture of the methyl 5-aryl nipecotinate (**3a,b**) in a two-step process. After hydrolysis in neat water, probably through a self-catalyzed mechanism, the subsequent protection[7] furnished the two carboxylic acids (*trans*-**6a** and *cis*-**6b**), which could be conveniently separated by crystallization with Et_2O (the *trans* isomer nicely precipitated under these conditions). 5-Phenyl-nipecotic acid has been previously obtained but without stereocontrol. See Ref. 2a.

The 5-arylnipecotamide framework was accessible from the epimerized mixture **3a,b** by reaction with methanol saturated with ammonia and KCN as a catalyst[8] in a sealed tube at 100 °C (**7a,b**, 79%). NH_3 in acetonitrile yielded the desired amides **7a,b** but reaction times were longer (72 h) and the yields somewhat lower. Recrystallization in EtOAc affords the *cis* epimer **7b** in 40%. Protection of the piperidine nitrogen (Boc) afforded the corresponding derivatives (**8a,b**) in almost quantitative yield. The carboxamides **7a,b** can be directly reduced with $LiAlH_4$ in THF to the corresponding primary amines, which upon recrystallization from EtOAc furnished the pure *cis* epimer **9b** (80%).



Scheme 2. Reagents and conditions: (a) H_2, PtO_2, AcOH, rt, 1 atm (90%); (b) KtBuO, MeOH, 60 °C (85%, *cis*/*trans* 5:1); (c) Boc_2O, CH_2Cl_2, Et_3 N, rt, and then NaOH 10%, MeOH, rt (86%, two steps).

The next goal was the synthesis of the 3-amino-5-arylpiperidine building block through a rearrangement from a carbonyl precursor. The first attempt was carried out starting from the protected nipecotamides **8a,b**; a Hofmann rearrangement was tested using PIFA [iodobenzene bis(trifluoroacetate)] as the halogen source without positive results.[9] The related Curtius rearrangement was studied next. The required carboxylic acid derivative was readily prepared through a high-yielding, selective sequence. Starting again from the **3a,b** mixture, the necessary protection of the piperidine nitrogen was carried out (Boc_2O), and the subsequent basic hydrolysis of the ester moiety (NaOH in MeOH)[10] afforded the *N*-Boc acids **10a,b** (90% from **3a,b**). Treatment of these carboxylic acids with DPPA (diphenylphosphoryl azide) and benzyl alcohol yielded the mixture of 3-*N*-Cbz-1-*N*-Boc-piperidines **11a,b** with complete retention of configuration.[11] The two epimers thus obtained were conveniently separated by flash chromatography. A solution of the diprotected *cis* isomer in MeOH was subjected to hydrogenolysis (H_2, Pd/C) to afford the Cbz-free aminopiperidine **12b** (55% overall yield).

In a series of related transformations, the cyclohexyl derivatives **4a,b** (*cis*/*trans* 1:2, obtained in the reduction of the 5-phenylnicotinate **2**) were purified by flash chromatography, and after the epimerization step, the *cis*-enriched mixture (*cis*/*trans* 5:1) was *N*-Boc protected and subsequently hydrolyzed to furnish the carboxylic acids **13a** and **13b** (1:5, 86% overall yield) (Scheme 2).

CONCLUSIONS

In conclusion, the diastereoselective syntheses of several piperidine derivatives were accomplished from a common, commercially available starting material in a few steps, using Suzuki coupling, pyridine hydrogenation, routine functional group (FG) transformations, and protecting group chemistry as the key reactions. This unified protocol allows the

synthesis of *cis* and *trans* scaffolds in a practical (multigram scale) manner and is suitable for a wide range of structural diversification using standard combinatorial chemistry techniques, amenable for solid-phase methods. All new compounds are racemates, but the resolution of these materials, if convenient or desirable at a later stage, may be routinely addressed (for instance, by chiral HPLC or through derivatization, being amines and carboxylic acids).

EXPERIMENTAL

Unless otherwise stated, all reactions were carried out using dry solvent under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography (TLC) was conducted with Merck silica-gel 60 F254 sheets and visualized via UV, $KMnO_4$, and ninhydrine solution. Silica gel (particle size 35–70 mm) was used for flash-column chromatography. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 and 300 spectrometers (at 200, 300 MHz and 50.3, 75.4 MHz respectively). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Melting points were determined in a capillary tube and are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus spectrometer, and only noteworthy absorptions are listed. The mass spectra (MS) were recorded on a Hewlett-Packard 5989 A (70 eV, low resolution) and Autospec-EQ (high resolution).

5-Phenylnicotinic Acid Methyl Ester (2)

A mixture of 5-bromonicotinic acid (**1**, 10.0 g, 49.4 mmol) and thionyl chloride (18.0 mL, 124.0 mmol) was stirred at reflux temperature for 24 h. The excess $SOCl_2$ was removed by distillation under reduced pressure, and the resulting residue was cooled in an ice bath. A mixture of MeOH (20 mL) and CH_2Cl_2 (30 mL) was slowly added. The resulting mixture was heated to reflux temperature for 1 h, then cooled, and partitioned between an aqueous 2 M NaOH solution and CH_2Cl_2. The organic extracts were dried, filtered, and concentrated under reduced pressure to yield methyl 5-bromonicotinate (10.7 g, 96%). An aqueous 2 M solution of Na_2CO_3 (37 mL) and a solution of phenylboronic acid (5.4 g, 44.4 mmol) in MeOH (20 mL) were added to a stirred solution of methyl 5-bromonicotinate (8.0 g, 37.2 mmol) and $Pd(PPh_3)_4$ (1.3 g, 1.2 mmol) in toluene (80 mL) under a nitrogen atmosphere. The stirred mixture was warmed at 80 °C for 4 h, then cooled, and partitioned between CH_2Cl_2 and 2 M aqueous Na_2CO_3 containing concentrated NH_3. The organic

layer was dried and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel of the residue (hexanes/EtOAc 7:3) afforded pure **2** (7.9 g, 89%); mp 44.5–45.0 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.19 (d, $J = 2.3$ Hz, 1H), 9.01 (d, $J = 2.3$ Hz, Hz, 1H), 8.48 (t, $J = 2.3$ Hz, 1H), 7.65–7.47 (m, 5H), 3.99 (s, 3H).

Trans- and *Cis*-5-phenylpiperidine-3-carboxylic Acid Methyl Esters (3a,b)

Pd/C [500 mg, 10% (w/w)] and PtO_2 (750 mg) were added to a solution of ester **2** (5.0 g, 23.5 mmol) in acetic acid (125 mL), and the mixture was hydrogenated at room temperature and atmospheric pressure. When the hydrogen uptake was complete (monitored by TLC, CH_2Cl_2/MeOH/diethylamine 90:9:1), the catalysts were removed by filtration over a short pad of Celite® and washed with acetic acid and CH_2Cl_2. The filtrates were evaporated under reduced pressure, and H_2O was added to the residue. NH_3 (aqueous solution, 20%) was added dropwise to reach pH 10, and the mixture was extracted several times with CH_2Cl_2. The collected organic layers were dried, filtered, and concentrated. A crude mixture of 4.65 g was obtained containing (by ^{1}H NMR analysis) 5-phenylpiperidine-3-carboxylic acid methyl esters (**3a,b**, *trans*/*cis* 2:1) and 5-cyclohexylpiperidine-3-carboxylic acid methyl esters (**4a,b**, *trans*/*cis* 2:1) in a 9:1 ratio. A solution of 1.86 g of this mixture and potassium *tert*-butoxide (5.0 g, 44.6 mmol) in anhydrous MeOH (300 mL) was stirred at reflux temperature for 12 h. The major part of MeOH was removed under reduced pressure, and the residue was poured into an ice/CH_2Cl_2 mixture and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated under reduced pressure to afford 1.60 g (85%) of a brown oil. Flash chromatography (CH_2Cl_2/MeOH/Et_2NH 90:9:1) on silica gel afforded a mixture of 5-phenylpiperidine-3-carboxylic acid methyl esters **3a,b** (1.41 g, 75%, *trans*/*cis* 1:5).

IR (NaCl): 3324, 2952, 1728 cm^{-1} ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18–7.35 (m, 5H), 3.76 (s, $COOCH_3$ *trans*, 3H), 3,69 (s, $COOCH_3$ *cis*, 3H), 3.36 (d, 1H), 3.17 (d, 1H), 2.56–2.80 (m, 5H), 2.30 (m, 1H), 1.80 (q, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 142.9, 128.6, 128.5, 126.9, 126.6, 52.0, 46.0, 41.7, 39.5, 39.1, 34.0, 32.5. MS (EI, *m*/*z*, %): 219 (M^+, 18), 128 (32), 87 (100). HRMS calcd. for $C_{13}H_{17}NO_2$ [M^+] 219.1259; found 219.1263. Further elution with CH_2Cl_2/MeOH/Et_2NH 85:14:1 afforded the cyclohexyl derivatives **4a,b** (0.18 g, 10%, *trans*/*cis* 1:5). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.71 (s, $COOCH_3$ *trans*, 3H), 3.67 (s, $COOCH_3$ *cis*, 3H), 3.34–3.25 (m, 1H), 3.06 (m, $J = 12.8$ Hz, 1H), 2.77–2.11 (m, 5H), 1.74–1.70 (m, 5H), 1.31–0.96 (m, 8H). MS

(EI, m/z, %): 225 (M^+, 30), 143 (M-82, 100). HRMS calcd. for $C_{13}H_{23}NO_2$ [M^+] 225.1729; found 225.1738.

Cis-(5-phenylpiperidin-3-yl)-methanol (5b)

A solution of $LiAlH_4$ (350 mg, 9.22 mmol) in anhydrous THF (60 mL) was slowly added via cannula to a solution of esters **3a,b** (1.0 g, 4.6 mmol, *trans*/*cis* 1:5) in anhydrous THF (25 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of a saturated solution of Rochelle's salt, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give an oil, which was purified by flash chromatography on silica gel. Elution with EtOAc/MeOH/Et_2NH (65:30:5) afforded pure *cis*-alcohol **5b** (554 mg, 85%).

IR (KBr): 3360, 3285, 2916, 1039 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.17 (m, 5H), 3.48 (m, 2H), 3.43 (bs, 2H), 3.36 (m, 2H), 2.75 (m, $J = 3.3$ Hz, $J = 12.0$ Hz, $J = 12.3$ Hz, 1 H), 2.59 (m, $J = 11.7$ Hz, $J = 12.0$ Hz, 1 H), 2.36 (t, $J = 11.7$ Hz, 1 H), 1.98 (bd, $J = 12.0$ Hz, 1H), 1.88 (m, 1 H), 1.31 (m, $J = 12.3$ Hz, $J = 12.3$ Hz, $J = 12.3$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 128.4, 126.9, 126.4, 65.6, 53.2, 49.9, 43.3, 40.1, 34.9. MS (EI, m/z, %): 191 (M^+, 24), 104 (100). HRMS calcd. for $C_{12}H_{17}NO$ [M^+] 191.1310; found 191.1321.

Trans- and-*Cis*-*N*-Fmoc-5-phenylpiperidine-3-carboxylic Acids (6a,b)

A suspension of esters **3a,b** (1.5 g, 6.8 mmol, *trans*/*cis* 1:5) in H_2O (20 mL) was stirred at reflux temperature for 24 h. The solvent was removed under reduced pressure to afford the corresponding 5-phenylpiperidine-3-carboxylic acids (1.4 g, 96%) as white powder. A degassed solution of this mixture of acids (1.35 g, 6.6 mmol) and Na_2CO_3 (1.75 g, 16.5 mmol) in H_2O (18 mL) and dioxane (15 mL) was slowly added to a cooled flask (0 °C) containing Fmoc-Cl (1.71 g, 6.6 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. Water was added, and the mixture was extracted with Et_2O. The aqueous phase was acidified to pH 2 with 1 M HCl and extracted with EtOAc. The organic phase was dried and concentrated under reduced pressure to afford a mixture of the epimeric acids **6a,b**. (2.4 g, 85%). The mixture was treated with Et_2O, which caused the precipitation of a white solid, which was filtered (the procedure was repeated three times) to afford pure *trans*-Fmoc-acid trans-**6a** (0.40 g, 14%).

IR (NaCl): 3037, 2912, 1732, 1647, 1450, 1189 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, $J = 7$ Hz, 2H), 7.58 (bs, 2H), 7.42–7.25 (m, 9H), 4.56–4.20 (m, 4H), 3.13–3.00 (m, 4H), 2.80 (t, $J = 3.8$ Hz, 1H), 2.42 (bd, $J = 13.8$ Hz, 1H), 1.92 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.5, 143.9, 142.2, 141.1, 141.8, 128.5, 127.6, 127.1, 127.0, 126.7, 125.0, 119.9, 67.7, 49.9, 47.2, 45.0, 38.8, 38.3, 32.4. MS (EI, m/z, %). 428 ($M^+ + 1$, 34), 178 (100).

The isomeric *cis*-acid **6b** (1.99 g, 71%) was isolated from the solution after evaporation of the solvent under reduced pressure. *Cis*-acid **6b**:

IR (NaCl): 3064, 3026, 2925, 1703, 1477, 1449, 1255 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, $J = 7.4$ Hz, 2H), 7.58 (d, $J = 6.2$ Hz, 2H), 7.43–7.16 (m, 9H), 4.51–4.25 (m, 4H), 2.88–2.50 (m, 5H), 2.34 (bd, $J = 13.2$ Hz, 1H), 1.82 (m, $J = 12.6$ Hz, $J = 12.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 155.2, 144.3, 141.6, 128.9, 127.9, 127.9, 127.3, 127.3, 125.2, 120.3, 67.4, 50.6, 47.6, 45.6, 41.8, 34.3, 26.7. MS (EI, m/z, %): 428 ($M^+ + 1$, 3), 178 (100). HRMS calcd. for $C_{27}H_{25}NO_4$ [$M^+ + 1$] 428.1862; found 428.1875.

Cis-5-phenylpiperidine-3-carboxamide (7b)

KCN (150 mg, 2.30 mmol, *caution*) was added to a stirred solution of esters **3a,b** (2.1 g, 9.60 mmol, *trans*/*cis* 1:5) in NH_3-saturated MeOH (200 mL) in a sealed tube. The mixture was stirred at 100 °C for 48 h (*caution*, internal pressure). The excess of NH_3 was Ar-degassed, and methanol was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and water. The organic phase was dried, filtered, and concentrated under reduced pressure to yield the epimeric mixture of amides **7a,b** (1.58 g, 79%, *trans*/*cis* 1:5). Pure *cis*-isomer **7b** can be obtained as a white foam by successive EtOAc washings of the mixture.

IR (KBr): 3304, 3048, 1667, 1559 cm^{-1}. ^1H NMR (200 MHz, CD_3OD) δ 7.29–7.19 (m, 5H), 3.15 (d, $J = 11.2$ Hz, 1H), 3.04 (d, $J = 11.2$ Hz, 1H), 2.75–2.52 (m, 4H), 2.05 (m, 1H), 1.87 (q, $J = 11.8$ Hz, $J = 12.4$ Hz, 1H). ^{13}C NMR (50 MHz, CD_3OD) δ 176.5, 142.2, 129.7, 128.3, 128.0, 50.0, 46.5, 42.3, 41.6, 35.3. MS (EI, m/z, %): 204 (M^+, 8), 72 (100). HRMS calcd. for $C_{12}H_{16}N_2O$ [M^+] 204.1263; found 204.1270.

Cis-*N*-Boc-5-phenylpiperidine-3-carboxamide (8b)

A stirred solution of carboxamides **7a,b** (500 mg, 2.40 mmol, *trans*/*cis* 1:5) in a 1:1 mixture of aqueous saturated $NaHCO_3$ solution and THF (300 mL) was cooled to 0 °C, and $(Boc)_2O$ (4.28 g, 19.6 mmol) was added.

The resulting mixture was stirred at room temperature for 24 h and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2, CH_2Cl_2) to yield the mixture of epimers **8a,b** (740 mg, 99%, *trans*/*cis* 1:5). Pure *cis*-isomer **8b** was obtained as a white foam by successive EtOAc/MeOH washings of the mixture.

IR (NaCl) 3300, 2928, 1666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 5H), 5.96 (bs, 1H), 4.40–4.09 (m, 2H), 2.90–2.46 (m, 4H), 2.18 (bd, 1H), 1.96 (m, $J = 12.9$ Hz, $J = 10.8$ Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 154.6, 142.1, 128.5, 127.0, 126.9, 80.1, 46.0, 42.9, 42.1, 41.8, 34.8, 28.4. MS (EI, *m*/*z*, %): 304 (M^+, 10), 203 (50), 57 (100). HRMS calcd. for $C_{17}H_{24}N_2O_3$ [M^+] 304.1787; found 304.1781.

Cis-(5-phenylpiperidin-3-yl)-methylamine (9b)

A solution of $LiAlH_4$ (645 mg, 17.03 mmol) in anhydrous THF (40 mL) was slowly added via cannula to a 0 °C cooled solution of carboxamides **7a,b** (650 mg, 3.19 mmol, *trans*/*cis* 1:5) in anhydrous THF (110 mL). The resulting mixture was stirred at 60 °C for 4 h, and then a saturated solution of Rochelle's salt was carefully added. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried, filtered, and concentrated under reduced pressure to afford the amine **9b** (575 mg, 80%) as a white foam.

IR (NaCl): 3285, 2922 cm^{-1}. ^1H NMR (200 MHz, CD_3OD) δ 7.32–7.17 (m, 5H), 3.10 (bt, 2H), 2.87–2.48 (m, 5H), 2.24 (t, $J = 12.2$ Hz, 1H), 2.04 (bd, $J = 12.6$ Hz, 1H), 1.70 (m, 1H), 1.31 (q, $J = 12.2$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 128.4, 127.0, 126.4, 53.5, 50.3, 46.2, 43.8, 40.8, 36.5. MS (EI, *m*/*z*, %): 190 (M^+, 4), 173 (47), 104 (100). HRMS calcd. for $C_{12}H_{18}N_2$ [M^+] 190.1470; found 190.1478.

Trans- and-*Cis*-*N*-Boc-5-phenylpiperidine-3-carboxylic Acids (10a,b)

Et_3N (290 μl, 2.05 mmol) and $(Boc)_2O$ (450 mg, 2.05 mmol) were added to a solution of esters **3a,b** (300 mg, 1.37 mmol, *trans*/*cis* 1:5) in CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 18 h, poured onto a cold saturated aqueous NH_4Cl solution, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2, EtOAc) to yield the corresponding *N*-Boc methyl esters (396 mg, 95%). To a solution of this material (375 mg, 1.22 mmol)

in MeOH (2 mL), 10% aqueous NaOH solution (2 mL) 10%, was added. The mixture was stirred at room temperature for 5 h, and MeOH was removed under reduced pressure. The residue was carefully acidified first by addition of 3 M HCl to pH 6 and then adjusted to pH 4 with citric acid. The aqueous phase was extracted with EtOAc, and the organic extracts were dried, filtered, and concentrated to afford the *N*-Boc acids **10a,b** (341 mg, 95%, *trans*/*cis* 1:5) as a white foam. Recrystallization in EtOAc/hexanes afforded the pure *cis* isomer **10b**.

IR (NaCl) 2977, 2930, 1693, 1428, 1168 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5H), 4.45 (bs, 1H), 4.25 (bs, 1H), 2.83–2.60 (m, 4H), 2.35 (bd, $J = 13.6$ Hz, 1H), 1.81 (q, $J = 12.4$ Hz, 1H), 1.47(s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.2, 154.5, 141.9, 128.6, 127.0, 126.9, 80.3, 50.1, 45.3, 41.5, 34.4, 28.5. MS (EI, *m*/*z*, %): 305 (M^+, 1), 249 (6), 57 (100).

Trans- and *Cis*-*N*-Boc-3-benzylcarbamate-5-phenylpiperidines (11a,b)

Diphenylphosphorazidate (2.63 mL, 12.2 mmol) and Et_3N (1.70 mL, 12.2 mmol) were added to a stirred solution of carboxylic acids **10a,b** (3.0 g, 10.2 mmol, *trans*/*cis* 1:5) in anhydrous benzene (250 mL). The resulting mixture was stirred at reflux temperature for 2 h, and then benzyl alcohol (2.15 mL, 20.5 mmol) was added. Stirring at reflux temperature was continued for 12 h, the reaction was cooled to room temperature, and the volatiles were removed under reduced pressure. The resulting residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The layers were separated, and the organic phase was washed with brine, dried, filtered, and concentrated under reduced pressure. The resulting residue (2.73 g, 65%) was purified by chromatography over silica gel. Elution with hexanes/EtOAc (9:1) afforded the *cis*-carbamate **11b** (2.20 g, 53%) as a white foam.

^1H NMR (300 MHz, 50 °C, $CDCl_3$) δ 7.36–7.19 (m, 10H), 5.11 (s, 2H), 4.87 (bs, 1H), 4.39 (bd, $J = 8.7$ Hz, 1H), 4.21 (bd, $J = 10.5$ Hz, 1H), 3.69 (m, 1H), 2.77 (m, 1H), 2.61 (t, $J = 12.3$ Hz, 1H), 2.45 (t, $J = 11.7$ Hz, 1H), 2.27 (bd, $J = 12.3$ Hz, 1H), 1.48 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 154.5, 141.7, 136.3, 128.6, 128.5, 128.1, 127.0, 126.9, 80.1, 66.8, 49.6, 47.8, 41.4, 38.7, 28.4, 26.5. MS (EI, *m*/*z*, %): 410 (M^+, 2), 309 (M^- 101, 2), 57 (100). HRMS calcd. for $C_{24}H_{30}N_2O_4$ [M^+] 410.2206; found 410.2218.

Further elution gave the *trans*-carbamate **11a** (496 mg, 11%).

^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.15 (m, 10H), 5.62 (bs, 2H), 4.21–4.04 (m, 2H), 2.98 (dd, $J = 2.7$ Hz, $J = 14.1$ Hz, 1H), 2.91–2.73 (m, 2H), 2.23 (bd, $J = 13.8$ Hz, 1H), 1.88–1.80 (m, $J = 3.9$ Hz,

$J = 14.1$ Hz, 1H), 1.72–1.65 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 151.2, 141.5, 135.3, 129.6, 128.6, 128.6, 128.5, 128.4, 126.9, 80.4, 70.6, 50.0, 47.4, 46.5, 35.1, 28.3, 26.4. MS (EI, *m/z*, %): 410 (M^+, 4), 341 (43), 290 (60), 203 (100).

Further elution afforded the *N,N′*-bis-(1-Boc-5-phenylpiperidin-3-yl)urea.

IR (NaCl) 3321, 2972, 1705, 1616, 1579, 1419, 1249, 1149 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.22 (m, 10H), 4.32 (m, 5H), 3.74 (m, 2H), 2.82–2.27 (m, 8H), 1.47 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.8, 141.8, 128.5, 126.8, 126.7, 80.3, 48.7, 46.4, 41.3, 38.9, 28.2.

Cis-N-Boc-3-amino-5-phenylpiperidine (12b)

Pd/C (100 mg, 10%) was added to a solution of *cis*-carbamate **11b** (150 mg, 0.37 mmol) in MeOH (15 mL). The resulting suspension was hydrogenated at room temperature and atmospheric pressure. When hydrogenation was complete (monitored by TLC), the catalysts were removed by filtration over a short pad of Celite® and washed with MeOH. The filtrates were dried, filtered, and concentrated under reduced pressure to give the *cis*-3-aminopiperidine **12b** (90 mg, 55% overall yield).

IR (NaCl) 3346, 2976, 2929, 1693, 1165 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 4.40–4.17 (m, 2H), 2.99–2.44 (m, 6H), 2.23 (bd, $J = 13.6$ Hz, 1H), 1.57–1.39 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 142.1, 128.8, 127.3, 127.1, 80.3, 49.9, 49.8, 48.1, 41.8, 39.9, 28.6. MS (EI, *m/z*, %): 276 (M^+, 5), 259 (6), 203 (25), 57 (100). HRMS calcd. for $C_{16}H_{24}N_2O_2$ [M^+] 276.1838; found 276.1849.

Trans- and-*Cis-N*-Boc-5-cyclohexylpiperidine-3-carboxylic Acids (13a,b)

Et_3N (2.80 mL, 19.9 mmol) and $(Boc)_2O$ (4.34 g, 19.9 mmol) were added to a solution of cyclohexyl derivatives **4a,b** (3.0 g, 13.3 mmol, *trans/cis* 1:5) in CH_2Cl_2 (250 mL). The mixture was stirred at room temperature for 18 h and then poured onto a cold saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic extracts were dried, filtered, evaporated, and purified by chromatography (SiO_2, EtOAc) to yield a light brown oil that was taken up in MeOH (20 mL). This solution was added to a 10% NaOH aqueous solution (20 mL), and the resulting mixture was stirred at room temperature for 5 h. MeOH was removed under reduced pressure, and the residue was carefully acidified first by adding 3 M HCl to pH 6 and then adjusted to pH 4 with citric acid. The resulting suspension was extracted with EtOAc, and the organic layer was dried, filtered, and concentrated under reduced pressure to

afford acids **13a,b** (3.42 g, 86%, *trans*/*cis* 1:5) as a white foam. Recrystallization in EtOAc/hexane afforded the major *cis* isomer **13b**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.31 (bs, 1H), 4.14 (bs, 1H), 2.68 (t, $J = 12.0$ Hz, 1H), 2.46–2.18 (m, 3H), 1.74 (bs, 5H), 1.46 (s, 9H), 1.31–1.01 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 154.6, 79.9, 47.1, 44.5, 41.7, 40.8, 31.4, 30.1, 29.9, 28.4, 26.5, 26.5. MS (EI, *m*/*z*, %): 311 (M^+, 2) 255 (7), 129 (24), 57 (100).

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