

A new asymmetric synthesis of 2,6-*cis*-diarylated piperidines.

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ABSTRACT

A new synthetic approach to a variety of enantioenriched 2,6-*cis*-diarylated piperidines has been developed. This new methodology hinges upon the diastereoselective reduction of enantioenriched endocyclic enecarbamate obtained through a two steps sequence involving a Suzuki-Miyaura cross coupling reaction between an aminovinyl phosphate and a variety of (hetero)aromatic boronic acids.

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1. Introduction

The piperidine ring system is one of the most common heterocyclic unit found in a wide range of alkaloids, drugs and drug candidates which possess a broad spectrum of interesting biological activities.¹ In particular, enantiopure 2,6-*cis*-disubstituted compounds represent a subclass of naturally occurring piperidines that have been extensively studied and play an important role as key targets for the pharmaceutical industry. For example, (–)-isosolenopsine **1** which is an active ingredient in the venom of fire ants has been reported to inhibit designated neuronal nitric oxide synthase (nNOS).²

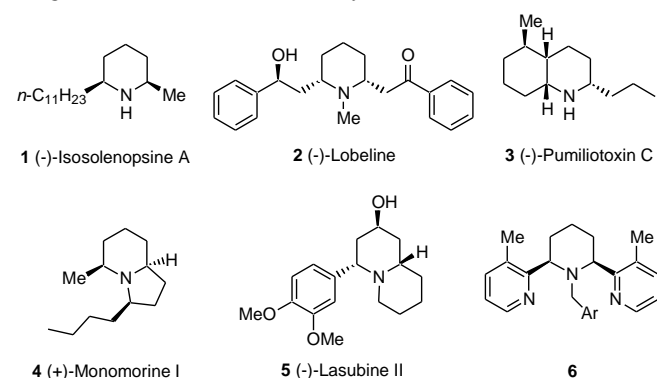


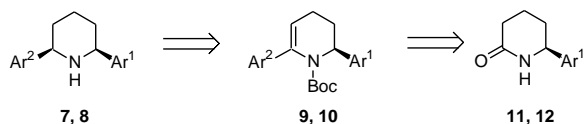
Figure 1. Examples of naturally occurring and synthetic pharmacologically active 2,6-*cis*-disubstituted piperidines.

(–)-Lobeline **2**, the major alkaloid of *lobelia inflata*, has been shown to inhibit dopamine uptake into synaptic vesicles via an interaction with the tetrabenazine (TBZ) binding site on VMATZ.³ Bicyclic (–)-pumiliotoxin **3** first isolated from *dendrobates pumilio* which possess a *cis*-fused perhydroquinoline skeleton is a potent neurotoxin that acts as a noncompetitive blocker for acetylcholine receptor channels.⁴ Indolizidine alkaloid (+)-monomorine **4** is a trail pheromone of the Pharaoh's ant *monomorium pharaonis* L.⁵ (–)-Lasubine **5** which was isolated from the leaves of the *lagerstroemia subcostata koehne* is a rare quinolizidine alkaloid bearing an aryl group alpha to nitrogen on the piperidine ring.⁶ In addition, *meso*-2,6-*cis*-diheteroarylated compounds such as **6** have been shown to bind to chemokine receptors, including CXCR4 and CCR5, and demonstrate protective effects against infection of target cells by a human immunodeficiency virus (HIV).⁷ Consequently, the important bioactivities of these compounds have stimulated the development of new synthetic approaches and considerable efforts have been mainly devoted to the enantioselective preparation of 2,6-*cis*-dialkylated piperidines.⁸ Paradoxically, to the best of our knowledge, only one synthesis of enantiopure 2,6-*cis*-diarylated piperidines has been reported so far. Thus Szymoniak et al.^{8j} developed an efficient methodology which allows access to these chiral piperidines based upon a sequential hydrozirconation/acetylation followed by a diastereoselective intramolecular reductive amination starting from a *N*-Boc protected chiral homoallylic amine.

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2. Results and discussion

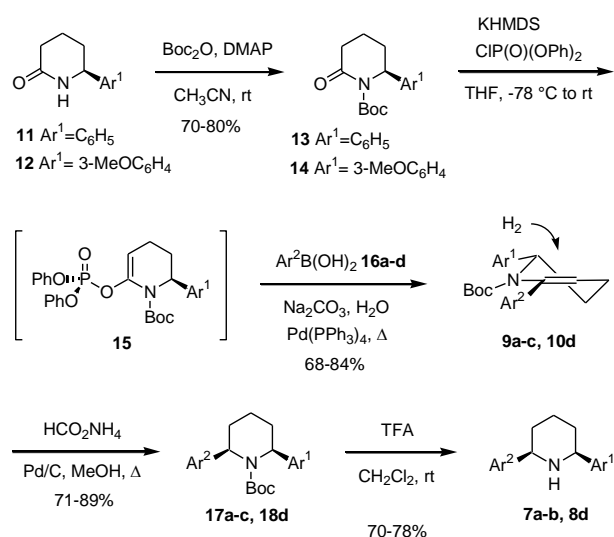
We have developed a new synthetic approach to a variety of enantiopure 2,6-*cis*-diarylated piperidines that hinges upon the diastereoselective reduction of endocyclic enecarbamates **9** and **10** as the key step (retrosynthetic scheme 1). These highly conjugated models would be obtained through a two steps sequence involving a Suzuki cross coupling reaction from the enantioenriched 6-arylpiperidin-2-ones **11**, **12**.



Scheme 1. Retrosynthetic analysis of enantioenriched 2,6-*cis*-diarylated piperidines.

The new synthetic route, depicted in scheme 1, required the preliminary elaboration of the chiral piperidinones **11**, **12** bearing an aryl group alpha to nitrogen (scheme 2). These enantioenriched lactams (e.e. >96%) were easily prepared in four steps from glutaric anhydride *via* a precedently reported procedure⁹ and then protected by reaction with Boc₂O to furnish carbamates **13**, **14**. The *N*-Boc group was initially used as an electron withdrawing protecting group since it could be easily removable under acidic conditions. We assumed that these cyclic protected lactams would possess the appropriate functionalities required for the connection of an additional aryl unit through a palladium-mediated Suzuki-Miyaura cross-coupling reaction. Since the pioneering work of Oshima et al.,¹⁰ several groups have used constitutionally diverse enol phosphates in a variety of cross-coupling reactions.¹¹ Particularly, Coudert's group developed a new and efficient methodology which allows access to a wide range of nitrogen heterocycles based upon a Suzuki-Miyaura cross coupling between lactam derived enol phosphates and boronic acids.¹² Exposure of protected chiral lactams **13**, **14** to KHMDS at -78 °C provided the corresponding potassium enolate which was intercepted by reaction with diphenyl phosphoryl chloride to deliver the sensitive aminovinyl phosphates **15** which were then used for the next step without further purification. These highly reactive electrophilic species were then allowed to react with a variety of (hetero)aromatic boronic acids **16a-d** in the presence of Pd(PPh₃)₄ catalyst and Na₂CO₃ in refluxing THF to lead to the formation of a series of

2,6-diarylated cyclic chiral enecarbamates **9a-c** and **10d**. With a reliable route to these enecarbamates in hand, the diastereoselective reduction of the endocyclic carbon-carbon double bond of these highly conjugated compounds was initiated. Assuming a pseudoequatorial aryl group orientation and Fürst-Plattner control (trans-diaxial addition) for the reduction of **9**, **10** we expected that 2,6-*cis* relative stereochemistry should be observed *via* catalytic hydrogenation of these enecarbamates.⁸ⁱ As anticipated, antiperiplanar addition of hydrogen from the less hindered face of the half-chair-like privileged conformation of **9**, **10** then providing the diastereomers **17**, **18** with a high level of selectivity. It should be noted that reduction of enecarbamate **9c** was less stereoselective. Indeed, two inseparable diastereoisomers detectable by ¹H NMR spectroscopy were obtained, probably due to the presence of a less hindered furyl group in our model. Finally, removal of the protecting group was cleanly achieved under acidic conditions by treatment of the carbamates **17a-b**, **18d** with trifluoroacetic acid to afford the targeted virtually enantiopure *cis*-2,6-diarylated piperidines **7a-b**, **8d**. The absolute and relative configuration of **7a-b**, **8d** was inferred by comparison of the specific rotation with the literature data, e.g. [α]_D = +14.9 for (2*R*, 6*S*)-**7a** (*c* 0.95 in MeOH), lit.^{8j} – 14.5 for (2*S*, 6*R*)-**7a** (*c* 1.00 in MeOH).



Scheme 2. Asymmetric synthesis of 2,6-diarylated piperidines **7**, **8**.

Table 1. Compounds **9a-c**, **10d**, **17a-c**, **18d**, **7a**, **b**, **8d** prepared

Entry	Ar ¹	Ar ²	Compound	Yield (%) ^a	Compound	Yield (%) ^a	<i>d.e.</i> (%) ^b	Compound	Yield (%) ^a	<i>d.e.</i> (%) ^b
1			9a	74	17a	85	>96	7a	70	>96
2			9b	84	17b	71	>96	7b	78	>96
3			9c	71	17c	77	84			
4			10d	68	18d	89	>96	8d	72	>96

^aAfter purification. ^bDetermined by ¹H NMR spectroscopy

3. Conclusion

We have developed a flexible and efficient route for the stereoselective synthesis of 2,6-*cis*-diarylated piperidines has been developed. This new methodology hinges upon the diastereoselective reduction of enantioenriched endocyclic enecarbamate obtained through a two steps sequence involving a Suzuki-Miyaura cross coupling reaction between an aminovinyl phosphate and a variety of (hetero)aromatic boronic acids. The extension of this approach to other scaffolds is in progress in our laboratory.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on Bruker AM 300 spectrometer. They were referenced against internal tetramethylsilane; Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. IR absorption spectra were run on a Perkin-Elmer 881. Optical rotations were recorded on Perkin Elmer 343 digital polarimeter at 589 nm. HPLC analyses were performed on a Hitachi-VWR LaChromElite L-2000. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. Flash chromatography was performed on Sorbent Technologies 32-63 μm 60 Å silica gel. Reactions were monitored by thin layer chromatography with Sorbent Technologies 0.20 mm silica gel 60 Å plates. Dry glassware was obtained by oven-drying and assembly under inert gas. Dry nitrogen was used as the inert atmosphere. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Methanol (MeOH), and ethanol (EtOH) were distilled over magnesium turnings, CH_2Cl_2 over CaH_2 and toluene over sodium.

4.2. Typical procedure for the preparation of the *N*-Boc lactams **13**, **14**

A solution of 6-arylpiperidin-2-one **11**, **12**⁹ (3 mmol), di-*tert*-butyl dicarbonate (720 mg, 3.3 mmol), and 4-dimethylaminopyridine (36 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h. Water (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 \times 30 mL) and dried over MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using EtOAc/Hexanes (20:80) as eluent to give **13**, **14**.

4.2.1. (6*S*)-2-Oxo-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester **13**

578 mg (70%); Mp 84-85 °C; $[\alpha]_{\text{D}}^{20}$ -19.6 (*c* 0.24, CHCl_3); ¹H NMR (CDCl_3): 1.25 (s, 9 H, 3 \times CH_3), 1.69-1.76 (m, 2 H, CH_2), 1.85-1.98 (m, 1 H, CH_2), 2.12-2.19 (m, 1 H, CH_2), 2.53-2.68 (m, 2 H, CH_2), 5.22 (t, *J* = 5.4 Hz, 1 H, NCH), 7.20-7.38 (m, 5 H, H_{arom}); ¹³C NMR (CDCl_3): C 171.6 (CO), 151.9 (CO), 142.3, 83.0, CH 128.7 (2 \times CH), 127.4, 125.7 (2 \times CH), 60.7 (NCH), CH₂ 34.6, 31.7, 17.3, CH₃ 27.5 (3 \times CH_3). Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: C, 69.79; H, 7.69; N, 5.09%. Found: C, 69.66; H, 7.92; N, 5.28%.

4.2.2. (2*S*)-2-(3-Methoxyphenyl)-6-oxopiperidine-1-carboxylic acid *tert*-butyl ester **14**

733 mg (80%); Oil; $[\alpha]_{\text{D}}^{20}$ -20.8 (*c* 1.44, CHCl_3); ¹H NMR (CDCl_3): 1.28 (s, 9 H, 3 \times CH_3), 1.65-1.83 (m, 2 H, CH_2), 1.88-1.99 (m, 1 H, CH_2), 2.08-2.23 (m, 1 H, CH_2), 2.45-2.67 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 5.19 (t, *J* = 5.4 Hz, 1 H, NCH), 6.73-6.82 (m, 3 H, H_{arom}), 7.26 (t, *J* = 7.9 Hz, 1 H, H_{arom}); ¹³C NMR (CDCl_3): C 171.6 (CO), 159.7 (CO), 154.8, 144.2, 82.9, CH 129.6, 118.0, 112.6, 111.5, 60.7 (NCH), CH₂ 34.5, 31.6, 17.6, CH₃ 55.3, 27.5 (3 \times CH_3). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$: C, 66.86; H, 7.59; N, 4.59%. Found: C, 66.80; H, 7.68; N, 4.45%.

4.3. Typical procedure for the synthesis of enecarbamates **9a-c**, **10d**

To a solution of *N*-Boc lactams **13**, **14** (2 mmol) and diphenyl phosphoryl chloride (0.62 mL, 3 mmol) in anhydrous THF (30 mL) cooled at -78 °C and under nitrogen atmosphere, was added dropwise under stirring a solution of KHMDS (6 mL, 0.5 M in toluene, 3 mmol). After 30 minutes at -78 °C, water (20 mL) was added and the resulting mixture was extracted with Et_2O (2 \times 50 mL) and dried over MgSO_4 . Evaporation of the solvent under vacuum yielded the aminovinyl phosphates **15** as a yellow oil which was directly used for the next coupling step. To a stirred solution of crude **15** (2 mmol) in THF (20 mL) maintained under nitrogen atmosphere, were added 2 M aqueous Na_2CO_3 solution (2 mL, 4 mmol), $\text{Pd}(\text{PPh}_3)_4$ (120 mg, 5 mol%) and the appropriate aromatic boronic acid (3 mmol). The mixture was stirred for 2 h at reflux, and then it was diluted with water (2 mL) and extracted with Et_2O (3 \times 50 mL). The combined organic layers were dried over MgSO_4 and concentrated under vacuum to give an orange oil which was purified by flash column chromatography using EtOAc/Hexanes (40:60) as eluent to afford compounds **9a-c**, **10d**.

4.3.1. (2*S*)-6-(3-Chlorophenyl)-2-phenyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester **9a**

547 mg (74%); Mp 70-71 °C; $[\alpha]_{\text{D}}^{20}$ -88.7 (*c* 0.78, CHCl_3); ¹H NMR (CDCl_3): 1.13 (s, 9 H, 3 \times CH_3), 2.14-2.32 (m, 4 H, 2 \times CH_2), 5.36 (t, *J* = 3.6 Hz, 1 H, NCH), 5.72 (t, *J* = 3.5 Hz, 1 H, CH), 7.19-7.26 (m, 4 H, H_{arom}), 7.31-7.43 (m, 5 H, H_{arom}); ¹³C NMR (CDCl_3): C 154.5 (CO), 142.9, 140.7, 137.3, 133.5, 81.4, CH 129.3, 128.5 (2 \times CH), 127.0, 126.9, 126.3 (2 \times CH), 125.5, 123.4, 116.7, 55.0 (NCH), CH₂ 27.5, 20.5, CH₃ 27.8 (3 \times CH_3). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{ClNO}_2$: C, 71.44; H, 6.54; N, 3.79%. Found: C, 71.15; H, 6.40; N, 3.98%.

4.3.2. (2*S*)-6-(2-Methoxyphenyl)-2-phenyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester **9b**

614 mg (84%); Oil; $[\alpha]_{\text{D}}^{20}$ -122.9 (*c* 0.76, CHCl_3); ¹H NMR (CDCl_3): 1.05 (s, 9 H, 3 \times CH_3), 2.06-2.26 (m, 4 H, 2 \times CH_2), 3.73 (s, 3 H, OCH_3), 5.14 (t, *J* = 3.6 Hz, 1 H, NCH), 5.67 (t, *J* = 3.5 Hz, 1 H, CH), 6.77-6.88 (m, 2 H, H_{arom}), 7.15-7.34 (m, 5 H, H_{arom}), 7.58 (d, *J* = 7.5 Hz, 2 H, H_{arom}); ¹³C NMR (CDCl_3): C 156.2 (CO), 154.1, 141.7, 135.7, 130.5, 80.2, CH 128.8, 128.1 (2 \times CH), 127.9, 126.8 (2 \times CH), 126.6, 120.4, 114.5, 109.9, 54.8 (NCH), CH₂ 27.3, 20.7, CH₃ 55.6, 27.7 (3 \times CH_3). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3$: C, 75.59; H, 7.45; N, 3.83%. Found: C, 75.91; H, 7.30; N, 3.95%.

4.3.3. (2S)-6-Furan-2-yl-2-phenyl-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester **9c**

461 mg (71%); Oil; $[\alpha]_{\text{D}}^{20}$ -96.3 (*c* 0.83, CHCl₃); ¹H NMR (CDCl₃): 1.28 (s, 9 H, 3 x CH₃), 1.93-2.25 (m, 3 H, 2 x CH₂), 2.35-2.45 (m, 1 H, CH₂), 5.40 (t, *J* = 3.6 Hz, 1 H, NCH), 5.69 (t, *J* = 3.4 Hz, 1 H, CH), 6.28 (d, *J* = 3.3 Hz, 1 H, H_{arom}), 6.38 (dd, *J* = 3.3-1.8 Hz, 1 H, H_{arom}), 7.19-7.46 (m, 6 H, H_{arom}); ¹³C NMR (CDCl₃): C 152.4 (CO), 139.9, 136.5, 128.4, 80.8, CH 128.3 (2 x CH), 126.6, 126.0 (2 x CH), 125.8, 114.8, 110.9, 104.7, 54.6 (NCH), CH₂ 27.1, 20.1, CH₃ 27.8 (3 x CH₃). Anal. Calcd for C₂₀H₂₃NO₃: C, 73.82; H, 7.12; N, 4.30%. Found: C, 73.71; H, 7.19; N, 4.15%.

4.3.4. (2S)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester **10d**

619 mg (68%); Oil; $[\alpha]_{\text{D}}^{20}$ -90.5 (*c* 1.89, CHCl₃); ¹H NMR (CDCl₃): 1.17 (s, 9 H, 3 x CH₃), 2.21-2.35 (m, 4 H, 2 x CH₂), 3.76 (s, 3 H, OCH₃), 3.83 (s, 6 H, 2 x OCH₃), 3.84 (s, 3 H, OCH₃), 5.37 (t, *J* = 3.3 Hz, 1 H, NCH), 5.63-5.69 (br. s, 1 H, CH), 6.61 (s, 2 H, H_{arom}), 6.67 (dd, *J* = 2.4-7.7 Hz, 1 H, H_{arom}), 7.02-7.07 (m, 2 H, H_{arom}), 7.23-7.29 (m, 1 H, H_{arom}); ¹³C NMR (CDCl₃): C 159.6 (CO), 154.5, 152.9 (2 x C), 142.7, 138.4, 137.0, 134.3, 80.9, CH 129.3, 118.7, 115.5, 113.0, 111.5, 102.3 (2 x CH), 54.9 (NCH), CH₂ 27.6, 20.5, CH₃ 61.0, 56.0 (2 x OCH₃), 55.2, 27.8 (3 x CH₃). Anal. Calcd for C₂₆H₃₃NO₆: C, 68.55; H, 7.30; N, 3.07%. Found: C, 68.72; H, 7.13; N, 2.92%.

4.4. Typical procedure for the synthesis of carbamates **17a-c**, **18d**

A suspension of compound **9a-c**, **10d** (1 mmol) in MeOH (15 mL) was stirred with activated Pd/C (10 mg, 10 mol%) and a solution of HCO₂NH₄ (252 mg, 4 mmol) in distilled water (2 mL) was then added. The reaction mixture was refluxed for 4 h, filtered on Celite™ and diluted with water. Extraction with CH₂Cl₂ (3 x 20 mL), drying over MgSO₄ and concentration under vacuum left an oily product which was purified by chromatography on silica gel using EtOAc/Hexanes (60:40) as eluent to give **17a-c**, **10d**.

4.4.1. (2R,6S)-2-(3-Chlorophenyl)-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester **17a**

316 mg (85%); Mp 86-87 °C; $[\alpha]_{\text{D}}^{20}$ -51.6 (*c* 0.41, CHCl₃); ¹H NMR (CDCl₃): 1.17 (s, 9 H, 3 x CH₃), 1.38-1.47 (m, 2 H, CH₂), 1.79-2.24 (m, 4 H, 2 x CH₂), 5.17-5.28 (m, 2 H, 2 x NCH), 7.17-7.35 (m, 9 H, H_{arom}); ¹³C NMR (CDCl₃): C 156.2 (CO), 148.1, 144.7, 127.9, 79.7, CH 128.2 (2 x CH), 126.8, 126.1 (2 x CH), 125.6 (4 x CH), 55.4 (NCH), 55.2 (NCH), CH₂ 28.2, 27.3, 14.4, CH₃ 28.0 (3 x CH₃). Anal. Calcd for C₂₂H₂₆ClNO₂: C, 71.05; H, 7.05; N, 3.77%. Found: C, 70.92; H, 7.12; N, 3.99%.

4.4.2. (2R,6S)-2-(2-Methoxyphenyl)-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester **17b**

261 mg (71%); Oil; $[\alpha]_{\text{D}}^{20}$ -16.4 (*c* 0.46, CHCl₃); ¹H NMR (CDCl₃): 1.11 (s, 9 H, 3 x CH₃), 1.34-1.45 (m, 2 H, CH₂), 1.83-2.18 (m, 3 H, 2 x CH₂), 2.25-2.37 (m, 1 H, CH₂), 3.84 (s, 3 H, OCH₃), 5.36 (br. s, 1 H, NCH), 5.52 (br. s, 1 H, NCH), 6.84 (dd, *J* = 8.1-0.9 Hz, 1 H, H_{arom}), 6.93 (td, *J* = 7.5-0.9 Hz, 1 H, H_{arom}), 7.16-7.33 (m, 7 H, H_{arom}); ¹³C NMR (CDCl₃): C 156.4 (CO), 155.9, 145.8, 131.6, 79.3, CH 128.6, 128.2 (2 x CH), 127.1, 126.0, 125.5 (2 x CH), 120.0, 110.2, 54.8 (NCH), 51.4 (NCH),

CH₂ 28.9, 26.7, 14.5, CH₃ 55.2, 28.0 (3 x CH₃). Anal. Calcd for C₂₃H₂₉NO₃: C, 75.17; H, 7.95; N, 3.81%. Found: C, 75.28; H, 8.12; N, 3.63%.

4.4.3. (2R,6S)-2-Furan-2-yl-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester **17c**

252 mg (77%); Oil; $[\alpha]_{\text{D}}^{20}$ -20.5 (*c* 0.16, CHCl₃); ¹H NMR (CDCl₃): 1.24 (s, 9 H, 3 x CH₃), 1.43-1.56 (m, 2 H, CH₂), 1.78-1.93 (m, 1 H, CH₂), 1.98-2.21 (m, 3 H, 2 x CH₂), 4.99 (br. s, 1 H, NCH), 5.36 (br. s, 1 H, NCH), 6.12-6.15 (m, 1 H, H_{arom}), 6.33-6.35 (m, 1 H, H_{arom}), 7.20-7.35 (m, 6 H, H_{arom}); ¹³C NMR (CDCl₃): C 156.6 (CO), 156.1, 143.6, 79.9, CH 140.9, 128.5 (2 x CH), 126.3, 125.6 (2 x CH), 110.3, 105.9, 55.5 (NCH), 49.8 (NCH), CH₂ 28.9, 25.2, 15.2, CH₃ 28.1 (3 x CH₃). Anal. Calcd for C₂₀H₂₅NO₃: C, 73.37; H, 7.70; N, 4.28%. Found: C, 73.42; H, 7.63; N, 4.33%.

4.4.4. (2S,6R)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)piperidine-1-carboxylic acid *tert*-butyl ester **18d**

407 mg (89%); Oil; $[\alpha]_{\text{D}}^{20}$ -38.4 (*c* 3.4, CHCl₃); ¹H NMR (CDCl₃): 1.22 (s, 9 H, 3 x CH₃), 1.39-1.48 (m, 2 H, CH₂), 1.83-2.25 (m, 4 H, 2 x CH₂), 3.82 (s, 3 H, OCH₃), 3.84 (s, 3 H, OCH₃), 3.86 (s, 6 H, 2 x OCH₃), 5.18-5.32 (m, 2 H, 2 x NCH), 6.51 (s, 2 H, H_{arom}), 6.77 (dd, *J* = 8.0-2.4 Hz, 1 H, H_{arom}), 6.83-6.92 (m, 2 H, H_{arom}), 7.22-7.29 (m, 1 H, H_{arom}); ¹³C NMR (CDCl₃): C 159.7 (CO), 156.2, 153.1, (2 x C), 146.3, 140.4, 136.3, 79.7, CH 129.3, 118.0, 114.7, 111.1, 102.6 (2 x CH), 55.8 (NCH), 55.2 (NCH), CH₂ 28.1 (2 x CH₂), 14.4, CH₃ 60.9, 56.0 (2 x OCH₃), 54.8, 27.6 (3 x CH₃). Anal. Calcd for C₂₆H₃₅NO₆: C, 68.25; H, 7.71; N, 3.06%. Found: C, 68.19; H, 7.95; N, 3.19%.

4.5. Typical procedure for the synthesis of 2,6-diarylpiperidines **7a-b**, **8d**

To a solution of compound **17a-b**, **18d** (0.3 mmol) in CH₂Cl₂ (2 mL) at room temperature was added trifluoroacetic acid (0.35 mL, 4.5 mmol). After stirring for 3 h, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ (10 mL) and saturated NaHCO₃ (10 mL). The layers were separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 10 mL). The combined organics were dried over MgSO₄, filtered and then concentrated *in vacuo* to provide an oily product which was purified by chromatography on silica gel using Hexanes/Et₂O (90:10) as eluent.

4.5.1. (2R,6S)-2-(3-Chlorophenyl)-6-phenylpiperidine (**7a**)

57 mg (70%); Oil; $[\alpha]_{\text{D}}^{20}$ +14.9 (*c* 0.95, MeOH), lit.^{8j} $[\alpha]_{\text{D}}^{20}$ -14.5 (*c* 1, MeOH) for the (2S,6R)-enantiomer; ¹H NMR (CDCl₃): 1.32-1.62 (m, 3 H, 2 x CH₂), 1.66-1.83 (m, 3 H, 2 x CH₂), 1.89-1.95 (m, 1 H, NH), 3.62-3.75 (m, 2 H, 2 x NCH), 7.17-7.40 (m, 9 H, H_{arom}); ¹³C NMR (CDCl₃): C 144.1 (2 x C), 132.5, CH 130.0, 128.8, 127.6, 127.4, 127.2 (4 x CH), 125.4, 62.9 (NCH), 62.6 (NCH), CH₂ 35.2, 35.1, 26.2. Anal. Calcd for C₁₇H₁₈ClN: C, 75.13; H, 6.68; N, 5.15%. Found: C, 75.01; H, 6.55; N, 5.32%.

4.5.2. (2R,6S)-2-(2-Methoxyphenyl)-6-phenylpiperidine (**7b**)

62 mg (78%); Mp 63-64 °C, lit.^{8j} 68 °C; $[\alpha]_{\text{D}}^{20}$ -17.0 (*c* 1.18, MeOH); ¹H NMR (CDCl₃): 1.36-1.96 (m, 6 H, 3 x CH₂), 3.76 (s, 3 H, OCH₃), 3.82 (dd, *J* = 11.1-2.5 Hz, 1 H, NCH), 4.13 (dd, *J* = 11.1-2.2 Hz, 1 H, NCH), 6.78 (d, *J* = 8.2 Hz, 1 H, H_{arom}), 6.89 (t, *J* = 7.4 Hz, 1 H, H_{arom}), 7.08-7.17 (m, 2 H, H_{arom}), 7.23 (t, *J* = 7.2 Hz, 2 H, H_{arom}), 7.37 (d, *J* = 7.1 Hz, 2 H, H_{arom}), 7.53 (dd, *J* = 7.5-1.6 Hz, 1 H, H_{arom}) [NH not observed]; ¹³C NMR (CDCl₃): C

156.6, 146.2, 133.7, **CH** 128.3 (2 x CH), 127.6, 127.0 (2 x CH), 126.9 (2 x CH), 120.8, 110.1, 55.3 (NCH), 55.2 (NCH), **CH₂** 34.9, 32.2, 25.9, **CH₃** 62.9. Anal. Calcd for C₁₈H₂₁NO: C, 80.86; H, 7.92; N, 5.24%. Found: C, 81.01; H, 7.80; N, 5.36%.

4.5.3. (2*S*,6*R*)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)piperidine (8d)

77 mg (72%); Oil; [α]_D²⁰ -53.0 (*c* 0.1, MeOH); ¹H NMR (CDCl₃): 1.45-1.64 (m, 2 H, CH₂), 1.78-1.86 (m, 2 H, CH₂), 1.94-2.05 (m, 2 H, CH₂), 3.72-3.81 (m, 2 H, 2 x NCH), 3.82 (s, 3 H, OCH₃), 3.83 (s, 3 H, OCH₃), 3.88 (s, 6 H, 2 x OCH₃), 6.70 (s, 2 H, H_{arom}), 6.78 (dd, *J* = 8.1-2.6 Hz, 1 H, H_{arom}), 7.03-7.06 (m, 2 H, H_{arom}), 7.22-7.28 (m, 1 H, H_{arom}) [NH not observed]; ¹³C NMR (CDCl₃): C 129.6, 153.1 (2 x C), 147.4, 141.7, 136.7, **CH** 129.3, 119.1, 112.5, 112.1, 103.5 (2 x CH), 63.0 (NCH), 62.6 (NCH), **CH₂** 34.8, 34.6, 25.8, **CH₃** 60.8, 56.1 (2 x OCH₃), 55.2. Anal. Calcd for C₂₁H₂₇NO₄: C, 70.56; H, 7.61; N, 3.92%. Found: C, 70.35; H, 7.85; N, 3.84%.

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References and notes

- (a) Jones, T. H.; Blum, M. S. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, Chapter 2, pp 33-84. (b) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, UK, 1985; Vol. 26, Chapter 3, pp 89-183. (c) Numata, A.; Ibuka, I. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, pp 193-315. (d) Fodor, G. B.; Colasanti, B. *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, Chapter 1, pp 1-90. (e) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1996; Vol. 10, Chapter 3, pp 155-315.
- Yi, G. B.; McClendon, D.; Desai, D.; Goddard, J.; Lister, A.; Moffitt, J.; Van der Meer, R. K.; Deshazo, R.; Lee, K. S.; Rockhold, R. W. *Int. J. Toxicol.* **2003**, *22*, 81-86.
- (a) Teng, L.; Crooks, P. A.; Sonsalla, P. K.; Dvoskin, L. P. *J. Pharmacol. Exp. Ther.* **1997**, *280*, 1432-1444. (b) Teng, L.; Crooks, P. A.; Dvoskin, L. P. *J. Neurochem.* **1998**, *71*, 258-265.
- (a) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Schultz, A. G.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207-1212. (b) Schultz, A. G.; Wang, A. H.; Alva, C.; Sebastian, A.; Glick, S. D.; Deecher, D. C.; Bidlack, J. M. *J. Med. Chem.* **1996**, *39*, 1956-1966.
 - Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Verwiël, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530-531.
 - (a) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515-2521. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445-7447.
 - Bridger, G. J.; McEachern, E. J.; Skerlj, R.; Schols, D. PCT Int. Appl. WO 2004093817, 2004.
 - (a) Katritzky, A. R.; Qui, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699-6703. (b) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955-13970. (c) Ciblat, S.; Besse, P.; Canet, J.-L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225-2235. (d) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503-2505. (e) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855-3857. (f) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067-3070. (g) Gonzalez-Gomez, J.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777-2780. (h) Kumar, R. S. C.; Sreedhar, E.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 1160-1163. (i) Humphrey, J. M.; Arnold, E. P.; Chappie, T. A.; Feltenberger, J. B.; Nagel, A.; Simon, W.; Suarez-Contreras, M.; Tom, N. J.; O'Neil, B. T. *J. Org. Chem.* **2009**, *74*, 4525-4536. (j) Coia, N.; Mokhtari, N.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2011**, *13*, 6292-6295. (k) Daly, M.; Cant, A. A.; Fowler, L. S.; Simpson, G. L.; Senn, H. M.; Sutherland, A. *J. Org. Chem.* **2012**, *77*, 10001-10009. (l) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290-5293. (m) Krishna, P. R.; Reddy, B. K. *Tetrahedron: Asymmetry* **2013**, *24*, 758-763. (n) Abrunhosa-Thomas, I.; Plas, A.; Vogrig, A.; Kandepedu, N.; Chalard, P.; Troin, Y. *J. Org. Chem.* **2013**, *78*, 2511-2526. (o) Kurogome, Y.; Kogiso, M.; Looi, K. K.; Hattori, Y.; Konno, H.; Hirota, M.; Makabe, H. *Tetrahedron* **2013**, *69*, 8349-8352. (p) Jäkel, M.; Qu, J.; Schnitzer, T.; Helmchen, G. *Chem. Eur. J.* **2013**, *19*, 16746-16755. (q) Simon, R. C.; Fuchs, C. S.; Lechner, H.; Zepeck, F.; Kroutil, W. *Eur. J. Org. Chem.* **2013**, 3397-3402. (r) Pelletier, G.; Constantineau-Forget, L.; Charrette, A. B. *Chem. Commun.* **2014**, 6883-6885. (s) Kumaraswamy, G.; Kumar, R. S.; Sampath, B.; Chandrahandra, Y.; Kumar, C. G.; Vemulapalli, S. P. B.; Bharatam, J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4439-4443.
- Sallio, R.; Lebrun, S.; Agbossou-Niedercom, F.; Michon, C.; Deniau, E. *Tetrahedron: Asymmetry* **2012**, *23*, 998-1004.
- Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531-2534.
- See, among others: (a) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757-1758. (b) Occhiato, E. G.; Lo Galbo, F.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 7324-7330. (c) Hansen, A. L.; Ebran, J.-P.; Gogsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464-6472. (d) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347-3350. (e) Steel, P. G.; Woods, T. M. *Synthesis* **2009**, 3897-3904. (f) Dubois, M.; Deniau, E.; Couture, A.; Grandclaude, P. *Tetrahedron* **2012**, *68*, 7140-7147. (g) Dubois, M.; Deniau, E.; Couture, A.; Grandclaude, P. *Synlett* **2012**, 1047-1051. (h) Sallio, R.; Lebrun, S.; Gigant, N.; Gillaizeau, I.; Deniau, E. *Eur. J. Org. Chem.* **2014**, 4381-4388.
- (a) Buon, C.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6373-6376. (b) Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron*, **2001**, *57*, 6969-6975. (c) Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993-5999. (d) Claveau, E.; Gillaizeau, I.; Blu, J.; Bruel, A.; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832-4836. (e) Bouet, A.; Cieslikiewicz, M.; Lewinski, K.; Coudert, G.; Gillaizeau, I. *Tetrahedron* **2010**, *66*, 498-503.