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PAPER

Radical-mediated nitrile translocation as the key step in the stereoselective transformation of 2-(4-chloro-2-cyanobutyl)aziridines to methyl *cis*-(1-arylmethyl-4-phenylpiperidin-2-yl)acetates†

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Non-activated 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines were used as building blocks for the stereoselective synthesis of novel *cis*-2-cyanomethyl-4-phenylpiperidines *via* a microwave-assisted aziridine to piperidine ring expansion followed by a radical-induced nitrile translocation through initial formation and subsequent cleavage of intermediate bicyclic iminyl radicals. Furthermore, these 2-(cyanomethyl)piperidines were shown to be eligible substrates for the preparation of methyl *cis*-(1-arylmethyl-4-piperidin-2-yl)acetates through a Pinner reaction using gaseous HCl in methanol.

Introduction

The piperidine ring comprises an important structural unit in natural products and biologically active agents.[1] In particular, the 4-arylpiperidine scaffold is known to be a key element in bioactive compounds involved in the binding to a wide variety of receptors.[2] A vast array of molecules containing this skeleton has been reported as neurokinin[3] and tachykinin[4] antagonists for the treatment of migraine, pain, arthritis and anxiety, and others are known for their activity as aspartic peptidase inhibitors[5] such as renin inhibitors to treat hypertension[6] and as cocaine antagonists.[7] Moreover, a number of drugs accommodate this 4-arylpiperidine unit in their structure, such as the analgesic meperidine, the antipsychotic haloperidol,[8] and levocabastine[9] and loperamide[10] used in the treatment of allergic conjunctivitis and diarrhea, respectively. Because of the broad medicinal relevance of piperidines, the search for general, efficient and stereoselective methods is of paramount value to organic synthesis.

In this paper, the use of 2-(4-chloro-2-cyano-2-phenylbutyl) aziridines as versatile building blocks in organic chemistry is demonstrated by the preparation of novel *cis*-2-cyanomethyl-4-phenylpiperidines *via* a radical-induced nitrile translocation of *cis*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles, obtained by microwave-promoted ring expansion of the aziridine substructures. Further elaboration of these 2-(cyanomethyl)piperidines provided an easy access to the corresponding (piperidin-2-yl) acetates as biologically relevant constrained amino acid derivatives.

Results and discussion

Although 2-(2-cyanoethyl)aziridines have recently been used by us as synthons for the development of straightforward and efficient strategies toward a variety of piperidines[11] and cyclopropanes,[12] their chemistry still remains a scarcely investigated field of research in the literature.[13] Encouraged by these previous results, new pathways were explored in this work for the conversion of 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines **1** and **9** into other functionalized 4-phenylpiperidines.

The starting aziridines ***rac*-1** (Scheme 1) and their diastereomeric counterparts ***rac*-9** (Scheme 2) were synthesized from the corresponding 2-(bromomethyl)aziridines[14] by treatment with α-lithiated phenylacetonitrile in THF, followed by a lithium diisopropylamide-mediated coupling with 1-bromo-2-chloroethane.[11] As described before by us, 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines **1** and **9** were then selectively transformed into 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **2** and **10** *via* a microwave-assisted 6-*exo*-*tet* cyclization and regiospecific ring-opening reaction sequence upon heating in acetonitrile for 30 minutes (Schemes 1 and 2).[11] It should be noted that the correct relative stereochemistry of aziridine substrates **1** and **9** has previously been assigned through X-ray diffraction analysis of their transformation products **2** and **10**.[11]

The initial objective of the present study comprised the radical synthesis of 5-phenyl-2-azabicyclo[3.2.1]octan-6-ones **8** starting from *cis*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles **2**. The rationale behind this methodology involves the formation of an exocyclic methylene radical **5** by means of Bu_3SnH, which

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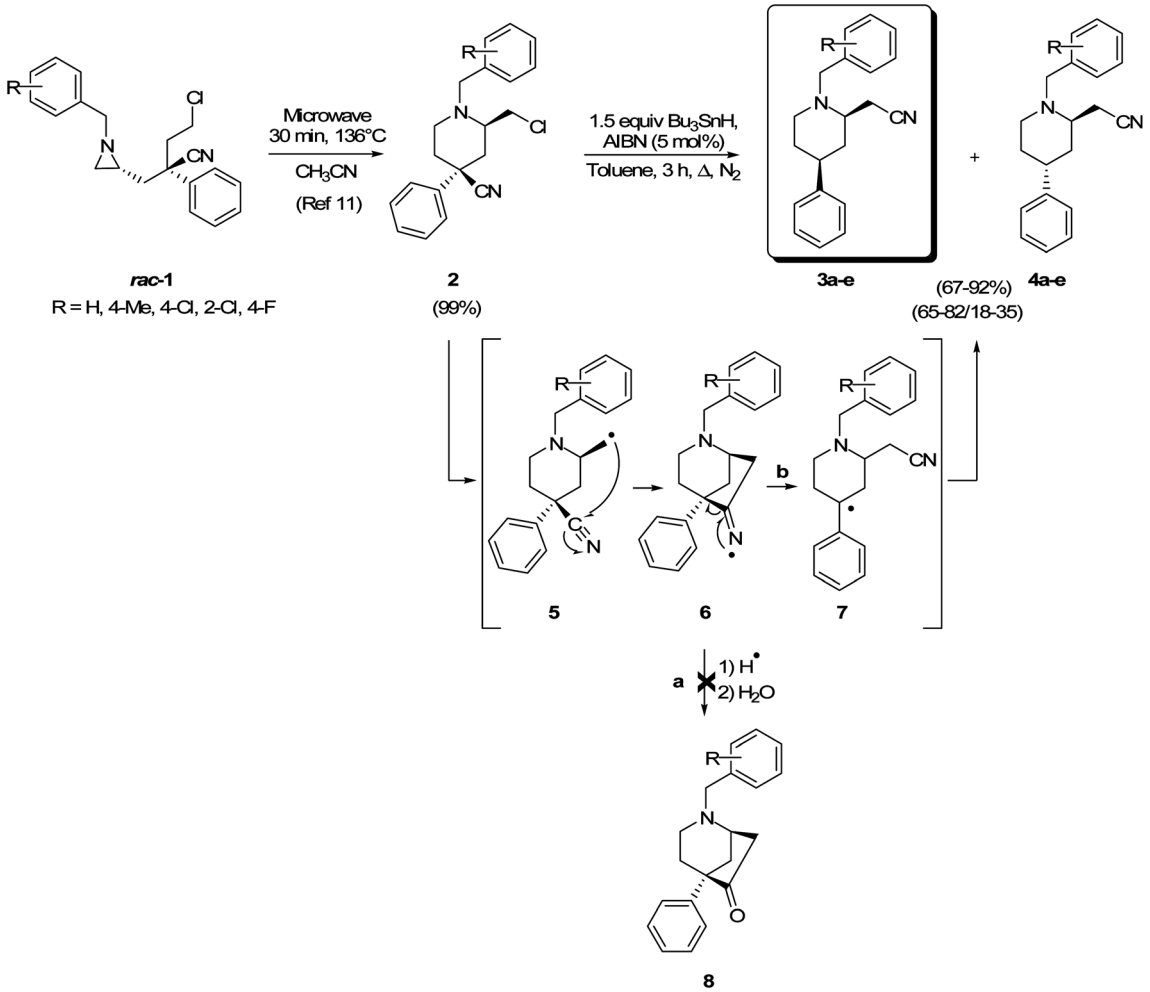
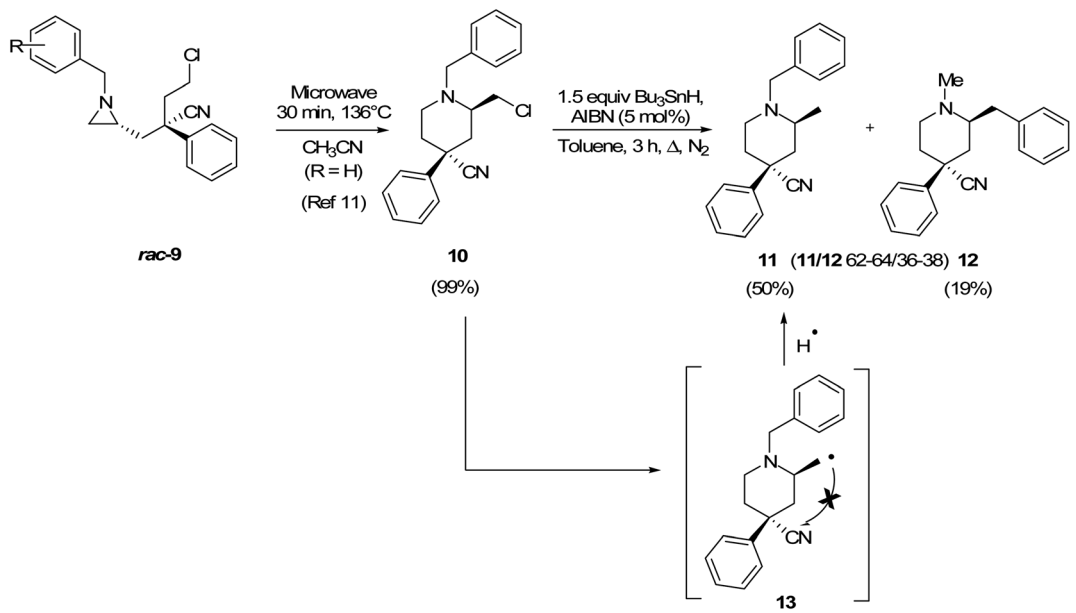


Scheme 1



Scheme 2

can induce a 5-*exo-dig* ring closure across the nitrile moiety to form a bicyclic iminyl radical **6**. Finally, aqueous workup of the latter intermediate **6** would afford 5-phenyl-2-azabicyclo[3.2.1] octan-6-ones **8** (Scheme 1, pathway **a**) as substructures of naturally occurring alkaloids,[15] based on literature precedents.[16] However, treatment of *cis*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles **2** with 1.5 equivalents of Bu_3SnH in toluene for three hours under reflux in the presence of 5 mol% of AIBN furnished a mixture of *cis*- and *trans*-2-cyanomethyl-4-phenylpiperidines **3** and **4**, with the *cis*-isomers **3** as the major constituents (ratio **3/4** 65–82/18–35), instead of the envisaged 5-phenyl-2-azabicyclo[3.2.1]octan-6-ones **8** (Scheme 1, Table 1). The reaction pathway for this peculiar rearrangement was initiated by the formation of an exocyclic methyl radical **5** through removal of the chlorine substituent. As expected, this primary radical **5**, which might be (partially) stabilized by the ring nitrogen atom, induced a 5-*exo-dig* ring closure across the nitrile moiety to form a bicyclic iminyl radical **6**. However, further rearrangement took place in which the iminyl radical **6** underwent ring opening toward a 2-cyanomethyl-4-phenylpiperidin-4-yl radical **7** (Scheme 1, pathway **b**). Termination of the radical pathway by trapping the latter intermediate **7** with a hydrogen radical gave rise to *cis*- and *trans*-2-cyanomethyl-4-phenylpiperidines **3** and **4** in an isomeric ratio of 65–82/18–35 (**3/4**) and a combined yield of 67–92% (Scheme 1).

The preferential formation of *cis*-piperidines **3** can be explained considering a thermodynamically-controlled formation of the more stable diequatorial conformers. Interestingly, the major diastereomers **3a–e** could be easily isolated from the mixtures by crystallization from hexane–EtOAc (15 : 1) (67–75% yield). Although the minor diastereomers **4a–b** were obtained in pure form through column chromatography on silica gel (hexane–EtOAc 9 : 1, 13–17% yield), allowing their full spectroscopic characterization, compounds **4c–e** could not be isolated by the same technique. The net conversion of this methodology concerns a nitrile translocation from the 4-position of the piperidine ring toward the exocyclic methylene group.

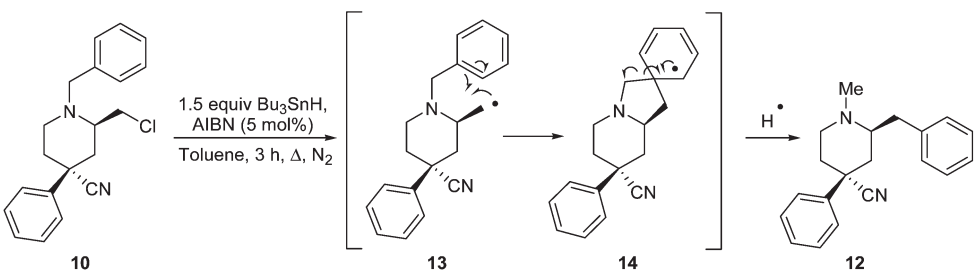
In the above-described transformation, the phenyl group acts as a radical-stabilizing functionality (benzylic position) to support the nitrile translocation reaction (rearrangement of intermediate **6** to **7**, Scheme 1). Other examples of 5-*exo-dig* radical cyclization reactions onto nitriles are rare,[16,17] and only a few reports concerning nitrile translocation reactions are known in the literature.[18a,19a,b] These reported translocations occurred through generation of a carbon radical in α-position with respect to a cyano, alkoxycarbonyl, sulfonyl or carbamoyl group (but never a phenyl group) at the end of the rearrangement process. Moreover, this is the first report of a nitrile translocation reaction proceeding through a bicyclic intermediate. From these elements, it can be concluded that the present approach clearly extends the scope of this synthetic strategy. The structure of *cis*-2-cyanomethyl-4-phenylpiperidines **3** as the major compounds was unambiguously assigned through X-ray diffraction analysis of *cis*-1-benzyl-2-cyanomethyl-4-phenylpiperidine **3a** (see ESI†).

In order to provide further evidence for the radical-mediated transformation of *cis*-2-(chloromethyl)piperidines **2** into *cis*-2-cyanomethyl-4-phenylpiperidines **3**, aziridine ***rac*-9** (R = H), the diastereomeric counterpart of aziridines ***rac*-1**, was rearranged into *trans*-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **10** upon heating in acetonitrile under microwave irradiation according a literature protocol.[11] Next, *trans*-piperidine **10** was treated with 1.5 equiv. of Bu_3SnH in toluene for three hours under reflux using 5 mol% of AIBN as the radical initiator, furnishing a mixture of 1-benzyl-2-methyl-4-phenylpiperidine-4-carbonitrile **11** and 2-benzyl-1-methyl-4-phenylpiperidine-4-carbonitrile **12** as the two main products in 50% and 19% yield (**11/12** 62–64/36–38), respectively. In this case, radical cleavage of the chlorine atom gave rise to the formation of the corresponding methylene radical **13**, which can undergo a termination reaction toward 1-benzyl-2-methyl-4-phenylpiperidine-4-carbonitrile **11** (Scheme 2). Due to the *trans* dispositioning of the chloromethyl group and the cyano group in piperidines **10**, addition of the initially formed methylene radical **13** across the cyano moiety is not possible. The formation of the side product 2-benzyl-1-methyl-4-phenylpiperidine-4-carbonitrile **12** might be explained through the generation of a spiro intermediate **14** *via* a 5-*exo-trig* cyclization of the exocyclic methylene radical **13** onto the *ipso* position of the phenyl ring, followed by rearomatization and ring opening of the spiro intermediate **14** (Scheme 3), in accordance with literature precedents.[18] The formation of piperidines **11** and

Table 1 Radical-induced nitrile translocation of cis-2-chloromethyl-4-phenylpiperidines 2 toward cis-2-cyanomethyl-4-phenylpiperidines 3 by means of Bu_3SnH in toluene[a]

Compound	Ar	Isolated yield (%)[b]	Ratio 3/4[c]
3a	C_6H_5	63	65/35
3b	4-MeC_6H_4	75	82/18
3c	4-ClC_6H_4	71	76/24
3d	2-ClC_6H_4	67	70/30
3e	4-FC_6H_4	69	72/28

[a] Reactions performed at reflux for 3 hours (N_2 atmosphere) [b] After crystallization or column chromatography [c] Based on ^1H NMR and/or LC of the crude reaction mixture.



Scheme 3

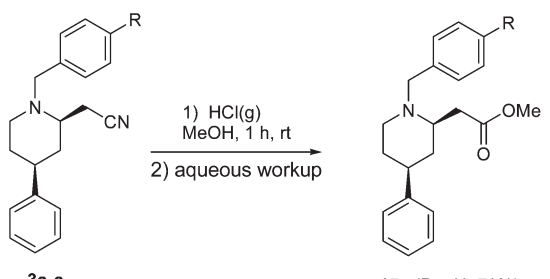
12 thus supports the proposed radical-induced nitrile translocation mechanism for the conversion of *cis*-piperidines **2** into rearrangement products **3** and **4** as depicted in Scheme 1.

Very little information regarding 2-cyanomethyl-4-phenylpiperidines is available in the literature, and the few examples reported have been synthesized from 2-(mesyloxymethyl)- or 2-(chloromethyl)piperidines upon treatment with potassium cyanide.[6,11] From a synthetic point of view, *cis*-2-cyanomethyl-4-phenylpiperidines **3** can be seen as valuable precursors for constrained β-amino acid derivatives. This class of compounds possesses unique pharmacological properties, and their application as building blocks for β-peptides makes these structures of high relevance in synthetic and medicinal chemistry.[19] Moreover, *cis*-2-carboxymethyl-4-phenylpiperidine derivatives have been patented as non-peptidic renin inhibitors, used for the treatment of cardiovascular, renal and chronic liver diseases, inflammations and metabolic syndromes.[6] Considering the above-described bioactivities, the cyano group in *cis*-2-cyanomethyl-4-phenylpiperidines **3** was transformed into a methyl ester *via* a Pinner reaction using gaseous HCl in dry methanol for one hour at room temperature, and subsequent aqueous workup afforded methyl *cis*-(1-arylmethyl-4-phenylpiperidin-2-yl)acetates **15** in 71–76% yield (Scheme 4). *Cis*-2-carbamoylmethyl-4-phenylpiperidines were observed as minor constituents under these reaction conditions as well (23–25%), and could be easily removed from the esters **15** by column chromatography on silica gel. Attempts to hydrolyze *cis*-2-cyanomethyl-4-phenylpiperidines **3** towards the corresponding amides upon treatment with H_2SO_4 in dichloromethane gave rise to complex reaction mixtures.

In conclusion, a short and convenient approach toward *cis*-1-arylmethyl-2-cyanomethyl-4-phenylpiperidines is reported starting from 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines *via* a novel type of radical-induced nitrile translocation of *cis*-2-chloromethyl-4-phenylpiperidine-4-carbonitriles. Acidic methanolysis of these 2-(cyanomethyl)piperidines provided an easy access to the corresponding (piperidin-2-yl)acetates as biologically relevant constrained amino acid derivatives.

Experimental part

^{1}H NMR spectra were recorded at 300 MHz with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz. Mass spectra were recorded on a mass spectrometer using either a direct inlet system (electron spray, 4000 V) or LC-MS coupling (UV detector). IR spectra were recorded on a FT-IR spectrometer. All compounds were analysed in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points are uncorrected. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use. Microwave reactions were performed in a Microwave Reactor (200 W_{max}) in a 80 mL sealed vessel using a fiber-optic temperature sensor. High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight.



Scheme 4

Synthesis of *cis*- and *trans*-1-arylmethyl-2-cyanomethyl-4-phenylpiperidines 3 and 4

As a representative example, the synthesis of *cis*- and *trans*-1-benzyl-2-cyanomethyl-4-phenylpiperidines **3a** and **4a** is described here. Bu_3SnH (0.93 mmol, 1.5 equiv.) and AIBN (0.062 mmol, 0.1 equiv.) were added to a solution of *cis*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **2a**[11] (0.62 mmol) in dry toluene (10 mL), and the resulting solution was heated under reflux for three hours under nitrogen atmosphere. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded a mixture of *cis*- and *trans*-1-benzyl-2-cyanomethyl-4-phenylpiperidines **3a** and **4a** in an isomeric ratio of 65/35 (**3a**/**4a**) and a combined yield of 76%. Isolation of *cis*-1-benzyl-2-cyanomethyl-4-phenylpiperidine **3a** was realized by crystallization from a hexane–EtOAc (15 : 1) solution, and *trans*-1-benzyl-2-cyanomethyl-4-phenylpiperidine **4a** was obtained in pure form through column chromatography on silica gel (hexane–EtOAc 9 : 1).

cis-1-Benzyl-2-cyanomethyl-4-phenylpiperidine 3a

White crystals. Mp = 102.5 °C. Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.88 (3H, m); 2.00–2.04 (1H, m); 2.09–2.20 (1H, m); 2.56–2.67 (3H, m); 2.72–2.80 (1H, m); 2.99 (1H, d × t, J = 11.6, 3.2 Hz); 3.17 (1H, d, J = 13.2 Hz); 4.09 (1H, d, J = 13.2 Hz); 7.18–7.40 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 23.9, 32.7, 40.2, 42.5, 53.2, 58.1, 58.3, 117.7, 126.6, 126.8, 127.3, 128.5, 128.6, 129.0, 138.4, 145.3. IR (cm^{-1}): ν_{CN} = 2247; ν_{max} = 2928, 2909, 2791, 1493, 1451, 1433, 1127, 759, 740, 699. MS (70 eV): *m*/*z* (%): 291 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{23}N_2$: 291.1856 MH^+; found: 291.1852.

cis-2-Cyanomethyl-1-(4-methylbenzyl)-4-phenylpiperidine 3b

White crystals. Mp = 78.2 °C. R_f = 0.35 (hexane–EtOAc 3 : 1). Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71–1.88 (3H, m); 1.99–2.17 (2H, m); 2.36 (3H, s); 2.57–2.67 (3H, m); 2.78 (1H, d × d, J = 17.1, 7.2 Hz); 3.00 (1H, d × t, J = 12.1, 3.3 Hz); 3.16 (1H, d, J = 13.2 Hz); 4.06 (1H, d, J = 13.2 Hz); 7.14–7.34 (9H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.2, 23.8, 32.8, 40.2, 42.6, 53.1, 58.06, 58.10, 117.8, 126.6, 126.9, 128.6, 129.0, 129.2, 135.2, 136.9, 145.3. IR (cm^{-1}): ν_{CN} = 2247; ν_{max} = 2934, 2800, 1513, 1494, 1452, 1128, 810, 756, 700. MS (70 eV): *m*/*z*

(%): 305 (M^+ + 1, 100). HRMS (ES) calcd for $C_{21}H_{25}N_2$: 305.2012 MH^+; found: 305.2009.

cis-1-(4-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine 3c

White crystals. Mp = 120.3 °C. R_f = 0.35 (hexane–EtOAc 3 : 1). Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65–1.89 (3H, m); 1.97–2.17 (2H, m); 2.54–2.68 (3H, m); 2.95 (1H, d × d, J = 16.8, 5.8 Hz); 3.00 (1H, d × t, J = 12.1, 3.3 Hz); 3.11 (1H, d, J = 13.2 Hz); 4.06 (1H, d, J = 13.2 Hz); 7.17–7.37 (9H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 23.9, 32.7, 40.2, 42.4, 53.1, 57.5, 58.0, 117.6, 126.6, 126.8, 128.7, 130.2, 133.0, 137.1, 145.2. IR (cm^{-1}): ν_{CN} = 2243, ν_{max} = 2936, 2817, 1490, 1451, 1084, 1015, 841, 758, 702. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{22}ClN_2$: 325.1466 MH^+; found: 325.1460.

cis-1-(2-Chlorobenzyl)-2-cyanomethyl-4-phenylpiperidine 3d

White crystals. Mp = 132.2 °C. Yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72–1.87 (3H, m); 2.01–2.06 (1H, m); 2.19–2.32 (1H, m); 2.53–2.74 (4H, m); 2.98 (1H, d × t, J = 12.1, 3.2 Hz); 3.45 (1H, d, J = 14.3 Hz); 3.99 (1H, d, J = 14.3 Hz); 7.16–7.35 and 7.65–7.68 (9H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 23.8, 32.8, 40.2, 42.4, 53.6, 54.8, 58.4, 117.9, 126.7, 126.9, 127.1, 128.4, 128.7, 129.5, 130.8, 133.9, 136.3, 145.3. IR (cm^{-1}): ν_{CN} = 2244; ν_{max} = 2917, 1442, 1134, 1034, 758, 696. MS (70 eV): m/z (%): 325/7 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{22}ClN_2$: 325.1466 MH^+; found: 325.1462.

cis-2-Cyanomethyl-1-(4-fluorobenzyl)-4-phenylpiperidine 3e

White crystals. Mp = 90.6 °C. Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66–1.89 (3H, m); 1.99–2.03 (1H, m); 2.06–2.17 (1H, m); 2.55–2.66 (3H, m); 2.80 (1H, d × d, J = 17.1, 6.1 Hz); 2.96 (1H, d × t, J = 12.1, 3.2 Hz); 3.12 (1H, d, J = 13.2 Hz); 4.06 (1H, d, J = 13.2 Hz); 7.00–7.06 and 7.19–7.39 (9H, m). ^{19}F NMR (282 MHz, ref = $CFCl_3$): δ (−115.60) – (−115.48) (1F, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 23.9, 32.7, 40.2, 42.4, 53.0, 57.43, 58.0, 115.3 (d, J = 20.8 Hz), 117.6, 126.8, 126.8, 128.8, 130.4 (d, J = 8.1 Hz), 134.2 (d, J = 2,3 Hz); 145.2; 162.2 (d, J = 245.8 Hz). IR (cm^{-1}): ν_{CN} = 2244; ν_{max} = 2938, 2808, 1602, 1508, 1453, 1220, 836, 758, 700. MS (70 eV): m/z (%): 309 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{22}FN_2$: 309.1762 MH^+; found: 309.1760.

trans-1-Benzyl-2-cyanomethyl-4-phenylpiperidine 4a

Yellow oil. R_f = 0.38 (hexane–EtOAc 3 : 1). Yield 13%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86–1.97 (2H, m); 2.15–2.19 (2H, m); 2.56–2.69 (1H, m); 2.79 (2H, d, J = 7.8 Hz); 2.82–2.92 (2H, m); 3.56–3.63 (1H, m); 3.76 (1H, d, J = 13.5 Hz); 3.86 (1H, d, J = 13.5 Hz); 7.32–7.53 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.7, 32.3, 35.6, 36.5, 45.8, 55.1, 59.1, 119.5, 126.6, 127.1, 127.5, 128.7, 128.8, 138.6, 145.4. IR (cm^{-1}): ν_{CN} = 2244; ν_{max} = 2923, 1493, 1453, 736, 699. MS (70 eV): m/z (%): 291 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{23}N_2$: 291.1856 MH^+; found: 291.1853.

trans-2-Cyanomethyl-1-(4-methylbenzyl)-4-phenylpiperidine 4b

Yellow oil. R_f = 0.38 (hexane–EtOAc 3 : 1). Yield 17%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72–1.84 (2H, m); 2.01–2.03 (2H, m); 2.33 (3H, s); 2.45–2.54 (1H, m); 2.64 (2H, d × d, J = 7.2, 1.1 Hz); 2.70–2.77 (2H, m); 3.40–3.49 (1H, m); 3.59 (1H, d, J = 13.2 Hz); 3.67 (1H, d, J = 13.2 Hz); 7.12–7.33 (9H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 13.7, 21.4, 32.5, 35.8, 36.7, 45.9, 55.0, 58.9, 119.6, 126.7, 127.1, 128.7, 128.8, 129.5, 135.6, 137.2, 145.5. IR (cm^{-1}): ν_{CN} = 2244; ν_{max} = 2922, 1451, 1366, 809, 751, 699. MS (70 eV): m/z (%): 305 (M^+ + 1, 100). HRMS (ES) calcd for $C_{21}H_{25}N_2$: 305.2012 MH^+; found: 305.2008.

Synthesis of *trans*-1-benzyl-2-methyl-4-phenylpiperidine-4-carbonitrile 11 and *trans*-2-benzyl-1-methyl-4-phenylpiperidine-4-carbonitrile 12

To a solution of *trans*-1-benzyl-2-chloromethyl-4-phenylpiperidine-4-carbonitrile **10** (1.24 mmol) in dry toluene (20 mL) were added Bu_3SnH (1.86 mmol, 1.5 equiv.) and AIBN (0.124 mmol, 0.1 equiv.), and the resulting solution was heated under reflux for three hours under nitrogen atmosphere. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo* afforded a mixture of *trans*-1-benzyl-2-methyl-4-phenylpiperidine-4-carbonitrile **11** and *trans*-2-benzyl-1-methyl-4-phenylpiperidine-4-carbonitrile **12** (ratio **11** : **12** 62–64 : 36–38). Compounds **11** and **12** were obtained in pure form through column chromatography on silica gel (hexane–EtOAc 9 : 1).

trans-1-Benzyl-2-methyl-4-phenylpiperidine-4-carbonitrile 11

Yellow oil. R_f = 0.30 (hexane–EtOAc 3 : 1). Yield 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, d, J = 6.1 Hz); 1.87 (1H, d × d, J = 13.5, 11.3 Hz); 1.98–2.04 (2H, m); 2.10 (1H, d (broad), J = 13.2 Hz); 2.47 (1H, d × t, J = 12.4, 7.6 Hz); 2.75–2.85 (1H, m); 2.92 (1H, d × t, J = 12.4, 3.3 Hz); 3.15 (1H, d, J = 13.2 Hz); 4.22 (1H, d, J = 13.2 Hz); 7.17–7.57 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.9, 36.3, 43.6, 45.4, 49.8, 54.6, 57.8, 122.5, 125.7, 127.1, 128.1, 128.4, 129.1, 139.2, 140.4. IR (cm^{-1}): ν_{CN} = 2236; ν_{max} = 2924, 1494, 1449, 1153, 759, 735, 697. MS (70 eV): m/z (%): 291 (M^+ + 1, 100). HRMS (ES) calcd for $C_{20}H_{23}N_2$: 291.1856 MH^+; found: 291.1858.

trans-2-Benzyl-1-methyl-4-phenylpiperidine-4-carbonitrile 12

Yellow oil. R_f = 0.27 (hexane–EtOAc 3 : 1). Yield 19%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (1H, d × d, J = 13.3, 11.3 Hz); 1.91 (1H, d × t, J = 13.3, 2.2 Hz); 2.02–2.18 (2H, m); 2.47 (1H, d × d, J = 13.3, 9.4 Hz); 2.52 (3H, s); 2.67–2.69 (1H, m); 2.75 (1H, t × d, J = 12.1, 3.9 Hz); 3.05 (1H, t × d, J = 12.1, 3.3 Hz); 3.30 (1H, d × d, J = 13.3, 4.1 Hz); 7.15–7.42 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 36.4, 40.0, 41.4, 43.1, 43.4, 54.4, 62.0, 122.2, 125.7, 126.6, 128.3, 128.8, 129.2, 129.5, 138.3, 140.2. IR (cm^{-1}): ν_{CN} = 2234; ν_{max} = 2953, 2793, 1601, 1495, 1448, 1380, 1148, 758, 741, 696. MS (70 eV): m/z (%): 291 (M^+ + 1, 100).

Synthesis of methyl *cis*-(1-arylmethyl-4-phenylpiperidin-2-yl) acetates 15

As a representative example, the synthesis of methyl *cis*-(1-benzyl-4-phenylpiperidin-2-yl)acetate **15a** is described here. Gaseous hydrochloric acid was bubbled through a solution of *cis*-1-benzyl-2-cyanomethyl-4-phenylpiperidine **3a** (1.05 mmol) in dry methanol (30 mL) for one hour at room temperature. The solvent was evaporated *in vacuo* and the reaction mixture was redissolved in chloroform and heated under reflux for three hours. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded methyl *cis*-(1-benzyl-4-phenylpiperidin-2-yl) acetate **15a** in 76% yield. Methyl *cis*-(1-benzyl-4-phenylpiperidin-2-yl)acetate **15a** was purified by means of column chromatography on silica gel (CH_2Cl_2·MeOH 95 : 5) to provide an analytically pure sample.

Methyl *cis*-(1-benzyl-4-phenylpiperidin-2-yl)acetate 15a

Yellow oil. R_f = 0.64 (CH_2Cl_2–MeOH 95 : 5). Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.76 (3H, m); 1.88–1.92 (1H, m); 2.06–2.19 (1H, m); 2.45 (1H, d × d, J = 16.0, 7.7 Hz); 2.56–2.66 (1H, m); 2.78–2.89 (2H, m); 2.94 (1H, d × t, J = 12.1, 3.2 Hz); 3.17 (1H, d, J = 13.2 Hz); 3.65 (3H, s); 4.09 (1H, d, J = 13.2 Hz); 7.15–7.35 (10H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 32.7, 40.3, 40.4, 42.9, 51.8, 53.4, 58.0, 59.3, 126.4, 127.0, 127.0, 128.4, 128.6, 129.0, 139.4, 146.1, 172.83. IR (cm^{-1}): ν_{CO} = 1735; ν_{max} = 2946, 1493, 1159, 734, 697. MS (70 eV): m/z (%): 324 (M^+ + 1, 100). HRMS (ES) calcd for $C_{21}H_{26}NO_2$: 324.1958 MH^+; found: 324.1954.

Methyl *cis*-[1-(4-methylbenzyl)-4-phenylpiperidin-2-yl]acetate 15b

Yellow oil. R_f = 0.59 (CH_2Cl_2–MeOH 95 : 5). Yield 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.78 (3H, m); 1.88–1.92 (1H, m); 2.04–2.18 (1H, m); 2.34 (3H, s); 2.46 (1H, d × d, J = 16.2, 8.7 Hz); 2.55–2.66 (1H, m); 2.86–2.91 (2H, m); 2.96 (1H, d × t, J = 11.6, 3.2 Hz); 3.19 (1H, d, J = 13.2 Hz); 3.66 (3H, s); 4.05 (1H, d, J = 13.2 Hz); 7.12–7.31 (9H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.2, 32.6, 40.1, 40.2, 42.8, 51.8, 53.2, 57.6, 59.2, 126.4, 127.0, 128.6, 129.1, 135.6, 136.7, 146.0, 172.78. IR (cm^{-1}): ν_{CO} = 1735; ν_{max} = 2947, 1436, 1159, 755, 699. MS (70 eV): m/z (%): 338 (M^+ + 1, 100). HRMS (ES) calcd for $C_{22}H_{28}NO_2$: 338.2115 MH^+; found: 338.2105.

Methyl *cis*-[1-(4-fluorobenzyl)-4-phenylpiperidin-2-yl]acetate 15c

Yellow oil. R_f = 0.64 (CH_2Cl_2–MeOH 95 : 5). Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.76 (3H, m); 1.86–1.92 (1H, m); 2.12 (1H, t × d, J = 11.5, 4.0 Hz); 2.45 (1H, d × d, J = 14.9, 6.6 Hz); 2.57–2.67 (1H, m); 2.75–2.87 (2H, m); 2.91 (1H, d × t, J = 11.5, 3.3 Hz); 3.14 (1H, d, J = 13.2 Hz); 3.67 (3H, s); 4.04 (1H, d, J = 13.2 Hz); 6.98–7.04 and 7.17–7.32 (9H, m). ^{19}F NMR (282 MHz, ref = $CFCl_3$): δ (−116.11)–(−114.92) (1F, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 32.6, 40.2, 40.3, 42.8, 51.8, 53.2, 57.1, 59.2, 115.1 (d, J = 21.9 Hz); 126.4, 126.9, 128.5, 130.4 (d, J = 8.1 Hz); 135.0, 146.0, 162.0 (d, J = 244.6 Hz); 172.7. IR (cm^{-1}): ν_{CO} = 1735; ν_{max} = 2930, 1508, 1219, 1154, 835, 758, 700. MS (70 eV): m/z (%): 342 (M^+ + 1, 100). HRMS (ES) calcd for $C_{21}H_{25}FNO_2$: 342.1864 MH^+; found: 342.1857.

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