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TETRAHEDRON: *ASYMMETRY*

A practical asymmetric synthesis of 2,6-*cis*-disubstituted piperidines

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Abstract

A highly diastereoselective intramolecular Mannich reaction involving enantiopure α-methylamine **7** and achiral aldehydes is employed to prepare enantiomerically pure 2,6-*cis*-disubstituted piperidines. This methodology provides an efficient and selective route to 2,6-*cis*-disubstituted piperidines, 2,6-*cis*-disubstituted 4-piperidones and 2,6-*cis*-disubstituted 4-piperidinols.

1. Introduction

Many natural compounds and drugs contain the piperidine ring system as a structural element. As this class of products exhibits a wide range of biological activities,[1] the elaboration of efficient regio- and stereoselective syntheses of chiral enantiopure piperidines is of great interest for organic chemists and pharmaceutical research. Among the numerous naturally occurring piperidines, *cis*- and *trans*-2,6-dialkylpiperidines, either monocyclic or included in bicyclic systems, form an important class of alkaloids isolated from amphibians, insects and plants. For example, pinidine **1** was extracted from several species of the family Pinaceae[2] while dihydropinidine **2** has been found in the Mexican bean beetle *Epilachna varivestis*.[3] Solenopsins **3** and isosolenopsins **4** are representative alkaloids of the fire ants' venom of the genus *Solenopsis* (Myrmicinae).[4] Monomorine **5** was identified as a pheromone of the pharaoh ant *Monomorium pharaonis* L[5] while its C-3 epimer, indolizidine 195 B **6**, was isolated from the poison frog *Dendrobates histrionicus*[6] (Fig. 1).

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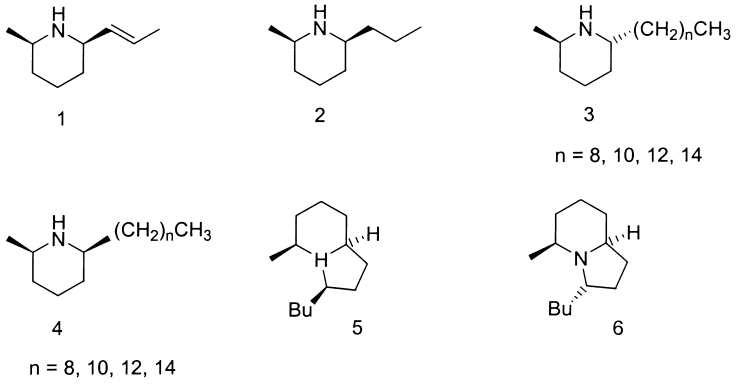
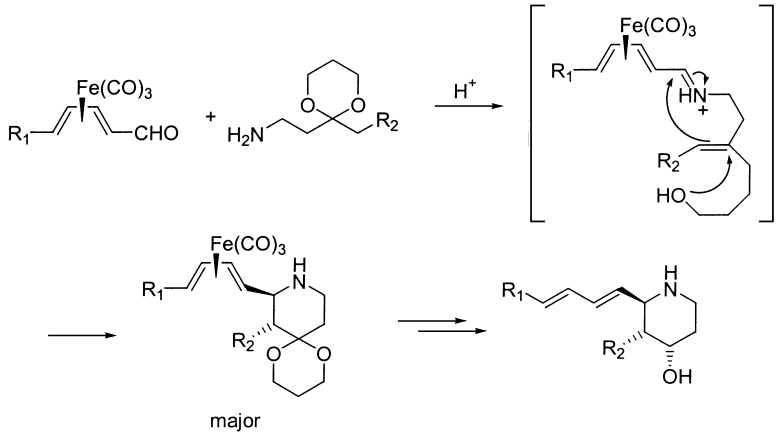


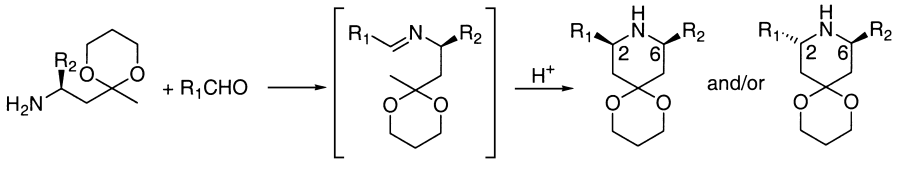
Figure 1.

Various strategies have been proposed for the stereoselective preparation of six-membered *N*-heterocyclic compounds,[7] many concerning the asymmetric syntheses of 2,6-dialkylpiperidine alkaloids[8] such as **1**–**6**. Part of our research program is devoted to the asymmetric synthesis of polysubstituted piperidines and we have recently described an access to *cis*- and *trans*-2-alkyl-4-hydroxypiperidines[9] and to *trans, cis*-2,3-dialkyl-4-hydroxypiperidines.[10] We have defined a one-pot stereoselective cyclisation method in which the piperidine nucleus is formed through an intramolecular Mannich-type[11] reaction involving a non-chiral amine with a planar chiral dienal iron tricarbonyl complex (Scheme 1).



Scheme 1.

Although this method permits, as shown, the asymmetric construction of diverse polysubstituted piperidines, a limitation is apparent since it does not allow the stereoselective elaboration of a 2,6-disubstitution pattern by the same pathway. We reasoned that this case requires the use of a chiral amine which must be involved in the cyclisation step with an achiral aldehyde (Scheme 2).



Scheme 2.

Thus, homochiral amine **7**[12] (Fig. 2) was engaged in the cyclisation step with various aromatic, heteroaromatic, ethylenic and saturated aldehydes **8**–**18**[13] (Table 1) in order to validate our approach and to examine the diastereoselection degree of the 2,6-disubstituted-piperidine ring formation.

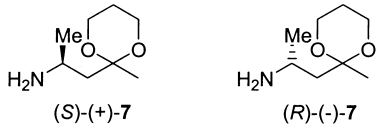
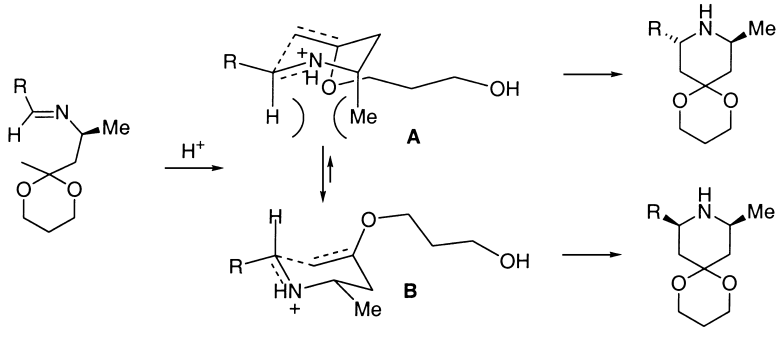


Figure 2.

2. Results and discussion

Reaction of aldehydes **8**–**18** with amine **7** in refluxing dichloromethane in the presence of magnesium sulphate as drying agent led quantitatively (TLC monitoring), in 1–3 h, to the corresponding imines. These unstable compounds were treated directly, for 2–3 h, with 2 equivalents of *para*-toluenesulphonic acid (previously dried under Dean–Stark conditions) at 70°C in toluene. Under these conditions, 2,6-disubstituted piperidines **19**–**29** were obtained in 60 to 96% yield after chromatographic purification. The results are collected in Table 1.

In all cases, the 2,6-*cis* diastereomer was formed highly predominantly. The 2,6-*trans* isomer was observed, by ^{1}H NMR spectroscopy, only in the case of the 2-furyl-6-methylpiperidine **29**. The relative configurations of the 2,6-*cis*-piperidines **19**–**29** were established unambiguously from ^{1}H NMR spectra, particularly with the signals corresponding to H-3 (axial and equatorial) and H-5 (axial and equatorial), showing typical coupling constants for a 2,6-diequatorial disubstitution in a chair conformation. As the presence of the 2,6-*trans* isomer was not detected by ^{1}H NMR for compounds **19**–**28**, we assume that the diastereomeric excess of the cyclised products is higher than 95%. To explain such a diastereoselectivity, we have considered a priori the transition states **A** and **B** (Scheme 3). It clearly appears that, due to a $A^{(1,3)}$ strain present in **A**, leading to the 2,6-*trans* isomer, this transition state is disfavoured compared to **B**, precursor of the observed 2,6-*cis* isomer (Scheme 3).



Scheme 3.

We then examined the enantiomeric purity of our piperidines by high performance liquid chromatography.[14] This was accomplished with the 2-phenyl-6-methylpiperidine **22**. A baseline separation was obtained for racemic **22** while only one peak was observed for (+)- and (−)-**22**, demonstrating that no racemisation occurs during the cyclisation.

Cleavage of the dioxane appendage[15] of piperidine (−)-**22** was then cleanly realised using a conventional procedure and furnished the parent 4-piperidone (−)-**30** in 90% yield (Scheme 4). Piperidone

Table 1
Diastereoselective formation of 2,6-*cis*-disubstituted piperidines **19**–**29** from amine **7** and aldehydes **8**–**18**

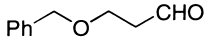
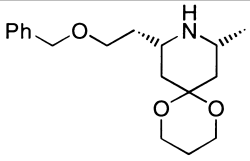
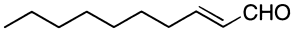
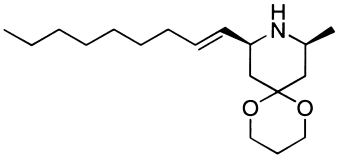
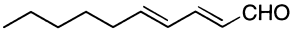
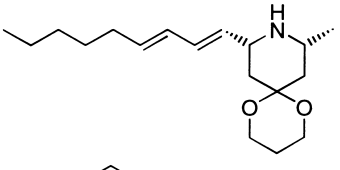
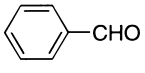
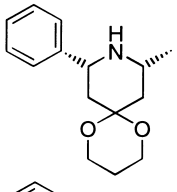
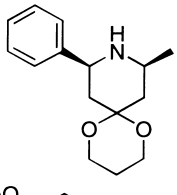
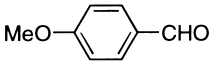
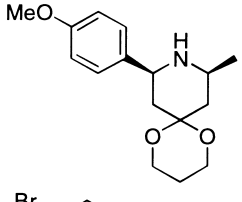
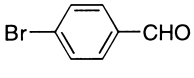
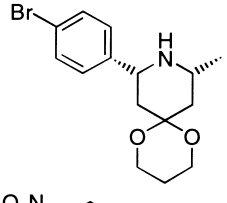
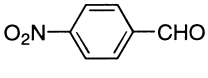
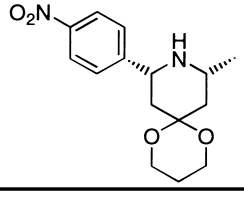
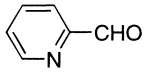
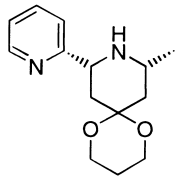
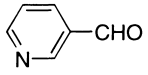
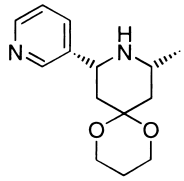
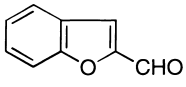
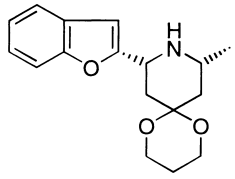
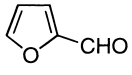
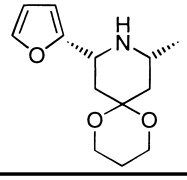
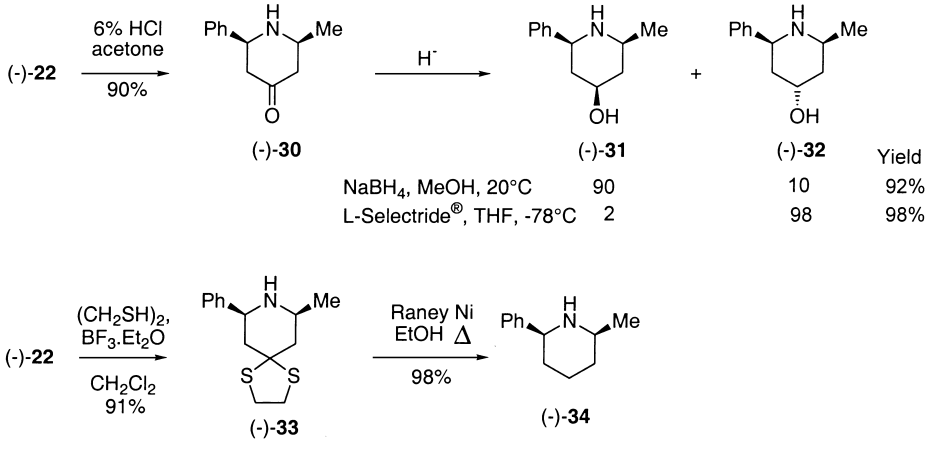
Aldehyde		amine	Major product		Yield (%)	d.e. (%)	$[\alpha]_D^{25}$
	**8**	(±)-**7**		**19**	70	≥95	-
	**9**	(+)-**7**		**20**	80	≥95	-2.3
	**10**	(-)-**7**		**21**	60	≥95	-2.1
	**11**	(-)-**7**		**22**	80	≥95	+8.3
		(+)-**7**		**22**	80	≥95	-8.4
	**12**	(±)-**7**		**23**	75	≥95	-
	**13**	(-)-**7**		**24**	63	≥95	+3.6
	**14**	(-)-**7**		**25**	96	≥95	+1.7

Table 1 (continued)

	**15**	**(-)-7**		**26**	86	≥95	-9.1
	**16**	**(-)-7**		**27**	65	≥95	+13.1
	**17**	**(-)-7**		**28**	83	≥95	-23.0
	**18**	**(-)-7**		**29**	65	85	-11.1

(−)-**30** was stereoselectively reduced with sodium borohydride and L-Selectride® to afford, respectively, equatorial 4-piperidinol (−)-**31** (92%, de: 80%) and its C-4 axial epimer (−)-**32** (95%, de: 95%). Finally, treatment of piperidine (−)-**22** with an excess of ethanedithiol in the presence of $BF_3 \cdot Et_2O$ gave in 91% yield the dithiolane derivative (−)-**33** which was quantitatively converted into the (−)-2,6-*cis*-2-phenyl-6-methylpiperidine **34** by hydrogenolysis realised in the presence of W2 Raney nickel[16] in refluxing ethanol (Scheme 4). The specific rotation of (−)-**34** ($[\alpha]_D^{25}$=−21, *c* 0.7, EtOH) was consistent with that recently reported for its enantiomer (lit.[8a]: ($[\alpha]_D^{25}$=22.1, *c* 0.69, EtOH).



Scheme 4.

3. Conclusion

We have described herein the enantioselective preparation of 2,6-*cis*-disubstituted piperidines via a highly diastereoselective intramolecular Mannich-type reaction using the homochiral amine **7**. As demonstrated, this method is applicable to a large variety of aldehydes and permits the rapid selective synthesis of 2,6-*cis*-disubstituted piperidines, 2,6-*cis*-disubstituted 4-piperidones and 2,6-*cis*-disubstituted 4-piperidinols (*cis,cis* or *trans,trans*, selectively). Extension of this method to other series of aldehydes, to differently and more substituted chiral amines, as well as its application to the field of total enantioselective synthesis of alkaloids is currently under progress.

4. Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz, respectively; chemical shifts are reported in ppm relative to $SiMe_4$. *J* values are given in hertz. Infrared spectra were recorded on an FTIR spectrometer. Electron impact (EI) mass spectra were obtained at 70 eV. Electron impact (EI) and fast atom bombardment (FAB) high resolution mass spectra were obtained from the Centre Régional de Mesures Physiques, Université de Rennes. Optical rotations were measured at 589 nm. Column chromatography was carried out on silica gel (70–230 mesh). Solvents were dried and freshly distilled following the usual procedures. All reactions were carried out under argon. Product solutions were dried over Na_2SO_4 prior to evaporation of the solvents under reduced pressure on a rotary evaporator.

4.1. Intramolecular Mannich-type cyclisation, general procedure

To a stirred solution of aldehyde (4 mmol) in CH_2Cl_2 (20 mL) was added $MgSO_4$ (1 g) followed by a solution of amine (±)-, (+)- or (−)-**7** (1 equiv.) in CH_2Cl_2 (5 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the amine (1–3 h), then cooled to room temperature and transferred via a cannula to a solution of dry *para*-toluenesulphonic acid (2 equiv.) in toluene (25 mL). The resulting mixture was heated at 70°C for 3 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (15 mL) was added and the protected piperidone was extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography using MeOH/ethyl acetate as eluent.

4.2. (±)-(2R,6S*)-1-Aza-2-(2′′-benzyloxyethyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **19***

Following the general procedure, amine (±)-**7** and aldehyde **8** gave, after chromatography (ethyl acetate:methanol, 9:1), 70% of protected piperidone **19**, as a pale yellow oil. R_f 0.40 (ethyl acetate:methanol, 5:1); ν_{max} (neat)/cm^{-1} 3314, 1143, 1097, 736; δ_H ($CDCl_3$) 7.33 (5H, m), 4.53 (2H, s), 3.92 (2H, t, *J*=5), 3.86 (2H, t, *J*=5), 3.59 (2H, t, *J*=5.5), 2.92 (2H, m, H-2 and H-6), 2.22 (2H, m), 2.00 (1H, br s, NH), 1.75 (4H, m), 1.14 (2H, m), 1.07 (3H, t, *J*=7); δ_C ($CDCl_3$) 128.1 (d), 127.3 (d), 114.4 (s), 97.1 (s), 72.6 (t), 67.7 (t), 58.9 (t), 50.8 (d), 47.6 (d), 40.9 (t), 38.9 (t), 35.9 (t), 25.4 (t), 22.0 (q).

4.3. (−)-(2S,6S)-1-Aza-2-(non-1′′-enyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **20**

Following the general procedure, amine (+)-**7** and aldehyde **9** gave, after chromatography (ethyl acetate:methanol, 9:1), 80% of protected piperidone (−)-**20**, as a pale yellow oil. R_f 0.31 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=−2.3 (*c* 0.97, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 1146, 1099, 1009, 963; δ_H ($CDCl_3$) 5.63 (1H, m), 5.45 (1H, dd, *J*=15.5 and 7.0), 3.93 (4H, m), 3.29 (1H, m, H-2), 2.93 (1H, m, H-6), 2.26 (1H, dt, *J*=13.5 and 3.0, H-3eq), 2.18 (1H, dt, *J*=13.5 and 3.0, H-5eq), 1.99 (2H, m), 1.72 (2H, m), 1.60 (1H, br s, NH), 1.45–1.00 (12H, m), 1.10 (3H, d, *J*=7.0), 0.85 (3H, t, *J*=7.0); δ_C ($CDCl_3$) 132.2 (d), 131.2 (d), 97.2 (s), 59.0 (t), 54.9 (d), 49.8 (d), 41.0 (t), 38.9 (t), 32.1 (t), 31.7 (t), 29.0 (t), 28.9 (t), 25.5 (t), 22.5 (t), 22.2 (q), 14.0 (q); *m/z* (EI) 295 ($M^{+\cdot}$, 20), 194 (100), 235 (100), 179 (30), 101 (75); HRMS (FAB) found: 296.2595; $C_{18}H_{33}NO_2$+H^+ requires: 296.2590.

4.4. (−)-(2S,6S)-1-Aza-2-(nona-1′′,3′′-dienyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **21**

Following the general procedure, amine (−)-**7** and aldehyde **10** gave, after chromatography (ethyl acetate:methanol, 9:1), 60% of protected piperidone (−)-**21**, as a pale yellow oil. R_f 0.32 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=−2.1 (*c* 0.85, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3313, 1145, 1100, 988; δ_H ($CDCl_3$) 6.16 (1H, dd, *J*=15.5 and 10.0), 6.00 (1H, m), 5.67 (1H, m), 5.55 (1H, dd, *J*=15.5 and 7.5), 3.92 (4H, m), 3.35 (1H, m, H-2), 2.93 (1H, m, H-6), 2.31 (1H, dt, *J*=12.5 and 2, H-3eq), 2.17 (1H, dt, 12.5 and 2.0, H-5eq), 2.05 (2H, m), 1.73 (2H, m), 1.52 (1H, br s, NH), 1.45–1.10 (8H, m), 1.10 (3H, d, *J*=8), 0.90 (3H, t, *J*=7.5); δ_C ($CDCl_3$) 134.9 (d), 132.9 (d), 130.6 (d), 129.6 (d), 97.2 (s), 59.1 (t), 54.8 (d), 47.7 (d), 41.2 (t), 38.5 (t), 32.5 (t), 31.3 (t), 28.9 (t), 25.5 (t), 22.4 (t), 22.2 (q), 14.0 (q); *m/z* (EI) 293 ($M^{+\cdot}$, 68), 101 (100), 41 (44); HRMS (FAB) found: 294.2434; $C_{18}H_{31}NO_2$+H^+ requires: 294.2433.

4.5. (−)-(2S,6S)-1-Aza-6-methyl-2-phenyl-1′,3′-dioxaspiro[5.5]undecane **22**

Following the general procedure, amine (+)-**7** and aldehyde **11** gave, after chromatography (ethyl acetate:methanol, 9:1), 83% of protected piperidone (−)-**22**, as a pale yellow oil. R_f 0.24 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=−8.4 (*c* 1.24, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3307, 1602, 1135, 1101, 701; δ_H ($CDCl_3$) 7.45–7.25 (5H, m), 3.95 (4H, m), 3.85 (1H, dd, *J*=12 and 2, H-2), 3.05 (1H, m, H-6), 2.45 (1H, td, *J*=12.5 and 2, H-3eq), 2.25 (1H, td, *J*=12.5 and 2.5, H-5eq), 1.80 (1H, m), 1.70 (1H, m), 1.60 (1H, br s, NH), 1.52 (1H, t, *J*=12.5, H-3ax), 1.25 (1H, t, *J*=12.5, H-5ax), 1.14 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 144.1 (s), 128.4 (d), 127.2 (d), 126.8 (d), 97.6 (s), 59.1 (t), 57.5 (d), 48.4 (d), 41.6 (t), 40.3 (t), 25.6 (t), 22.4 (q); HRMS (FAB) found: 248.1651; $C_{15}H_{21}NO_2$+H^+ requires: 248.1651.

4.6. (+)-(2R,6R)-1-Aza-6-methyl-2-phenyl-1′,3′-dioxaspiro[5.5]undecane **22**

Following the general procedure, amine (−)-**7** and aldehyde **11** gave, after chromatography (ethyl acetate:methanol, 9:1), 80% of protected piperidone (+)-**22**, as a pale yellow oil. $[\alpha]_D^{25}$=8.3 (*c* 1.2, $CHCl_3$). Other data were identical with those reported for (−)-**22**.

4.7. (±)-(2S*,6S*)-1-Aza-2-(4′′-methoxyphenyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **23**

Following the general procedure, amine (±)-**7** and aldehyde **12** gave, after chromatography (ethyl acetate:methanol, 9:1), 75% of protected piperidone **23**, as a pale yellow oil. R_f 0.26 (ethyl acetate:methanol, 5:1); ν_{max} (neat)/cm^{-1} 3303, 1135, 1103; δ_H (C_6D_6) 7.32 (2H, d, *J*=8.5), 6.78 (2H, d, *J*=8.5), 3.90 (1H,

dd, *J*=12 and 2, H-2), 3.56 (4H, m), 3.28 (3H, s), 2.97 (1H, m, H-6), 2.47 (1H, td, *J*=12 and 2, H-3eq), 2.24 (1H, td, *J*=12 and 2, H-5eq), 1.60 (1H, t, *J*=12, H-3ax), 1.33 (1H, t, *J*=12, H-5ax), 1.32 (1H, m), 1.26 (2H, m), 0.92 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 158.9 (s), 136.2 (s), 128.1 (d), 113.9 (d), 97.7 (s), 59.3 (t), 57.0 (q), 55.4 (d), 48.6 (d), 41.6 (t), 40.3 (t), 25.7 (t), 22.4 (q).

*4.8. (+)-(2*R*,6*R*)-1-Aza-2-(4′′-bromophenyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane* ***24***

Following the general procedure, amine (−)-**7** and aldehyde **13** gave, after chromatography (ethyl acetate:methanol, 9:1), 63% of protected piperidone (+)-**24**, as a pale yellow oil. R_f 0.61 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=3.6 (*c* 1.13, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3306, 1135, 1103, 831; δ_H ($CDCl_3$) 7.41 (2H, d, *J*=9.5), 7.22 (2H, d, *J*=9.5), 3.91 (4H, m), 3.79 (1H, dd, *J*=11 and 2, H-2), 3.00 (1H, m, H-6), 2.33 (1H, td, *J*=11 and 2, H-3eq), 2.24 (1H, td, *J*=11 and 2, H-5eq), 1.73 (2H, m), 1.55 (1H, br s, NH), 1.43 (1H, t, *J*=11.5, H-3ax), 1.18 (1H, t, *J*=11.5, H-5ax), 1.10 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 143.1 (s), 131.4 (d), 128.5 (d), 120.8 (s), 97.3 (s), 59.1 (t), 56.8 (d), 48.2 (d), 41.0 (t), 40.8 (t), 25.5 (t), 22.3 (q); HRMS (FAB) found: 326.0751; $C_{15}H_{20}NO_2{}^{79}Br+H^+$ requires: 326.0756.

*4.9. (+)-(2*R*,6*R*)-1-Aza-2-(4′′-nitrophenyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane* ***25***

Following the general procedure, amine (−)-**7** and aldehyde **14** gave, after chromatography (ethyl acetate:methanol, 9:1), 96% of protected piperidone (+)-**25**, as a yellow solid. Mp=102°C. R_f 0.64 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=1.7 (*c* 1.05, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3303, 1597, 1511, 1346, 1135, 855; δ_H ($CDCl_3$) 8.19 (2H, d, *J*=8.5), 7.57 (2H, d, *J*=8.5), 3.96 (5H, m), 3.06 (1H, m, H-6), 2.35 (2H, m), 1.77 (2H, m), 1.60 (1H, br s, NH), 1.45 (1H, t, *J*=11.5, H-3ax), 1.29 (1H, t, *J*=11.5, H-5ax), 1.17 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 148.7 (d), 139.2 (s), 134.4 (d), 123.4 (s), 97.2 (s), 59.2 (t), 59.1 (t), 55.0 (d), 48.3 (d), 40.8 (t), 40.6 (t), 25.4 (t), 22.2 (q); HRMS (FAB) found: 293.1499; $C_{15}H_{20}N_2O_4+H^+$ requires: 293.1501.

*4.10. (−)-(2*R*,6*R*)-1-Aza-6-methyl-2-(2′′-pyridinyl)-1′,3′-dioxaspiro[5.5]undecane* ***26***

Following the general procedure, amine (−)-**7** and aldehyde **15** gave, after chromatography (ethyl acetate:methanol, 5:1), 86% of protected piperidone (−)-**26**, as a colourless oil. R_f 0.25 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=−9.1 (*c* 0.95, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3301, 1591, 1434, 1144, 1090, 755; δ_H ($CDCl_3$) 8.55 (1H, m), 7.66 (1H, t, *J*=8.0), 7.32 (1H, d, *J*=8.0), 7.16 (1H, m), 3.95 (5H, m), 3.07 (1H, m, H-6), 2.59 (1H, td, *J*=12.5 and 2, H-3eq), 2.24 (1H, td, *J*=12.5 and 2, H-5eq), 1.92 (1H, br s, NH), 1.81 (1H, m), 1.71 (1H, m), 1.52 (1H, t, *J*=12, H-3ax), 1.23 (1H, t, *J*=12.5, H-5ax), 1.18 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 161.8 (s), 149.1 (d), 136.6 (d), 122.1 (d), 120.9 (d), 97.5 (s), 59.2 (t), 59.0 (d), 48.2 (d), 41.7 (t), 38.6 (t), 25.5 (t), 22.3 (q); HRMS (FAB) found: 249.1607; $C_{14}H_{20}N_2O_2+H^+$ requires: 249.1603.

*4.11. (+)-(2*R*,6*R*)-1-Aza-6-methyl-2-(3′′-pyridinyl)-1′,3′-dioxaspiro[5.5]undecane* ***27***

Following the general procedure, amine (−)-**7** and aldehyde **16** gave, after chromatography (ethyl acetate:methanol, 5:1), 65% of protected piperidone (+)-**27**, as a colourless oil. R_f 0.43 (ethyl acetate:methanol, 1:1); $[\alpha]_D^{25}$=13.1 (*c* 1.17, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3303, 1578, 1511, 1345, 1104, 715; δ_H ($CDCl_3$) 8.63 (1H, m), 8.52 (1H, m), 7.75 (1H, m), 7.27 (1H, m), 3.94 (5H, m), 3.06 (1H, m, H-6), 2.38 (1H, td, *J*=11.5 and 2, H-3eq), 2.24 (1H, td, *J*=11.5 and 2, H-5eq), 1.75 (2H+NH, m), 1.52 (1H, t, *J*=11.5, H-3ax), 1.24 (1H, t, *J*=11.5, H-5ax), 1.15 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 151.7 (s), 127.5 (d),

123.6 (d), 97.0 (s), 59.1 (t), 56.9 (d), 48.1 (d), 41.2 (t), 40.4 (t), 25.4 (t), 22.3 (q); HRMS (FAB) found: 249.1608; $C_{14}H_{20}N_2O_2+H^+$ requires: 249.1603.

4.12. (−)-(2R,6R)-1-Aza-2-(2′′-benzofuryl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **28**

Following the general procedure, amine (−)-**7** and aldehyde **17** gave, after chromatography (ethyl acetate:methanol, 9:1), 83% of protected piperidone (−)-**28**, as a colourless oil. R_f 0.25 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}=-23.0$ (*c* 0.97, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1668, 1101, 736; δ_H ($CDCl_3$) 7.54 (1H, d, *J*=7.5), 7.46 (1H, d, *J*=7.5), 7.23 (2H, d, *J*=7.5), 6.57 (1H, s), 4.14 (1H, dd, *J*=10 and 2, H-2), 3.95 (4H, m), 3.07 (1H, m, H-6), 2.67 (1H, td, *J*=13.5 and 2, H-3eq), 2.28 (1H, td, *J*=13.5 and 2, H-5eq), 1.90–1.60 (4H, m), 1.26 (1H, t, *J*=13.5, H-5ax), 1.16 (3H, d, *J*=7.0); HRMS (FAB) found: 288.1599; $C_{17}H_{21}NO_3+H^+$ requires: 288.1600.

4.13. (−)-(2R,6R)-1-Aza-2-(2′′-furyl)-6-methyl-1′,3′-dioxaspiro[5.5]undecane **29**

Following the general procedure, amine (−)-**7** and aldehyde **18** gave, after chromatography (ethyl acetate:methanol, 9:1), 65% of protected piperidone (−)-**29**, as a colourless oil. R_f 0.43 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}=-11.1$ (*c* 1.14, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3311, 1145, 1101, 1007, 741; δ_H ($CDCl_3$) 7.29 (1H, m), 6.26 (1H, m), 6.11 (1H, m), 3.87 (5H, m), 3.00 (1H, m, H-6), 2.53 (1H, td, *J*=12.5 and 2, H-3eq), 2.19 (1H, td, *J*=12.5 and 2, H-5eq), 1.66 (3H, m), 1.55 (1H, t, *J*=12.5, H-3ax), 1.16 (1H, t, *J*=12.5, H-5ax), 1.10 (3H, t, *J*=7.0); δ_C ($CDCl_3$) 156.4 (s), 127.5 (d), 109.9 (d), 104.7 (d), 97.1 (s), 59.1 (t), 50.7 (d), 48.0 (d), 41.6 (t), 36.8 (t), 25.5 (t), 22.2 (q); HRMS (FAB) found: 238.1442; $C_{13}H_{19}NO_3+H^+$ requires: 238.1443.

4.14. (−)-(2S,6S)-6-Methyl-2-phenylpiperidin-4-one **30**

To a stirred solution of protected piperidone (−)-**22** (250 mg, 1 mmol) in acetone (15 mL) was added 6% hydrochloric acid (10 mL). The resulting mixture was stirred at room temperature for 10 days. The organic solvent was eliminated under reduced pressure and the residue was diluted with an excess of 1 M aqueous NaOH. The piperidone was then extracted with dichloromethane (4×20 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate) afforded piperidone (−)-**30** (170 mg, 90%) as a white solid. Mp=65–67°C; R_f 0.60 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}=-72.0$ (*c* 1.19, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3310, 1703, 1135, 1101, 700; δ_H ($CDCl_3$) 7.35 (5H, m), 3.96 (1H, dd, *J*=8.5 and 7.5, H-2), 3.14 (1H, m, H-6), 2.52 (2H, m), 2.42 (1H, dd, *J*=12.5 and 2), 2.25 (1H, t, *J*=12), 1.85 (1H, br s, NH), 1.27 (3H, d, *J*=7.0); δ_C ($CDCl_3$) 208.8 (s), 142.6 (s), 128.7 (d), 127.8 (d), 126.5 (d), 61.0 (d), 53.8 (d), 49.9 (t), 48.7 (t), 22.6 (q); HRMS (EI) found: 189.1157; $C_{12}H_{15}NO$ requires: 189.1154.

4.15. (−)-(2S,4S,6S)-6-Methyl-2-phenylpiperidin-4-ol **31**

To a stirred solution of piperidone (−)-**30** (95 mg, 0.5 mmol) in methanol (8 mL) was added at room temperature sodium borohydride (0.5 mmol). The resulting mixture was stirred for 10 min before addition of saturated aqueous NH_4Cl (3 mL). The piperidinol was extracted with dichloromethane (4×15 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvents, followed by column chromatography (ethyl acetate:methanol, 9:1), gave separated piperidinols (−)-**31** (79 mg, 83%) and (−)-**32** (9 mg, 9%). Piperidinol (−)-**31**: white solid. Mp=100°C; R_f 0.38 (ethyl acetate:methanol,

1:1); $[\alpha]_D^{25}$=−53.7 (*c* 0.86, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3203, 1135, 1106, 1071, 1001, 704; δ_H ($CDCl_3$) 7.30 (5H, m), 4.28 (1H, m, H-4), 4.15 (1H, dd, *J*=11 and 2.5, H-2), 3.29 (1H, H-6), 2.08 (2H, br s, OH and NH), 1.80 (3H, m), 1.46 (1H, dt, *J*=12 and 2), 1.10 (3H, d, *J*=7.0); δ_C (CD_3OD) 145.5 (s), 129.8 (d), 128.5 (d), 128.2 (d), 66.6 (d), 57.1 (d), 48.5 (d), 41.3 (t), 41.2 (t), 22.4 (q); HRMS (EI) found: 191.1317; $C_{12}H_{17}NO$ requires: 191.1310.

4.16. (−)-(2S,4R,6S)-6-Methyl-2-phenylpiperidin-4-ol ***32***

To a cold (−78°C) stirred solution of piperidone (−)-**30** (95 mg, 0.5 mmol) in THF (5 mL) was added dropwise L-Selectride® (550 μL of a 1 M solution in THF). After 10 min of stirring at −78°C, methanol (1 mL) was added and the resulting solution was allowed to warm to room temperature. Water (5 mL) was added and the piperidinol was extracted with dichloromethane (4×25 mL). Evaporation of the solvents under reduced pressure, followed by column chromatography (ethyl acetate:methanol, 9:1), gave piperidinol (−)-**32** (92 mg, 96%), exclusively, as a white solid. Mp=114°C; R_f 0.59 (ethyl acetate:methanol, 1:1); $[\alpha]_D^{25}$=−33.8 (*c* 0.82, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3251, 1086, 1036, 756, 698; δ_H ($CDCl_3$) 7.28 (5H, m), 3.75 (1H, m, H-4), 3.65 (1H, dd, *J*=11 and 2.5, H-2), 2.84 (1H, H-6), 2.15 (2H, br s, OH and NH), 2.08 (1H, m), 1.97 (1H, m), 1.45 (1H, q, *J*=11.5), 1.14 (4H, m); δ_C ($CDCl_3$) 143.9 (s), 128.4 (d), 127.2 (d), 126.7 (d), 69.3 (d), 59.7 (d), 50.7 (d), 43.2 (t), 43.0 (t), 22.3 (q).

4.17. (−)-(2S,6S)-1-Aza-6-methyl-2-phenyl-1′,3′-dithiaspiro[5.4]decane ***33***

To a stirred solution of protected piperidone (−)-**22** (250 mg, 1 mmol) in dichloromethane (10 mL) was added dropwise, at room temperature, ethanedithiol (5 equiv.) then $BF_3 \cdot Et_2O$ (5 equiv.). After 1 h of stirring, an excess of 2 M aqueous NaOH was added and the resulting mixture was extracted with dichloromethane (4×20 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate:methanol, 9:1), gave protected piperidone (−)-**33** as a colourless oil (241 mg, 91%). R_f 0.79 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$=−1.9 (*c* 0.9, $CHCl_3$); δ_H ($CDCl_3$) 7.31 (5H, m), 3.91 (1H, dd, *J*=11 and 2, H-2), 3.34 (4H, m), 3.04 (1H, m, H-6), 2.22 (1H, td, *J*=12 and 2, H-3eq), 2.13 (1H, td, *J*=12 and 2, H-5eq), 2.05 (1H, t, *J*=12, H-3ax), 1.80 (1H, t, *J*=12, H-5ax), 1.60 (1H, br s, NH), 1.14 (3H, d, *J*=7.0). This unstable compound was directly engaged in the next step.

4.18. (−)-(2S,6S)-6-Methyl-2-phenylpiperidine ***34***

To a stirred solution of protected piperidone (−)-**33** (132 mg, 0.5 mmol) in absolute ethanol (10 mL) was added freshly prepared W2 Raney nickel[16] (500 mg). The resulting suspension was heated at reflux for 30 min then cooled to room temperature. The suspension was then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH and the piperidine was extracted with dichloromethane (4×10 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate:methanol, 5:1), gave piperidine (−)-**34** (86 mg, 98%) as a colourless oil. $[\alpha]_D^{25}$=−21.0 (*c* 0.7, $CHCl_3$) (lit.[8a] $[\alpha]_D^{25}$=22.2 (*c* 0.69, EtOH) for its enantiomer). Spectral data were identical with those recently reported for (+)-**34**.[8a]

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