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A rapid stereoselective access to highly substituted piperidines

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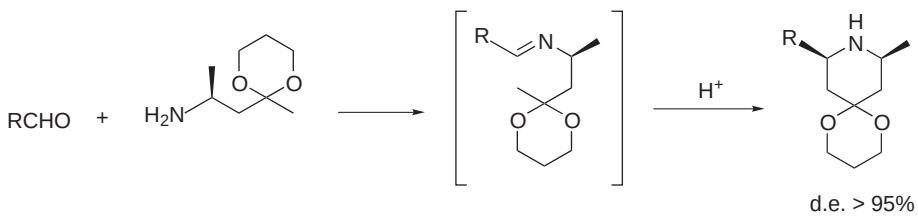
Abstract

An intramolecular Mannich reaction, involving various achiral aldehydes together with an α-chiral amine is employed as the key step for a stereocontrolled synthesis of highly substituted piperidine systems. Accordingly, 12 new piperidines bearing four asymmetric centers were prepared in six steps from commercial ketones. © 2000 Published by Elsevier Science Ltd.

Due to the wide range of potent biological activities associated to piperidine containing alkaloids and non-natural analogs, these compounds constitute important targets for pharmaceutical research.[1] Since this framework is present in very simple structures and in complex ones, including notably those bearing many stereogenic centers, considerable efforts have been devoted to solve the problems of the stereocontrol of mono to highly substituted piperidine systems.[2] Nevertheless, it remains of interest to develop new stereoselective accesses to these skeletons. In this context, we have recently proposed an efficient route to various 2,6-disubstituted piperidines.[3] Our approach, based on the use of diverse achiral aldehydes involved in a Mannich-type reaction[4] with an α-chiral amine, gives the 2,6-*cis*-isomers exclusively (Scheme 1).



Scheme 1.

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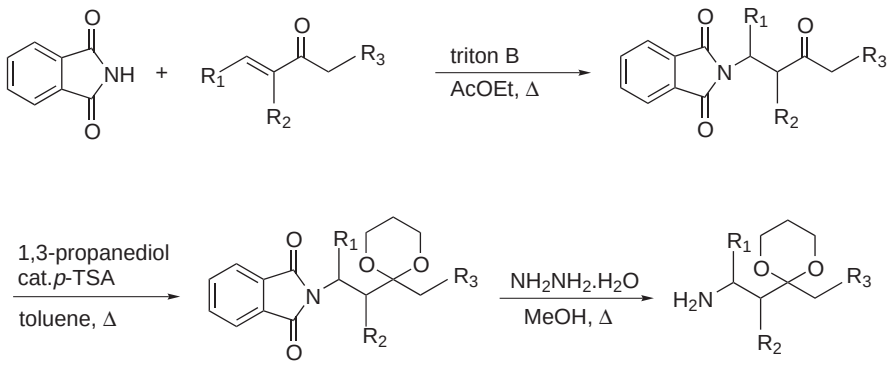
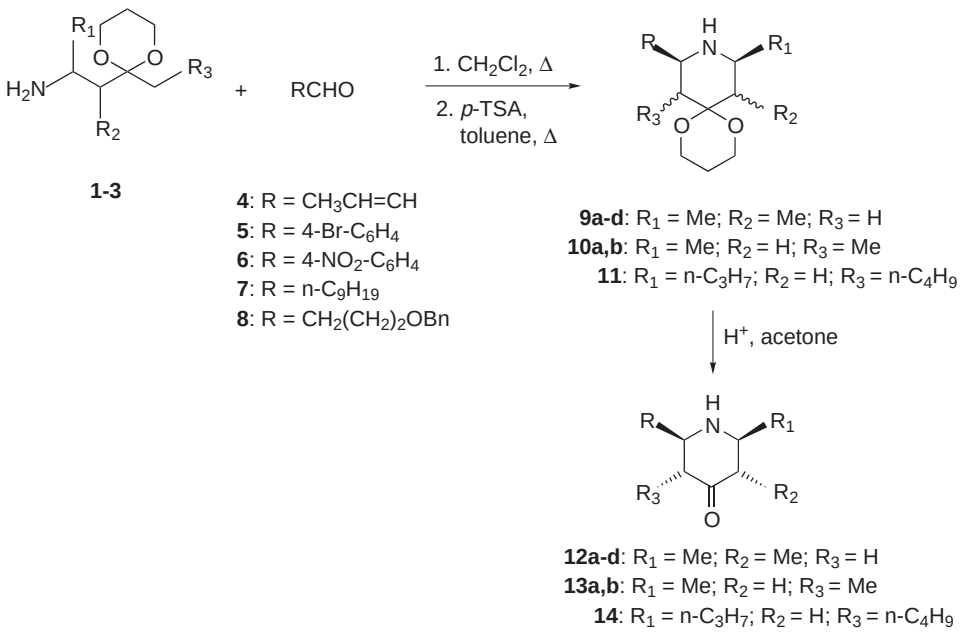
Since we could explain such a diastereoselectivity by the enforced position of the asymmetric center in the transition state,[3] we wished to extend this approach to the selective synthesis of higher substituted piperidine systems from more substituted amines, such as **1**, **2** and **3**, still bearing a chiral center at the crucial α-position. Thus, racemic amines **1** (1:1 diastereoisomeric mixture), **2** and **3** were conveniently prepared, in 50, 60 and 55% overall yield, respectively, following the conventional three steps synthesis[5] summarized in Scheme 2.



1: R_1 = Me; R_2 = Me; R_3 =H
2: R_1 = Me; R_2 = H; R_3 = Me
3: R_1 = n-C_3H_7; R_2 = H; R_3 = n-C_4H_9

Scheme 2.



1-3

4: R = CH_3CH=CH
5: R = 4-Br-C_6H_4
6: R = 4-NO_2-C_6H_4
7: R = n-C_9H_{19}
8: R = $CH_2(CH_2)_2OBn$

9a-d: R_1 = Me; R_2 = Me; R_3 = H
10a,b: R_1 = Me; R_2 = H; R_3 = Me
11: R_1 = n-C_3H_7; R_2 = H; R_3 = n-C_4H_9

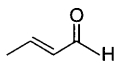
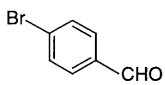
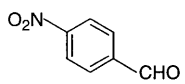
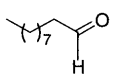
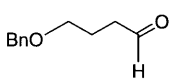
12a-d: R_1 = Me; R_2 = Me; R_3 = H
13a,b: R_1 = Me; R_2 = H; R_3 = Me
14: R_1 = n-C_3H_7; R_2 = H; R_3 = n-C_4H_9

Scheme 3.

Crude amines **1–3** were then directly engaged in the one-pot cyclisation procedure with aliphatic, ethylenic and aromatics aldehydes **4–8**. In all cases, the formation of the expected piperidines **9a–d**, **10a**,**b** and **11** occurred. Even if a mixture of epimers was always obtained, it has to be noted that only a 2,6-*cis*-substitution (NMR data) was achieved, confirming here the key role of the α-amino chiral center in the stereochemical behavior of the cyclisation (Scheme 3). We have also noticed that ratios of epimers of **9a–d**, **10a**,**b** and **11** could obviously evolve depending on some parameters such as reaction time and amount (1.2–2 equiv.) of *para*-toluenesulfonic acid. Then, we decided to deprotect the keto function of **9a–d**, **10a**,**b** and **11** under acidic conditions in order to prepare the parent 4-piperidones. Thus, epimeric mixtures of **9a–d**, **10a**,**b** and **11** were treated with 6% hydrochloric acid in acetone[6a] for several days at room temperature.

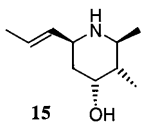
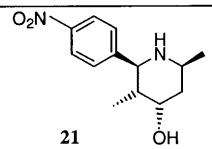
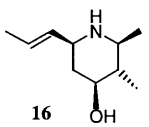
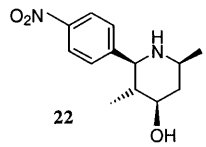
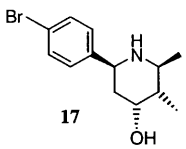
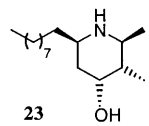
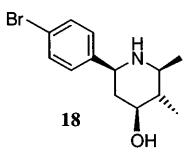
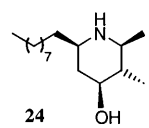
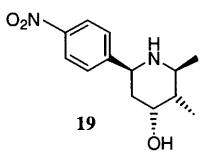
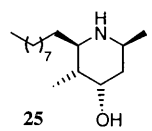
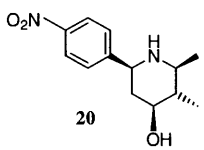
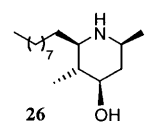
In each case, only one epimer was cleanly and efficiently (80–90% yield) isolated (Table 1). Confirmation of the pseudo equatorial position of the three substituents of 4-piperidones **12a–d**, **13a**,**b** and **14** was unambiguously obtained from the ^{1}H NMR data.

Table 1
Formation of piperidones **12a–d**, **13a**,**b** and **14** from amines **1–3** and aldehydes **4–8**

Amine	Aldehyde	Product	R_1	R_2	R_3	Overall Yield (%)
1	 **4**	**12 a**	CH_3	CH_3	H	49
1	 **5**	**12 b**	CH_3	CH_3	H	54
1	 **6**	**12 c**	CH_3	CH_3	H	59
2	**6**	**13 a**	CH_3	H	CH_3	52
1	 **7**	**12 d**	CH_3	CH_3	H	49
2	**7**	**13 b**	CH_3	H	CH_3	46
3	 **8**	**14**	$CH_3(CH_2)_2$	H	$CH_3(CH_2)_3$	42

Finally, and as we wished to prepare four asymmetric centers containing piperidines, compounds **12a–d** and **13a,b** were submitted to L-Selectride® and sodium borohydride, reducing agents prone to give opposite attacks on cyclanones. Compounds obtained by reduction of **12a–d** and **13a,b** are listed in Table 2. Tetrasubstituted 4-piperidinols **15–26** were obtained in 65–90% yield. As expected,[6] in all cases the use of L-Selectride® at −78°C in dry THF afforded the axial piperidinol (Table 2) as sole product (the other epimer was not detected from NMR spectra) while the equatorial isomer (Table 2) was stereoselectively (d.e. ca. 80%) obtained by treatment with $NaBH_4$ at room temperature in methanol. The relative configurations of each compounds **15–26** were unambiguously established from the ^1H NMR spectra.[7]

Table 2
Stereoselective reductions of piperidones **12a–d** and **13a,b**

Piperidones	Reducing agent[a]	Product	Yield[b] (d.e.) (%)	Piperidones	Reducing agent[a]	Product	Yield[b] (d.e.) (%)
12 a	A	 **15**	75 (>95)	**13 a**	A	 **21**	84 (>95)
12 a	B	 **16**	65 (79)	**13 a**	B	 **22**	80 (80)
12 b	A	 **17**	80 (>95)	**12 d**	A	 **23**	79 (>95)
12 b	B	 **18**	75 (80)	**12 d**	B	 **24**	70 (79)
12 c	A	 **19**	90 (>95)	**13 b**	A	 **25**	73 (>95)
12 c	B	 **20**	85 (81)	**13 b**	B	 **26**	70 (79)

[a]Reducing agents: A = L-Selectride®; B = $NaBH_4$. [b]Isolated yields.

In conclusion, we have described herein a rapid and efficient stereoselective access to highly substituted piperidines. Twelve piperidines bearing four asymmetric centers were prepared in six steps from readily available ketones. Furthermore, we could demonstrate here that this strategy should allow a facile stereoselective access to skeletons containing five asymmetric centers, in three steps, starting from amine of type **1**–**3** in which R_1, R_2 and R_3 are different from H.

As we could verify through the enantioselective synthesis of 2,6-disubstituted and 2,4,6-trisubstituted piperidine alkaloids[6b] that the conditions used here induce no racemization, we assume that non racemic amines such as **1**, **2** or **3** containing only one optically pure chiral center (those bearing the amino group) will allow the enantioselective preparation of tetra- to penta-substituted piperidines. In order to verify this purpose, efforts are currently devoted to the enantioselective synthesis of these amines which will be used in the elaboration of complex piperidine alkaloids.

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7. Selective data for the respecting compounds **15**–**26**
   Axial piperidinols: ^{1}H NMR (400 MHz, $CDCl_3$): **15** δ: 5.60 (dq, 1H, J=15.0, 6.5 Hz), 5.43 (ddd, 1H, J=15.0, 7.0, 1.5 Hz), 3.87–3.83 (m, 1H, H-4), 3.55–3.48 (m, 1H, H-2), 2.83–2.75 (m, 1H, H-6), 1.78 (dt, 1H, J=13.5, 3.0 Hz), 1.73 (br s, 2H), 1.64 (d, 3H, J=7.0 Hz), 1.49 (td, 1H, J=12.0, 3.0 Hz), 1.31–1.22 (m, 1H), 1.04 (d, 3H, J=6.5 Hz), 0.94 (d, 3H, J=7.0 Hz). **17** (400 MHz, CD_3OD) δ: 7.67 (d, 2H, J=8.5 Hz), 7.51 (d, 2H, J=8.5 Hz), 5.03 (br s, 2H), 4.35 (dd, 1H, H-2, J=12.0, 3.0 Hz), 4.12–4.08 (m, 1H, H-4), 3.21–3.13 (m, 1H, H-6), 2.12 (dt, 1H, J=13.5, 3.0 Hz), 2.01 (td, 1H, J=12.0, 3.0 Hz), 1.66–1.56 (m, 1H), 1.32 (d, 3H, J=6.5 Hz), 1.19 (d, 3H, J=7.0 Hz). **19** δ: 8.14 (d, 2H, J=8.5 Hz), 7.57 (d, 2H, J=8.5 Hz), 4.28 (dd, 1H, H-2, J=12.0, 4.0 Hz), 3.93–3.89 (m, 1H, H-4), 3.00–2.90 (m, 1H, H-6), 1.95 (dt, 1H, J=13.5, 3.0 Hz), 1.87 (br s, 2H), 1.69 (td, 1H, J=12.0, 2.5 Hz), 1.47–1.37 (m, 1H), 1.10 (d, 3H, J=6.0 Hz), 1.00 (d, 3H, J=6.5 Hz). **21** δ: 8.19 (d, 2H, J=8.5 Hz), 7.59 (d, 2H, J=8.5 Hz), 4.03–3.99 (m, 1H, H-4), 3.87 (d, 1H, H-2, J=10.5 Hz), 3.33–3.23 (m, 1H, H-6), 1.87 (dt, 1H, J=13.5, 3.0 Hz), 1.77–1.68 (m, 1H), 1.65 (br s, 2H), 1.55 (td, 1H, J=11.5, 2.5 Hz), 1.09 (d, 3H, J=6.0 Hz), 0.70 (d, 3H, J=7.0 Hz). **23** δ: 3.88–3.83 (m, 1H, H-4), 2.97–2.88 (m, 1H, H-2), 2.79–2.70 (m, 1H, H-6), 1.82 (dt, 1H, J=13.5, 3.0 Hz), 1.65 (br s, 2H), 1.23–1.34 (m, 18H), 1.05 (d, 3H, J=6.0 Hz), 0.95 (d, 3H, J=7.0 Hz), 0.87 (t, 3H, J=6.5 Hz). **25** δ: 3.87–3.81 (m, 1H, H-4), 3.11–3.01 (m, 1H, H-6), 2.66–2.58 (m, 1H, H-2), 1.76 (dt, 1H, J=13.5, 3.0 Hz), 1.72 (br s, 2H), 1.58–1.51 (m, 1H), 1.18–1.41 (m, 17H), 1.06 (d, 3H, J=6.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 0.86 (t, 3H, J=6.5 Hz).

Equatorial piperidinols: ^{1}H NMR (400 MHz, $CDCl_3$): **16** δ: 5.60 (dq, 1H, $J=15.0$, 6.5 Hz), 5.45 (ddd, 1H, $J=15.0$, 7.0, 1.5 Hz), 3.27–3.13 (m, 2H, H-4 and H-2), 2.44–2.33 (m, 1H, H-6), 2.04–1.91 (m, 3H), 1.67 (d, 3H, $J=6.0$ Hz), 1.30 (q, 1H, $J=11.5$ Hz), 1.13 (d, 3H, $J=6.0$ Hz), 1.10–1.03 (m, 1H), 1.01 (d, 3H, $J=6.0$ Hz). **18** δ: 7.45 (d, 2H, $J=8.5$ Hz), 7.26 (d, 2H, $J=8.5$ Hz), 3.71 (dd, 1H, H-2, $J=11.5$, 2.5 Hz), 3.39–3.30 (m, 1H, H-4), 2.55–2.47 (m, 1H, H-6), 2.11–2.05 (m, 1H), 1.74 (br s, 2H), 1.52 (q, 1H, $J=11.5$ Hz), 1.21–1.15 (m, 4H), 1.05 (d, 3H, $J=6.5$ Hz). **20** δ: 8.19 (d, 2H, $J=8.5$ Hz), 7.58 (d, 2H, $J=8.5$ Hz), 3.89 (dd, 1H, H-2, $J=11.5$, 2.5 Hz), 3.43–3.35 (m, 1H, H-4), 2.58–2.50 (m, 1H, H-6), 2.16–2.09 (m, 1H), 1.61 (br s, 2H), 1.51 (q, 1H, $J=11.5$ Hz), 1.21–1.19 (m, 4H), 1.07 (d, 3H, $J=6.5$ Hz). **22** δ: 8.19 (d, 2H, $J=8.5$ Hz), 7.56 (d, 2H, $J=8.5$ Hz), 3.42–3.32 (m, 2H, H-2 and H-4), 2.95–2.84 (m, 1H, H-6), 2.16 (br s, 2H), 2.05–1.99 (m, 1H), 1.54–1.47 (m, 1H), 1.33 (q, 1H, $J=11.5$ Hz), 1.13 (d, 3H, $J=6.0$ Hz), 0.75 (d, 3H, $J=7.0$ Hz). **24** δ: 3.24–3.16 (m, 1H, H-4), 2.64–2.55 (m, 1H, H-2), 2.39–2.30 (m, 1H, H-6), 2.04–1.80 (m, 3H), 1.45–1.35 (m, 2H), 1.36–1.22 (m, 15H), 1.13 (d, 3H, $J=6.0$ Hz), 1.10–1.03 (m, 1H), 1.00 (d, 3H, $J=6.0$ Hz), 0.87 (t, 3H, $J=6.5$ Hz). **26** δ: 3.21–3.12 (m, 1H, H-4), 2.73–2.64 (m, 1H, H-6), 2.19 (td, 1H, H-2, $J=9.0$, 2.5 Hz), 2.01–1.83 (m, 3H), 1.66–1.56 (m, 1H), 1.41–1.21 (m, 16H), 1.12–1.03 (m, 4H), 0.97 (d, 3H, $J=6.5$ Hz), 0.86 (t, 3H, $J=6.5$ Hz).