Enantioselective Ring Expansion of Prolinols: An Efficient and Short Synthesis of 2-Phenylpiperidin-3-ol Derivatives and 3-Hydroxypipecolic Acids

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Abstract: A very short route to 2-phenylpiperidin-3-ol derivatives and 3-hydroxypipecolic acids is described. The approach uses two key steps: a one-pot reduction/Grignard addition sequence applied to alkyl proline esters and a ring expansion applied to the corresponding prolinols.

Key words: reduction, Grignard addition, aziridinium, ring expansion, 2-phenylpiperidin-3-ols, 3-hydroxypipecolic acids

Functionalized chiral piperidines are present in a great variety of natural products and synthetic compounds with important biological activity.[1] For our part, we were interested in the synthesis of 2-substituted piperidin-3-ols, as these compounds are frequently encountered in living systems due to their ability to mimic carbohydrates in a variety of enzymatic processes.[2] 2-Phenylpiperidin-3-ols **A**, which are precursors of non-peptidic NK-1 receptor antagonists such as **I**[3] and **II**,[4] have a *cis*-relationship between the phenyl and the ether group on the piperidine ring, and are important for high-affinity binding to the human NK-1 receptor (Figure 1).[5] Furthermore, 3-hydroxypipecolic acids **B** are also of importance as they are attractive chiral building blocks for the synthesis of biologically active natural products such as tetrazomine **III**, which possesses antitumor and antibiotic properties.[6] These compounds can be considered as ring-expanded homologues of prolinols or constrained analogues of serine, which permit their use in conformational and ligand-binding studies involving bioactive peptides and peptidomimetics (Figure 1).[7]

Various synthetic strategies have been reported for the synthesis of compounds of type **I**, **II** and **B** using, for example, resolution techniques or asymmetric synthesis.[8–10] In the course of our studies on the synthesis and applications of optically active 3-hydroxypiperidines via a ring expansion of prolinols,[11,12] we were interested in the ring expansion of prolinols **C** in order to produce 2-phenylpiperidin-3-ols **A** (Scheme 1).

After the recent publication by O'Brien et al.[13a] of the asymmetric synthesis of piperidines from pyrrolidines, we would like to disclose our very short route to 2-phenylpiperidin-3-ols **A** and 3-hydroxypipecolic acids **B** using the ring expansion of prolinols **C**. As these prolinols can be synthesized from either L-proline or D-proline, all the stereoisomers of 3-hydroxypipecolic acids should be attainable using this methodology (Scheme 1).

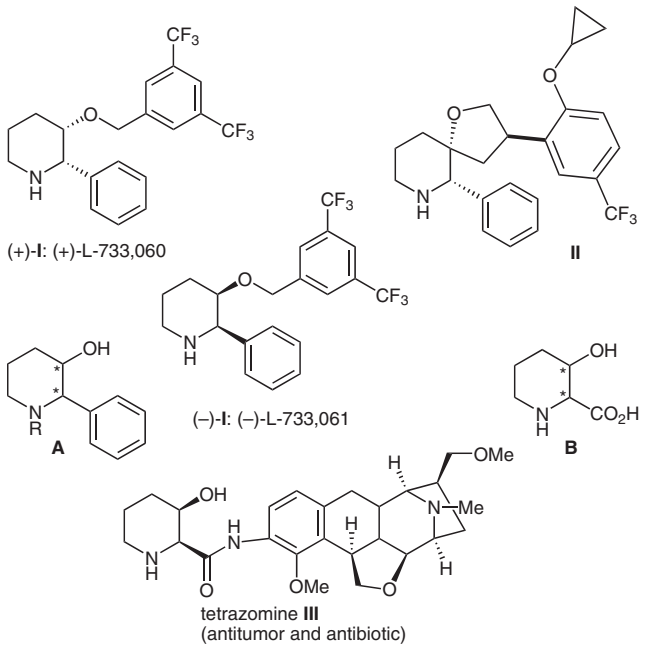

Figure 1

Access to optically active prolinols **C** was achieved either from the commercially available *N*-Boc-L-proline methyl ester (**1a**) or from *N*-benzyl-L-proline ethyl ester (**1b**) in a one-pot reaction.[14a–14c] These two compounds were transformed into the corresponding amino alcohols **2a/3a** and **2b/3b**, respectively, using DIBAL-H followed by the addition of phenylmagnesium bromide (CH_2Cl_2, –78 °C → r.t.).[15] In the case of *N*-Boc proline ester **1a**, the ratio **2a/3a** was excellent (99:1).[14d] In contrast, in the case of *N*-benzyl proline ester **1b** a 1:1 ratio of **2b/3b** was observed. The diastereomers **2a** and **3a** as well as **2b** and **3b** could be separated by flash chromatography on silica gel (Scheme 2).[13a]

As reported by one of us,[14c] the excellent diastereoselectivity obtained in the transformation of **1a** into **2a** and **3a**, can be explained by the formation of aluminoxyacetal intermediates **R1** and **R2**, in which the aluminum atom is coordinated to the most basic oxygen atom of the *N*-Boc

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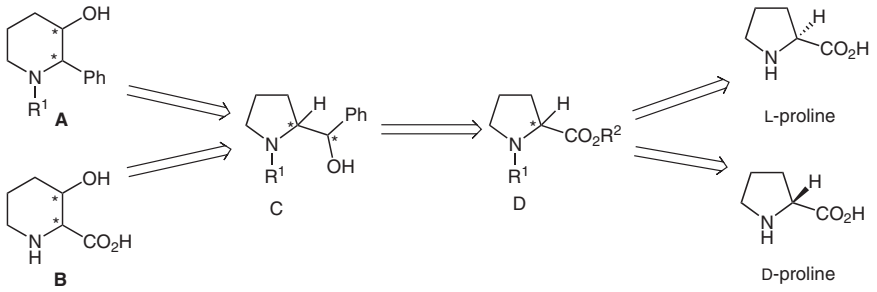
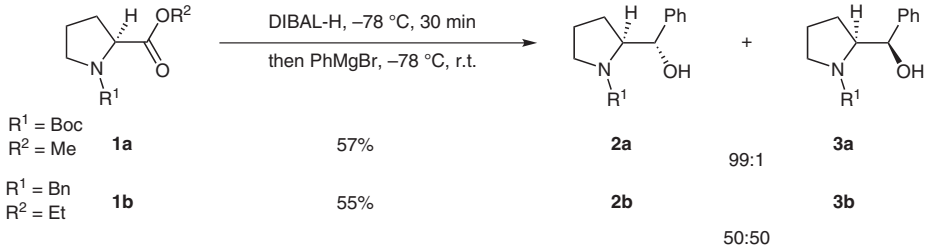
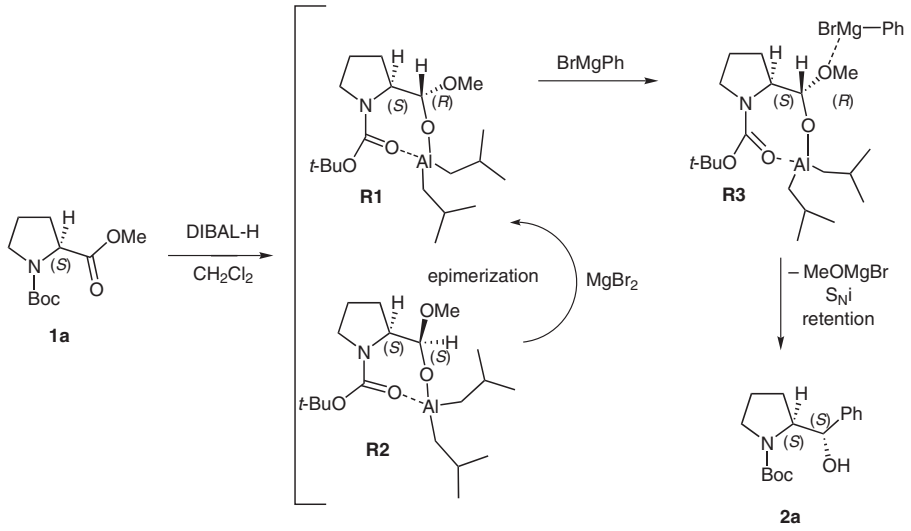


Scheme 1



Scheme 2



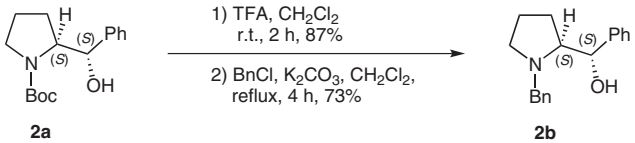
Scheme 3

group (Scheme 3). Due to the presence of $MgBr_2$ in the commercially available Grignard reagent, **R2** epimerizes to **R1**. Indeed, calculations have shown that **R1** is more stable than **R2**.[14c] The aluminoxyacetal **R1** can then undergo a S_Ni reaction with phenylmagnesium bromide, with retention of configuration, to furnish **2a** as the major isomer (Scheme 3).

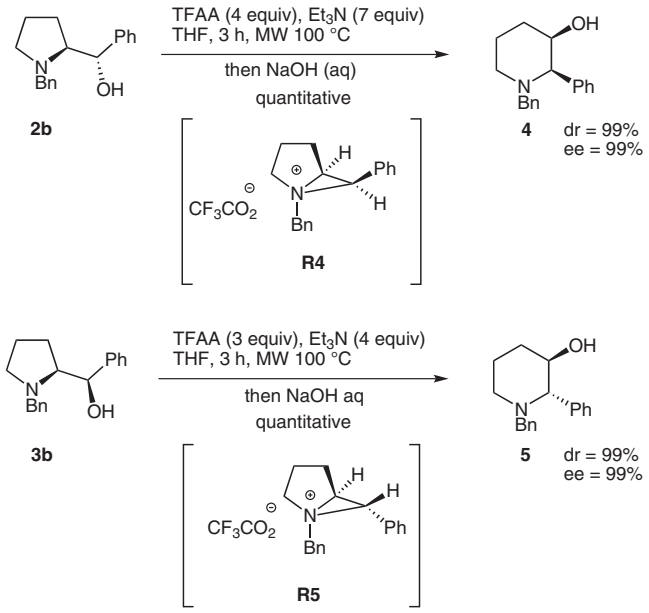
The complexation of the aluminum with the *N*-Boc group was necessary in order to obtain excellent diastereoselectivity, since when an *N*-benzyl group was present in **1b**, no diastereoselectivity was observed.[14c]

We have to point out that **2a** can be converted into **2b** by treatment with TFA (CH_2Cl_2, r.t., 2h) followed by a *N*-benzylation (BnCl, K_2CO_3, CH_2Cl_2, reflux) (Scheme 4).

Having **2b** and **3b** in hand, these products were transformed into 3-hydroxypiperidines **4** and **5** via aziridiniums **R4** and **R5** using our standard conditions e.g. TFAA (3–4 equiv), Et_3N (4–7 equiv), 3 h, 100 °C under microwave (MW) irradiation and then saponification using NaOH.[12] Both compounds **4** and **5** were obtained in quantitative yield with excellent diastereoselectivities (up to 99%) and enantioselectivities (up to 99%) (Scheme 5).[12s,16]



Scheme 4



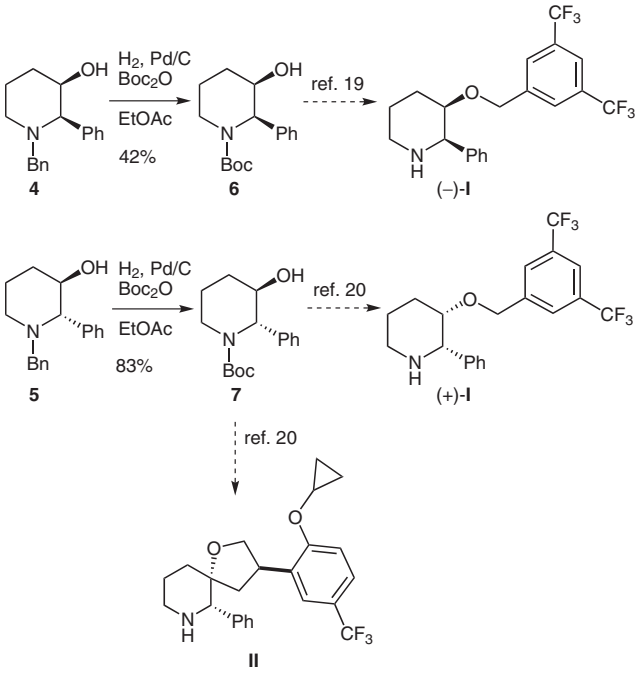
Scheme 5

Thus, compounds of type **C** can be transformed in two steps into compounds of type **A**.[13b,17,18]

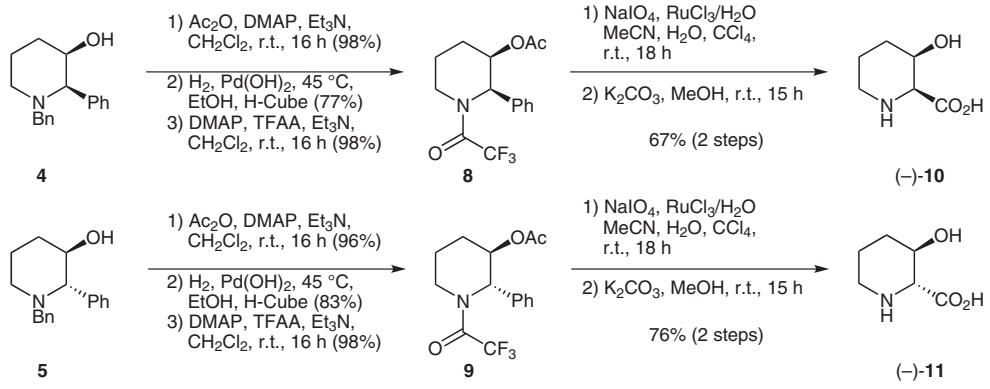
We were able to transform **4** into **6**,[19] which is an intermediate involved in the synthesis of the non-peptidic NK-1 receptor antagonist L-733,061, after hydrogenation in the presence of Boc_2O. Compound **7**,[20] which is an intermediate used in the synthesis of two non-peptidic NK-1 receptor antagonists L-733,060 and spiropiperidine **II**, was obtained from **5** also in a one-pot reaction (H_2, Pd/C, Boc_2O) (Scheme 6).

Furthermore, the substituted piperidin-3-ols **4** and **5** were converted into the corresponding 3-hydroxypipecolic acids (–)-**10** and (–)-**11**, respectively. First, compounds of type **A** (**4** and **5**) were acetylated (Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 98–96%) and, after careful hydrogenation [H_2, $Pd(OH)_2$, H-Cube™ (Thales Nanotechnology Inc.), 45 °C, 77–83%], a trifluoroamidation was achieved (DMAP, TFAA, Et_3N, CH_2Cl_2, r.t., 98%) leading to **8** and **9** in good yields. Treatment of these latter compounds with $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ (CCl_4, MeCN, H_2O, r.t.) followed by saponification (K_2CO_3, MeOH, r.t.) furnished the desired 3-hydroxypipecolic acids (–)-**10** and (–)-**11**, respectively, in 67% and 76% yield (for the two steps) (Scheme 7).[21]

In conclusion, by using a diastereoselective DIBAL-H reduction/Grignard addition sequence and a ring expansion of prolinols, compounds **D** were transformed into 2-phenylpiperidin-3-ols in two steps, which were transformed into 3-hydroxypipecolic acids in five steps. Following the same strategy, 3-hydroxypipecolic acids (+)-**10** and (+)-**11** should be obtained from D-proline. The synthesis of biologically active piperidines using these methodologies is under progress in our laboratory, and the results will be reported in due course.



Scheme 6



Scheme 7

Acknowledgments

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(15) **Ester reduction/alkylation method**: DIBAL-H (1.0 M in hexane, 2.61 mL, 2.61 mmol, 1.2 equiv) was added to a solution of *N*-benzylproline ethyl ester (500 mg, 2.17 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at –78 °C. The resulting solution was stirred at –78 °C for 30 min, followed by the addition of commercially available PhMgBr (1.0 M in THF, 6.52 mL, 6.52 mmol, 3 equiv) dropwise at –78 °C. The solution was then allowed to slowly warm to r.t. overnight. Sat. aq NH_4Cl (10 mL) was added to quench the reaction. Sat. sodium tartrate solution (10 mL) was added to the resulting gel. The mixture was stirred at r.t. for 30 min, then the organic layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a separable mixture of diastereomers **2b** and **3b**, which was purified by flash chromatography (SiO_2; EtOAc–PE, 8:2) to give **2b** as a yellow solid (155 mg, 27.5%) and **3b** as a pale-yellow oil (155 mg, 27.5%).
Compound 2b:[17,20b] R_f = 0.1 (EtOAc–PE, 8:2); mp 93–95 °C; $[\alpha]_D^{20}$ +106 (*c* 1.1, $CHCl_3$). IR (neat): 3017, 1495, 1454 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.20 (m, 10 H), 4.39 (d, *J* = 5.2 Hz, 1 H), 3.67 (d, *J* = 13.0 Hz, 1 H), 3.34 (d, *J* = 13.0 Hz, 1 H), 3.08 (m, 1 H), 2.96 (m, 1 H), 2.40 (m, 1 H), 1.94 (m, 1 H), 1.80–1.71 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.8 (s), 139.5 (s), 128.8 (d), 128.7 (d), 128.6 (d), 128.4 (d), 128.4 (d), 128.3 (d), 128.3 (d), 127.1 (d), 127.0 (d), 126.2 (d), 75.3 (d), 70.2 (d), 61.2 (t), 54.3 (t), 29.4 (t), 24.3 (t). MS: *m/z* (%) = 160 (100)[$M^{+\cdot}$ – $CHOHPh^{\cdot}$], 91 (71) [$PhCH_2^+$].
Compound 3b:[17,20b] R_f = 0.2 (EtOAc–PE, 8:2); $[\alpha]_D^{20}$ –54 (*c* 1, $CHCl_3$). IR (neat): 3620, 2940, 2820, 1496, 1457 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.41–7.19 (m, 10 H), 4.89 (d, *J* = 3.1 Hz, 1 H), 4.18 (d, *J* = 12.7 Hz, 1 H), 3.46 (d, *J* = 12.7 Hz, 1 H), 3.05 (m, 1 H), 2.89 (m, 1 H), 2.33 (dd, *J* = 17, 8.1 Hz, 1 H), 1.73 (m, 1 H), 1.65–1.56 (m, 2 H), 1.32 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.5 (s), 139.1 (s), 128.8 (d), 128.6 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.6 (d), 127.2 (d), 127.0 (d), 126.8 (d), 125.5 (d), 70.2 (d), 69.2 (d), 58.3 (t), 54.7 (t), 24.0 (t), 23.2 (t). MS: *m/z* (%) = 160 (100)[$M^{+\cdot}$ – $CHOHPh^{\cdot}$], 91 (71) [$PhCH_2^+$].

(16) **General procedure for the ring expansion of pyrrolidines to piperidines:** Trifluoroacetic anhydride (3–4 equiv) was added to a stirred solution of *N*-alkyl pyrrolidine (1 equiv) in THF under argon at r.t. and Et_3N (4–7 equiv) was added. The solution was stirred and heated at 100 °C for 3 h under microwave irradiation. The resulting solution was cooled to r.t. and a solution of aqueous 3.75 M NaOH was added. After stirring for 30 min, EtOAc was added and the two layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give the crude product.
Compound 4: Chromatography (SiO_2; EtOAc–PE, 7:3), R_f = 0.33 (EtOAc–PE, 7:3); ee >99% determined by supercritical fluid chromatography on Daicel Chiralpak OD-H column (MeOH 5%, flow rate 5 mL/min, *t* = 3.94 min); $[\alpha]_D^{20}$ –25 (*c* 1.15, $CHCl_3$). IR (neat): 3588, 3016, 2946, 1493, 1454 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.51–7.19 (m, 10 H), 3.87 (d, *J* = 13.6 Hz, 1 H), 3.74 (m, 1 H), 3.34 (d, *J* = 1.7 Hz, 1 H), 3.0 (m, 1 H), 2.88 (d, *J* = 13.6 Hz, 1 H), 2.05–1.89 (m, 3 H), 1.61 (m, 1 H), 1.47 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.1 (s), 139.1 (s), 128.7 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.4 (d), 126.6 (d), 73.9 (d), 72.4 (d), 59.4 (t), 53.4 (t), 31.3 (t), 19.9 (t). MS: *m/z* (%) = 267 (3)[$M^{+\cdot}$], 266 (3), 222 (15), 210 (6), 194 (15), 177 (13), 176 (100) [$M^{+\cdot}$ – $PhCH_2^{\cdot}$], 106 (10), 91 (52) [$PhCH_2^+$].
Compound 5:[17,20b] Chromatography (SiO_2; EtOAc–PE, 8:2), R_f = 0.2 (EtOAc–PE, 8:2); ee >99% determined by supercritical fluid chromatography on Daicel Chiralpak OD-H column (MeOH 5%, flow rate 5 mL/min, t = 4.14 min); mp 139–141 °C; $[\alpha]_D^{20}$ +27 (*c* 1, $CHCl_3$). IR (neat): 3588, 3016, 2946, 1493, 1454 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.55–7.14 (m, 10 H), 3.66 (d, *J* = 13.6 Hz, 1 H), 3.59 (m, 1 H), 2.91 (d, *J* = 8.6 Hz, 1 H), 2.89 (m, 1 H), 2.83 (d, *J* = 13.6 Hz, 1 H), 2.09 (m, 1 H), 1.93 (m, 1 H), 1.70–1.60 (m, 2 H), 1.38 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.1 (s), 139.6 (s), 128.8 (d), 128.7 (d), 128.6 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.6 (d), 126.9 (d), 126.7 (d), 76.0 (d), 73.9 (d), 59.3 (t), 52.4 (t), 32.5 (t), 23.3 (t). MS: *m/z* (%) = 267 (3)[$M^{+\cdot}$], 266 (3), 222 (15), 210 (6), 194 (15), 177 (13), 176 (100) [$M^{+\cdot}$ – $PhCH_2^{\cdot}$], 106 (10), 91 (52) [$PhCH_2^+$].

(17) Langlois et al. have shown that the ring expansion of substituted pyrrolidinols **3b** using TFAA (1.5 equiv), Et_3N (3 equiv), in refluxing THF for 44 h, led to the ring-expanded compound **5** in 22% yield, together with the starting material, see: Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, *39*, 9447.

(18) For a related rearrangement under different conditions, see: Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223.

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