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A Facile Synthesis of New Homochiral β-Amino Alcohols with Norbornane Framework

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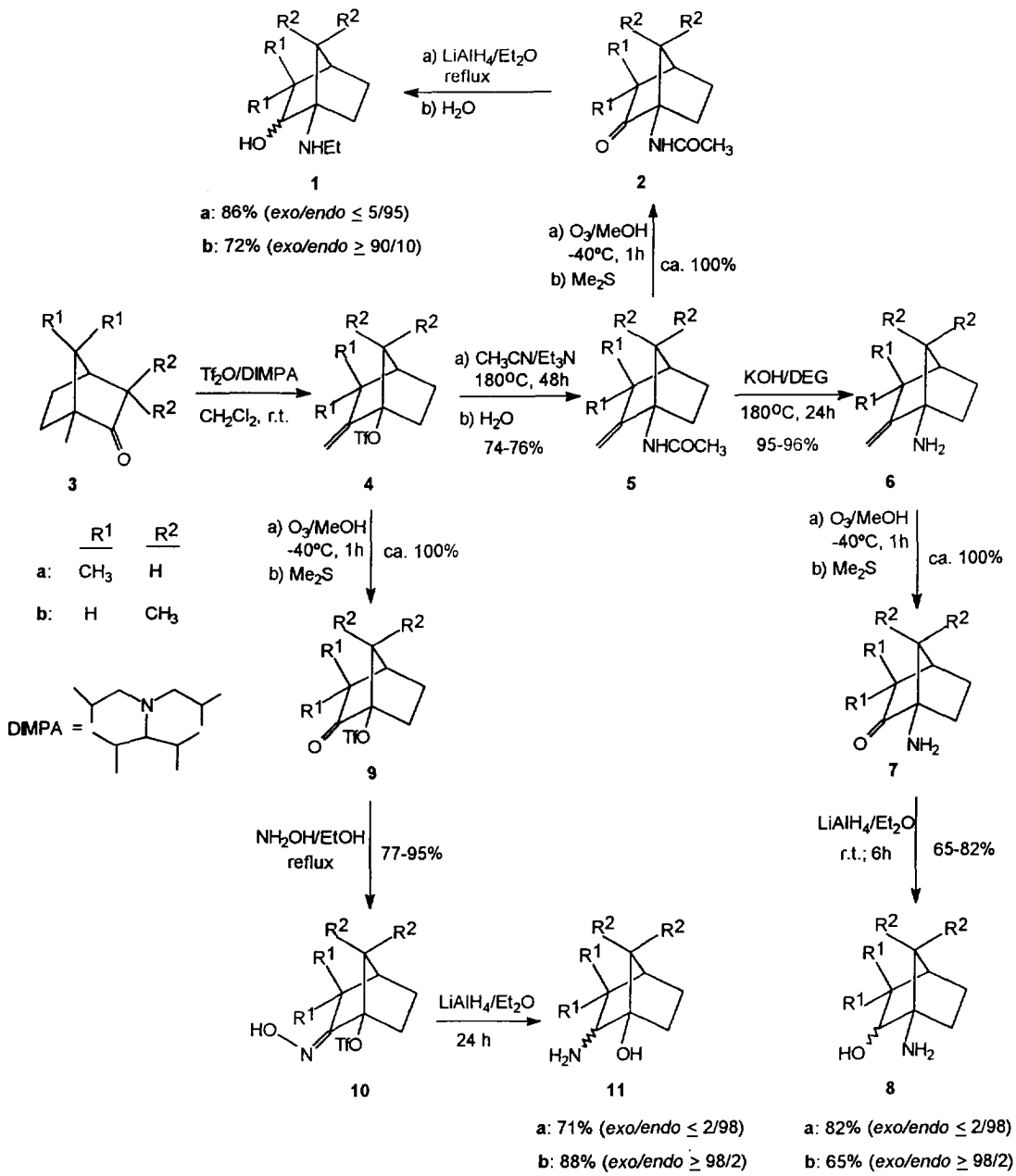
Abstract: New homochiral 1,2-amino hydroxy derivatives of norbornane are easily prepared starting from naturally occurring 2-norbornanones.

Homochiral β-amino alcohols are becoming increasingly important due to their potential application in different fields. The 1,2-aminoalcohol moiety is present in many important natural products and drugs,[1] and has a high relevance in the development of new enzyme inhibitors.[2] Moreover, β-amino alcohols have an enormous potential in asymmetric transformations as chiral ligands in metal-mediated organic reactions,[3] where the stiffness of the chiral intermediate complex plays an important role in order to increase the reactivity of the system.[4] Thus, sterically hindered 2-amino-3-hydroxynorbornanes have been successfully used as chiral ligands in many reactions.[1,3,5]

In continuation of our work on the enantiospecific synthesis of homochiral ligands from naturally occurring 2-norbornanones **3**,[6] we report here on the synthesis of the new homochiral β-amino alcohols **1** and **11**, as well as an alternative for the synthesis of the known amino alcohols **8** (Scheme).[7,8] The reaction of (+)-camphor **3a** or (-)-fenchone **3b** with triflic anhydride (Tf_2O) and DIMPA in CH_2Cl_2 at room temperature gives the homochiral bridgehead triflates **4a** or **4b** in good yields.[9] The key step in the preparation of β-amino alcohols **1** and **8** consists in the solvolysis of the triflate **4** in CH_3CN/Et_3N by heating at 180°C for 48h in a sealed tube; this new variation of the Ritter reaction[10] affords the 1-acetylaminonorbornanes **5** in good yields.


a) LiAlH4/Et2O
reflux
b) H2O
1
2
a: 86% (exo/endo ≤ 5/95)
b: 72% (exo/endo ≥ 90/10)
a) O3/MeOH
-40°C, 1h
b) Me2S
ca. 100%
Tf2O/DIMPA
CH2Cl2, r.t.
a) CH3CN/Et3N
180°C, 48h
b) H2O
74-76%
KOH/DEG
180°C, 24h
95-96%
3
4
5
6
a: R1 = CH3, R2 = H
b: R1 = H, R2 = CH3
DIMPA =
a) O3/MeOH
-40°C, 1h
b) Me2S
ca. 100%
9
7
NH2OH/EtOH
reflux
77-95%
LiAlH4/Et2O
r.t.; 6h
65-82%
LiAlH4/Et2O
24 h
10
11
8
a: 71% (exo/endo ≤ 2/98)
b: 88% (exo/endo ≥ 98/2)
a: 82% (exo/endo ≤ 2/98)
b: 65% (exo/endo ≥ 98/2)

Scheme 1

The hydrolysis of **5** followed by ozonolysis of the hydrochloride of the formed bridgehead amines **6** affords the amino ketones **7**, whose diastereoselective reduction with $LiAlH_4$ furnishes the homochiral β-amino alcohols *endo*-**8a** or *exo*-**8b**. The secondary β-amino alcohols *endo*-**1a** or *exo*-**1b** were obtained straightforwardly by ozonolysis of the amides **5** followed by reduction with $LiAlH_4$ in boiling ether. Finally the β-amino alcohols *endo*-**11a** or *exo*-**11b** were prepared by reduction of the oximes **10**[11,12] with $LiAlH_4$.

The products were identified by IR, ^{1}H- and ^{13}C-NMR and mass spectral data.[13] The indicated yields are of isolated products, and all of the amino alcohols were purified by crystallization of the corresponding hydrochlorides in methanol/ether. The d.e. of **1**, **8** and **11** were determinated by ^{1}H-NMR.

In summary, we have presented a facile and convenient method for the preparation of new homochiral β-amino alcohols with rigid structures, which are very promising chiral ligands. The high diastereofacial selectivity of the $LiAlH_4/Et_2O$ reductions of the amino ketones **2** and **7** and the oximes **10** are noteworthy. It is still higher than the reported in the cases of camphenilonoxime[11] and **3a**,[14] which can be accounted for by Cram's rigid model.[15]

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13) Specific rotations and ^{13}C-NMR (75 MHz; TMS) spectra of the synthesized products: (-)-**2a**: ^{13}C-NMR ($CDCl_3$): δ 217.7, 169.7, 68.3, 45.9, 43.0, 38.0, 26.1, 23.9, 23.6, 23.4, 21.3. $[\alpha]_D^{20}$ = -35.8 (c=1.05, MeOH). (-)-**2b**: s. lit.[16] $[\alpha]_D^{20}$ = -29.5 (c=0.46, MeOH). (+)-**5a**: s. lit.[10] $[\alpha]_D^{20}$ = +22.1 (c=1.54, MeOH). (+)-**5b**: ^{13}C-NMR ($CDCl_3$): δ 170.5, 153.4, 102.9, 69.7, 48.0, 41.8, 35.9, 30.3, 27.6, 24.3, 19.2, 18.9. $[\alpha]_D^{20}$ = +86.0 (c=0.79, MeOH). (+)-**6a**: s. lit.[17] (+)-**6b**: ^{13}C-NMR ($CDCl_3$): δ 157.3, 101.2, 67.8, 46.6, 42.2, 35.9, 34.1, 27.2, 18.6, 18.2. $[\alpha]_D^{20}$ = +18.6 (c=0.79, MeOH). *endo*-(-)-**1a**: ^{13}C-NMR ($CDCl_3$): δ 80.5, 70.6, 45.9, 38.6, 38.3, 36.9, 30.8, 25.5, 22.5, 20.6, 16.0. $[\alpha]_D^{20}$ = -22.1 (c=0.60, hydrochloride, MeOH). *exo*-(+)-**1b**: ^{13}C-NMR ($CDCl_3$): δ 73.0, 68.3, 46.4, 43.4, 39.5, 38.3, 29.2, 27.0, 20.6, 20.1, 16.4. $[\alpha]_D^{20}$ = +12.9 (c=0.81, hydrochloride, MeOH). *endo*-(-)-**8a**: s. lit.[7] ^{13}C-NMR ($CDCl_3$): δ 83.6, 66.2, 46.4, 41.8, 38.8, 30.8, 26.0, 25.9, 20.6. $[\alpha]_D^{20}$ = -12.1 (c=0.78, MeOH). *exo*-(-)-**8b**: s. lit.[8] $[\alpha]_D^{20}$ = -16.8 (c=1.08, CH_2Cl_2). *endo*-(-)-**11a**.HCl: ^{13}C-NMR (CD_3OD): δ 89.1, 73.7, 53.5, 49.6, 47.7, 41.2, 34.3, 32.8, 30.7. $[\alpha]_D^{20}$= -16.0 (c=0.94, MeOH). *exo*-(+)-**11b**.HCl: ^{13}C-NMR (CD_3OD): δ 81.9, 57.6, 47.2, 42.5, 36.3, 34.4, 27.5, 20.3, 19.8. $[\alpha]_D^{20}$ = +25.8 (c=1.0, MeOH).

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