Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 5, pp. 1257-1260, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00136-X

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

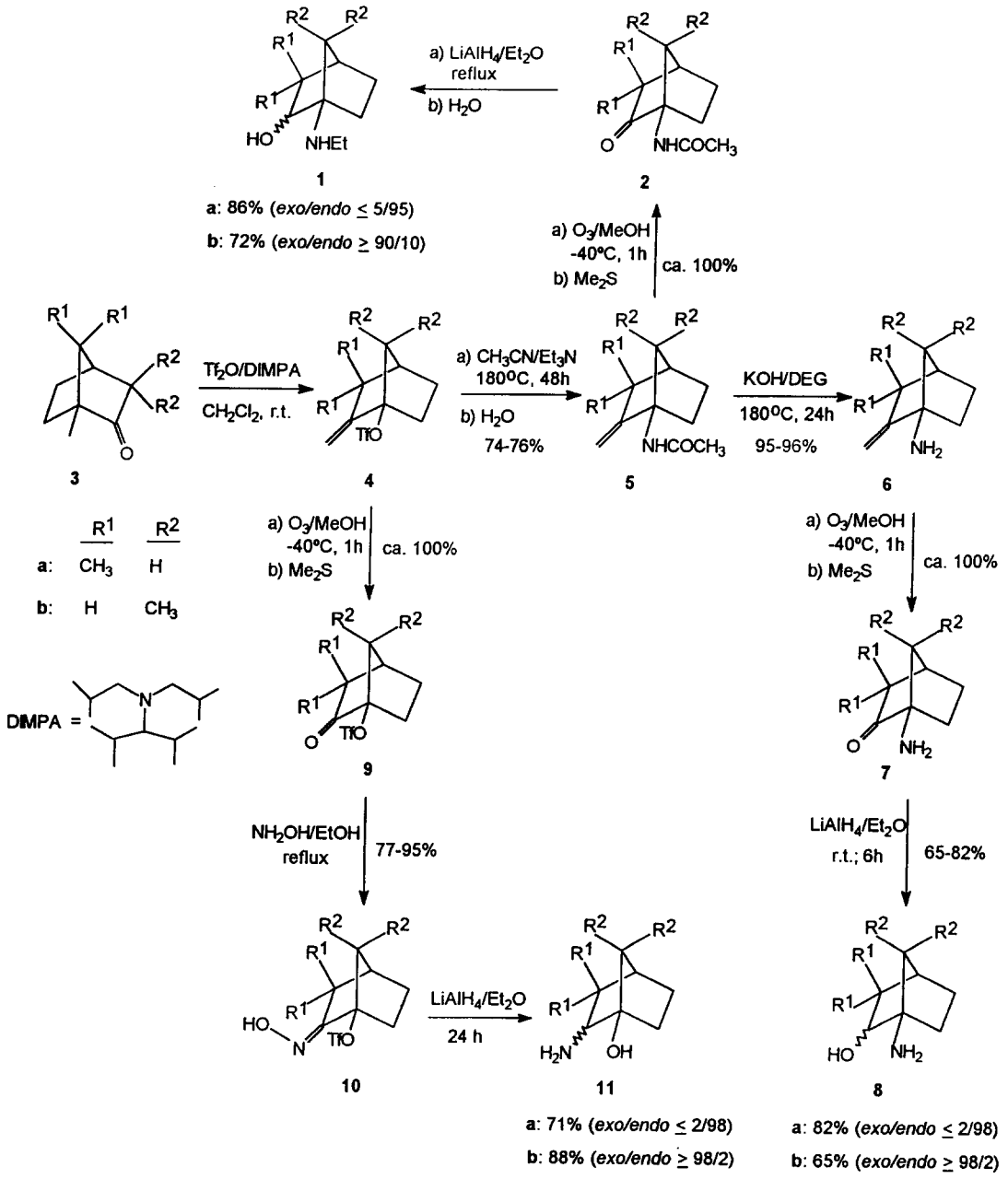
A. García Martínez*[a], E. Teso Vilar[b], A. García Fraile[b], S. de la Moya Cerero[a], P. Martínez Ruiz[a] and L. R. Subramanian[c]

[a]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain; [b]Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Ciudad Universitaria, 28040 Madrid, Spain; [c]Institut für Organische Chemie der Universität, Auf der Morgenstelle 18, D-72076 Tübingen, Germany.

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

Acknowledgment. We thank the DGCICYT (Spain) for financial support of this work (Grant PB 91-0354). S. de la M.C. and P. M. R. thank the Ministerio de Educación y Ciencia and Universidad Complutense de Madrid, respectively, for a fellowship.

References and notes

1) For reviews see: (a) Reetz, M. T. *Angew. Chem. Int., Ed. Engl.* **1991**, *30*, 1531; (b) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360; (c) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241.

2) Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219.

3) For reviews see: (a) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

4) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

5) For recent examples see: (a) Aboulhoda, S. J.; Létinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1865; (b) Tanaka, K.; Osuga, H.; Shogase, Y.; Suzuki, H. *Tetrahedron Lett.* **1995**, *36*, 915; (c) Goralski, C. T.; Hasha, D. L.; Nicholson, L. W.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 5165; (d) Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1175.

6) Martínez, A. G.; Teso, E.; García, A.; de la Moya, S.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1373.

7) Ebisu, K.; Batty, L. B.; Higaki, J. M.; Larson, H. O. *J. Am. Chem. Soc.* **1965**, *87*, 1399.

8) Yan, T. H.; Tan, C. W.; Lee, H. C.; Lo, H. C.; Huang, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.

9) Martínez, A.G.; Teso, E.; Osío, J.; Manrique, J.; Rodríguez, E.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 607.

(*Received in UK* 4 *March* 1996)

10) Martínez, A. G.; Teso, E.; García, A.; de la Moya, S.; Rodríguez, E.; Martínez, P.; Subramanian, L. R.; Gancedo, A. G. *J. Med. Chem.* **1995**, *38*, 4474.

11) Spreitzer, H.; Buchbauer, G.; Püringer, Ch. *Tetrahedron* **1989**, *45*, 6999.

12) Martínez, A.G.; Teso, E.; García, A.; de la Moya, S.; Díaz, C.; Subramanian, L. R.; Maichle, C. *Tetrahedron: Asymmetry* **1994**, *5*, 949.

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).

14) Eliel, E. L.; Nasipuri, D. S. *J. Am. Chem. Soc.* **1965**, *30*, 3809.

15) Cram, D. J.; Kopecky, K. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

16) Kirmse, W.; Arend, G. *Chem. Ber.* **1972**, *105*, 2746.

17) a) Nickon, A.; Nishida, T.; Frank, J. *J. Org. Chem.* **1971**, *36*, 1075. b) Kalinowski, H. O.; Berger, S.; Braun, S. *"^{13}C-NMR-Spectroskopie"*, George-Thieme-Verlag: Stuttgart, **1984**, 258.