ORGANIC LETTERS

2006
Vol. 8, No. 16
3509−3512

Highly Enantioselective Synthesis of β-Amino Alcohols

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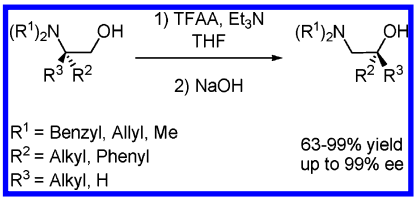
Received May 9, 2006

ABSTRACT



***N,N*-Dialkyl-β-amino alcohols derived from α-amino acids can be rearranged enantiospecifically by using TFAA/Et_3N/NaOH to give 1,2-amino alcohols with enantiomeric excess up to 99%.**

β-Amino alcohol moieties are present in a large variety of naturally occurring and pharmacologically active molecules.[1] The amino alcohol relative stereochemistry is highly important for the biological activity of these molecules. These entities can also be used as chiral auxiliaries in asymmetric synthesis.[2,3]

Linear *N*,*N*-dialkyl-β-amino alcohols have been shown to rearrange, via an aziridinium ion, into β-halogenoamines (on treatment with $SOCl_2$,[4] MsCl,[5] TsCl,[5] $SOBr_2$,[6] CBr_4/PPh_3,[7] DAST,[8] or Deoxofluor[9]), into β-mesylamines (on treatment with Ms_2O[10,11]), and into thiocyanates (on treatment with KSCN[12]). Recently we have shown that prolinols can be rearranged enantiospecifically to give optically active piperidin-3-ols, via an aziridinium intermediate, by using TFAA/Et_3N/NaOH.[13,14] In this Letter, we would like to report that these latter conditions can be applied to linear optically active β-amino alcohols of type **A** to produce 1,2-amino alcohols of type **B** in a very regio-, stereo-, and enantioselective process (Scheme 1).

N,*N*-Dibenzyl-β-amino alcohols **2a**,[15] **2c**,[5] **2e**,[16] **2f**,[17] **2g**, and **2h**[18] were prepared from the commercially available amino alcohols by using benzyl bromide (2.2 equiv) in the

(1) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576 and references therein.

(2) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.

(3) For recent examples of stereoselective synthesis of enantiopure β-amino alcohols see: (a) Keinicke, L.; Fristrup, P.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2005**, *127*, 15756−15761. (b) Cooper, T. S.; Larigo, A. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Org. Biomol. Chem.* **2005**, *3*, 1252−1262.

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(5) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647−649 and references therein.

(6) Nagle, A. S.; Salvatore, R. N.; Chong, B.-D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011−3014.

(7) Lehmann, T.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2863−2866.

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(9) Ye, C.; Shreeve, J. M. *J. Fluorine Chem.* **2004**, *125*, 1869−1872.

(10) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766−6776.

(11) For an interesting example of the utilization of Ms_2O in the formation of an aziridinium intermediate, see: Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183−2186.

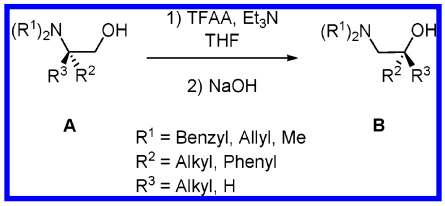
(12) Anderson, J. C.; Cubbon, R.; Harding, M.; James, D. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3461−3490.

(13) For comprehensive reviews, see: (a) Cossy, J.; Gomez Pardo, D. *Chemtracts* **2002**, *15*, 579−605. (b) Cossy, J.; Gomez Pardo, D. *Targets Heterocycl. Syst.* **2002**, *6*, 1−26.

(14) (a) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693−1699. (b) Brandi, A.; Cicchi, S.; Paschetta, V.; Gomez Pardo, D.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357−9359. (c) Déchamps, I.; Gomez Pardo, D.; Karoyan, P.; Cossy, J. *Synlett* **2005**, 1170−1172. (d) Roudeau, R.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2006**, *62*, 2388−2394 and references therein.

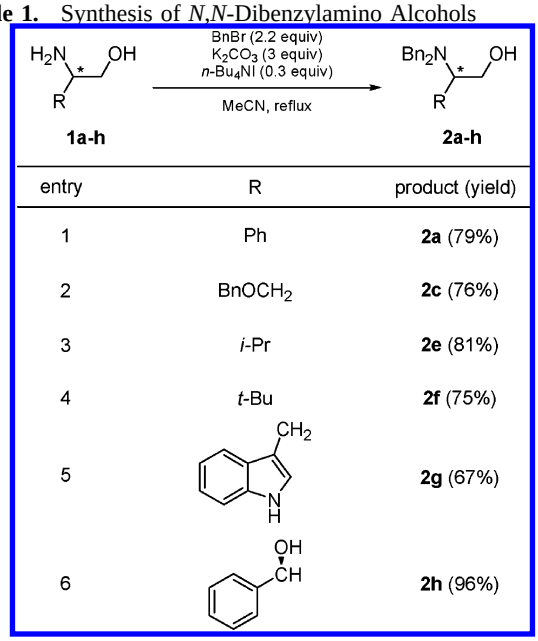
10.1021/ol061133d CCC: $33.50
Published on Web 07/07/2006

Scheme 1



presence of K_2CO_3 (3 equiv) and *n*-tetrabutylammonium iodide (0.3 equiv) in refluxing acetonitrile (Table 1). *N*,*N*-Dibenzyl-*β*-amino alcohols **2b** and **2d** are commercially available.

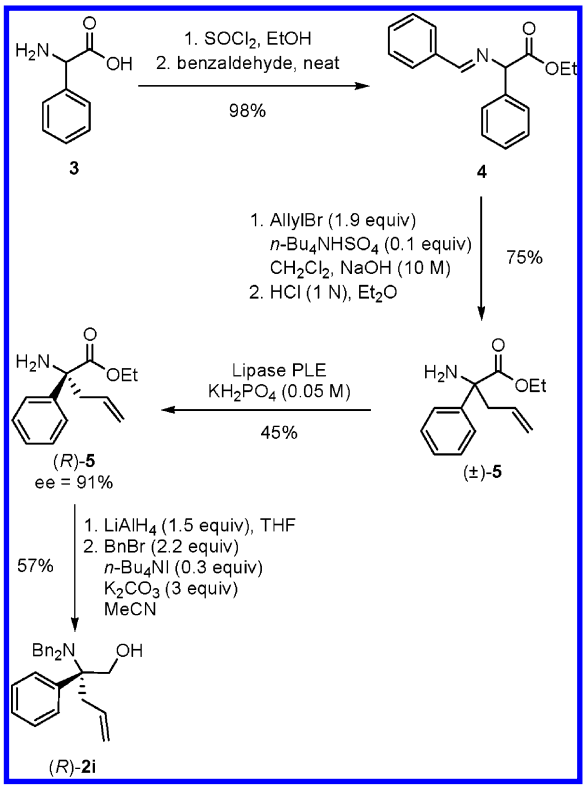
Table 1. Synthesis of *N*,*N*-Dibenzylamino Alcohols



entry	R	product (yield)
1	Ph	**2a** (79%)
2	$BnOCH_2$	**2c** (76%)
3	*i*-Pr	**2e** (81%)
4	*t*-Bu	**2f** (75%)
5		**2g** (67%)
6		**2h** (96%)

The optically active amino alcohol (*R*)-**2i** was synthesized from the racemic phenylglycine **3**. Esterification with $SOCl_2$ in ethanol followed by treatment with benzaldehyde furnished the corresponding imine **4**. After alkylation under catalytic phase transfer conditions (AllylBr, *n*-Bu_4NHSO_4, NaOH, CH_2Cl_2) and hydrolysis of the imino group, the racemic amino ester **5** was obtained in 75% yield. The resulting α-allylphenylglycine ethyl ester **5** was subjected to a kinetic enzymatic resolution by using lipase PLE[19] to provide the (*R*)-enantiomer of **5** in 45% yield and 91% enantiomeric excess.[20,21] This latter compound was then converted to the corresponding amino alcohol (*R*)-**2i** in 57% yield by reduction with $LiAlH_4$, followed by bis-*N*-benzylation with benzyl bromide (K_2CO_3, *n*-Bu_4NI, CH_3CN, microwaves irradiation, 120 °C, 3 h) (Scheme 2).

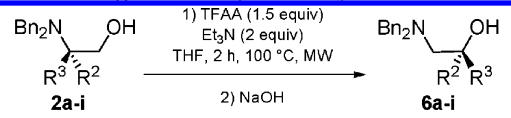
Scheme 2

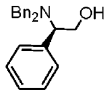
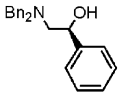
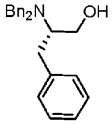
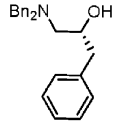
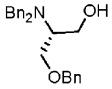
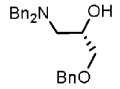
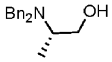
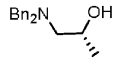
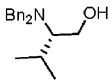
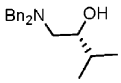
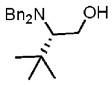
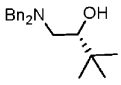
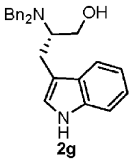
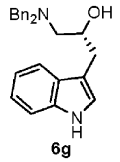
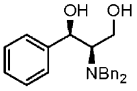
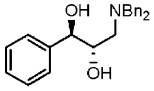
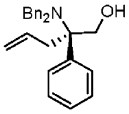
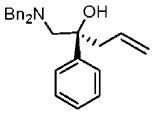


N,*N*-Dibenzylamino alcohols **2a**−**i** were treated with trifluoroacetic anhydride (TFAA, 1.5 equiv) and Et_3N (2 equiv) and heated at 100 °C under microwave (MW) irradiation. After 2 h, the reaction mixture was treated with NaOH (3.75 N) to provide the *N*,*N*-dibenzyl-*β*-amino alcohols **6a**−**i** in good yields and with excellent enantiomeric excess (Table 2).[22] The (*S*)-absolute configuration of **6a**[23] was determined by comparison of the $[\alpha]_D$ of the (*S*)-*N*,*N*-2-dibenzylamino-1-phenylethanol synthesized from the commercially available (*S*)-2-amino-1-phenylethanol. The (*R*)-absolute configuration was established for compounds **6b**,[24] **6d**,[24] and **6e**[25] by comparison of the $[\alpha]_D$ reported in the literature. We have to point out that in the case of amino-1,3-diol **2h** the amino-1,2-diol **6h** was obtained in 66% yield indicating that the reaction is very regio- and diastereoselective. Furthermore, almost no loss of chirality was observed in the case of the amino alcohol **6i**, possessing a tertiary hydroxyl group, as it was obtained from **2i** with 63% yield

(15) Cepanec, I.; Litvić, M.; Mikuldaš, H.; Bartolinčić, A.; Vinković, V. *Tetrahedron* **2003**, *59*, 2435−2439.
(16) Ma, D.; Xie, W.; Zou, B.; Lei, Q.; Pei, D. *Tetrahedron Lett.* **2004**, *45*, 8103−8105.
(17) Brunin, T.; Cabou, J.; Bastin, S.; Brocard, J.; Pélinski, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1241−1243.
(18) Rozwadowska, M. D. *Tetrahedron* **1997**, *53*, 10615−10622.
(19) Lipase PLE was purchased from Sigma.
(20) Betsbrugge, J. V.; Tourwé, D.; Kaptein, B.; Kierkels, H.; Broxterman, R. *Tetrahedron* **1997**, *53*, 9233−9240.
(21) Determined by chiral HPLC, using a Chiralpack AD-H column.
(22) Similar yield and ee were obtained when heating **2b** in a sealed tube at 100 °C for 2 h.
(23) Shibata, T.; Takahashi, T.; Konishi, T.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2458−2460.
(24) Schwerdtfeger, J.; Kolczewski, S.; Weber, B.; Fröhlich, R.; Hoppe, D. *Synthesis* **1999**, *9*, 1573−1592.
(25) Koppenhoefer, B.; Trettin, U.; Wächtler, A. *Synthesis* **1994**, *12*, 1141−1142.

Table 2. Rearrangement of *N*,*N*-Dibenzylamino Alcohols



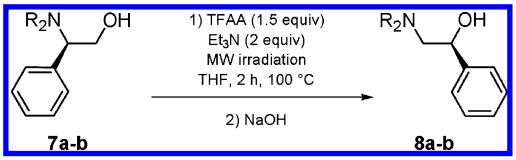
entry	substrates	products	yield(ee)
1	 **2a**	 **6a**	93%(99%)[a]
2	 **2b**	 **6b**	97%(95%)[b]
3	 **2c**	 **6c**	76%(95%)[b]
4	 **2d**	 **6d**	99%[c](99%)[a]
5	 **2e**	 **6e**	88%
6	 **2f**	 **6f**	99%
7	 **2g**	 **6g**	97%[d]
8	 **2h**	 **6h**	66%[e]
9	 **2i** (ee = 91%)	 **6i**	63%[f](88%)[a]

[a] Determined by chiral HPLC (see the Supporting Information for details). [b] Determined by application of the modified Mosher method.[26] [c] TFAA (4,5 equiv), Et_3N (9 equiv), reflux, 37 h. [d] TFAA (3 equiv), Et_3N (4 equiv). [e] TFAA (1,1 equiv), Et_3N (1,5 equiv). [f] TFAA (2 equiv), Et_3N (3 equiv), rt, 48 h.

and 88% ee [starting from ee (**2i**) 91%]. Even for amino alcohols of type **A** possessing a quaternary center, the rearrangement is enantiospecific as compounds of type **B** were obtained with good enantiomeric excess.

N-Alkyl groups have almost no influence on the rearrangement, as the *N*,*N*-diallylamino alcohol **7a**[27] and the *N*,*N*-dimethylamino alcohol **7b**[28] led to the amino alcohols **8a**[29] and **8b**[30] in 85% and 72% yield, and in 99% and 95% enantiomeric excess, respectively (Table 3). The (*S*)-configuration of **8a** and **8b** were established by comparison with the $[\alpha]_D$ reported in the literature.[29,30]

Table 3. Rearrangement of Diallyl- and Dimethylamino Alcohols

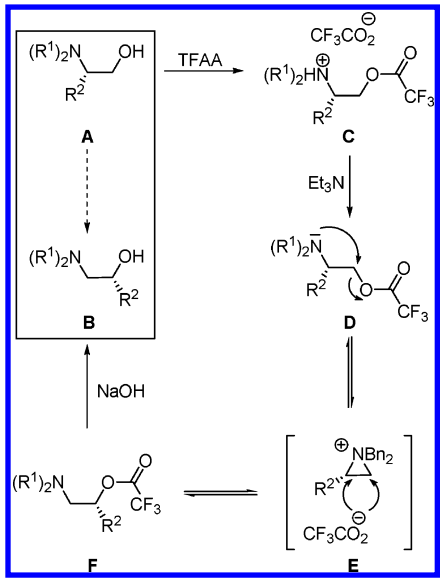


entry	R	yield, %	ee,[a] % (configuration)
1	allyl (**8a**)	85	99 (*S*)
2	Me (**8b**)	72	95 (*S*)

[a] Determined by chiral HPLC (see the Supporting Information for details).

The stereospecificity of this reaction can be rationalized by the intermediacy of an aziridinium ion of type **E**.[13] This aziridinium is formed from the ammonium trifluoroacetate ester **C**, which is transformed to the aziridinium **E**, via the amino ester **D**, after treatment with Et_3N. As a trifluoroacetate anion is liberated into the reaction media, this anion can attack the more substituted carbon atom of the aziridinium **E**, producing the aminoester **F**. By analogy with the work of Gmeiner,[10] we assume that compounds **D** and **F** are in equilibrium, and that the secondary trifluoroacetate ester **F** is the thermodynamic product. After saponification of **F**, amino alcohols of type **B** are liberated (Scheme 3). Due to the high ee observed in the rearrangement it is unlikely that the reaction proceeds via a planar carbocation intermediate.

Scheme 3



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(27) Fiaux, H.; Popowycz, F.; Favre, S.; Schütz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237−4246.

The treatment of 1,2-amino alcohols with TFAA/Et_3N/NaOH is a very powerful procedure that allows the synthesis of β-amino alcohols of type **B** with high yield and enantiomeric excess. Furthermore, the *N*,*N*-dibenzyl-β-amino alcohols of type **B** can be used to provide chiral 2-amino-1-alkylethanols by hydrogenolysis of benzyl groups.[25] Further studies with amino alcohols of type **B** as chiral auxiliaries, as well as in the synthesis of natural products, are currently underway.

Acknowledgment. Sanofi-Aventis is greatly acknowledged for financial support (Grant to T.-X.M.)

Supporting Information Available: General experimental procedure and characterization data of compounds **2a**, **2c**, **2e**−**i**, **6a**−**i**, **7a**,**b**, and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061133D

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(29) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693−4706.

(30) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350−4360.