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Synthesis of Enantiomerically Pure 3-Amino-1,2-diols by Reductive Amination of Racemic 2,3-Dialkoxyketones

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Abstract: The reductive amination of racemic 2,3-dialkoxyketones by tetrabutylammonium triacetoxyborohydride in the presence of (*R*) or (*S*)-α-methylbenzylamine allows the stereocontrolled access to 3-amino-1,2-diols in high enantiomerical purity via a partial dynamic resolution.

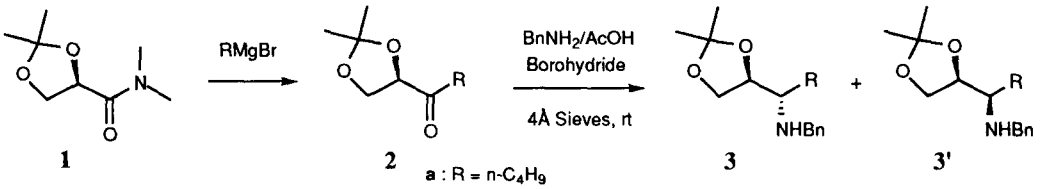
The stereocontrolled synthesis of aminoalcohols and aminodiols have attracted much interest in recent years because these core units are implicated in the synthesis of various biologically active molecules such as proteases inhibitors,[1] glycosphingolipides[2] or polyhydroxylated nitrogen heterocycles.[3]

They may be prepared by reaction of an epoxyalcohol with a nitrogen nucleophile.[4,5] However, the regioselectivity of such a reaction is rather difficult to control. An other attractive approach was furnished by the stereocontrolled addition of organometallic compounds on the imines derived from optically active α-alkoxyaldehydes. These compounds are however difficult to synthesize.[6]

We wish to report here a method which allows the stereoselective controlled preparation of 3-amino-1,2-diols in high enantiomerical purity by reductive amination of racemic 2,3-dialkoxyketones.

The reductive amination allows the direct transformation of a ketone into an amine and avoids the isolation of the corresponding imines which is difficult to achieve for multifonctionnalized ketones.[7] We have previously shown that this reaction applied to α-epoxyketones or 1,3-dihydroxyketones afforded the corresponding amines in high diastereoselectivity.[8,9]

In a first experiment, we studied the reductive amination of the ketone **2a** which was prepared by addition of a Grignard reagent to the optically active dimethylamide **1**.[10]



1 **2** **3** **3'**

a : R = n-C_4H_9

Scheme 1

0040-4039/98/$ - see front matter
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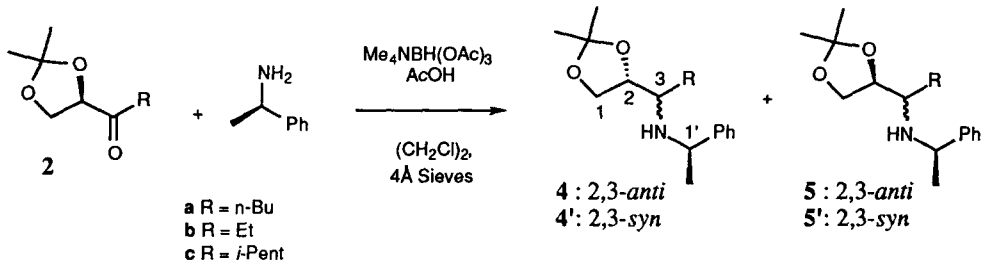
We used benzylamine and tetramethylammonium triacetoxyborohydride (TABH)[11] which is the most satisfactory reducing agent for these reactions (scheme 1). The amines **3** and **3'** were obtained in a very good yield (95%) but in a rather disappointing diastereomerical ratio (*anti*:*syn* 68:32). The use of a more hindered amine such as benzhydrylamine slightly increased this ratio up to 75:25 but, whatever the solvent and the hydride, we were unable to ameliorate these results. Then, we thought that the use of a chiral amine could perhaps induce a double stereodifferentiation, a phenomena which was previously observed during the addition of organometallic compounds to chiral imines.[12]



Scheme 2

We decided to use α-methylbenzylamine which is available in high enantiomerical purity both in *R* and *S* form and, using the *R* isomer, we were rather surprised to observe the formation of four diastereomers (Scheme 2). Moreover, the ratio were variyng with the nature of the solvent. In methanol with cyanoborohydride as reducing agent, two major diastereomers were obtained, the configuration of which were determined 2*S*,3*S*,1'*R* (**5a**) and 2*S*,3*R*,1'*R* (**5'a**) in addition of 10% of a mixture of two other diastereoisomers. In contrast, in acetonitrile or in 1,2-dichloroethane, the ratio were reversed and the 2*R*,3*R*,1'*R* isomer **4a** was obtained in >50% yield (Table 1).[13] Moreover, the reaction of **ent-2a** and **rac-2** with the same *R* amine also afforded the compound **4a** as the major diastereomer. Thus, whatever the absolute configuration of the starting ketone, the *anti* compound **4a** was mainly obtained demonstrating that the configuration of the aminodiol was highly depending on the stereochemistry of the chiral amine.

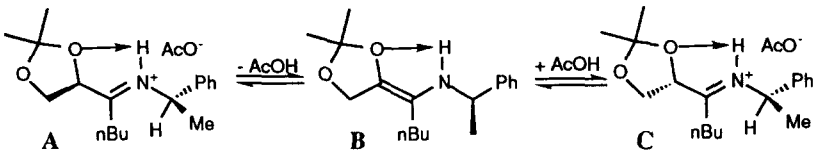
These results may be explained by an epimerisation during the formation of the iminium salts and (or) during the reduction of these intermediates. Although, this phenomena was not observed during the reductive amination of the epoxyketones,[8] such an isomerisation was previously described during the hydrogenation of imines derived from cyclic ketones.[14] It should be favoured in this case by the formation of an internal hydrogen bond between the iminium salt and the oxygen in α position. The major formation of one diastereo-

Table 1 Reductive amination of ketones 2 with (*R*)-α-methylbenzylamine

Substrate	Borohydride	Solvent	4% [a]	4'%	5%	5'%
2a	$NaBH_3CN$	MeOH	7	4	35	54
ent-2a	"	"	62	34	2	2
2a	TABH	CH_3CN	53	10	13	24
2a	"	$(ClCH_2)_2$	54	9	10	27
ent-2a	"	"	68	10	7	15
rac-2a	"	"	60 (47)[b]	10	8	22
rac-2b	"	"	64 (49)[b]	9	3	24
rac-2c	"	"	57 (40)[b]	c	c	c

a) measured by GC; b) isolated yield of pure compound; c) not determined

mer might be the result of a thermodynamic equilibration between A and C (scheme 3).



Scheme 3

A computational study using AM1 calculations has shown a difference of 0.4 kcal/mol between A and C, after minimization, in favour of the latter which leads to major products **4a** and **4'a**[15]. Moreover, in these lowest energy conformers, the C=N bond and the C-O bond in α position are nearly coplanar due to the formation of a hydrogen bond between the iminium moiety and the oxygen. So the σ_{CH} and π^*_{CN} orbitals implied in the epimerisation process present the best overlapping to give the enamine (Figure 1). Thus, the suppression of this hydrogen bond in methanol would explain the decrease of the epimerisation in this solvent.

However, the weak value obtained during the energetic comparison suggests that this reaction is mainly controlled by a kinetic effect resulting from a difference between the relative reduction rates of the two iminium salts A and C.

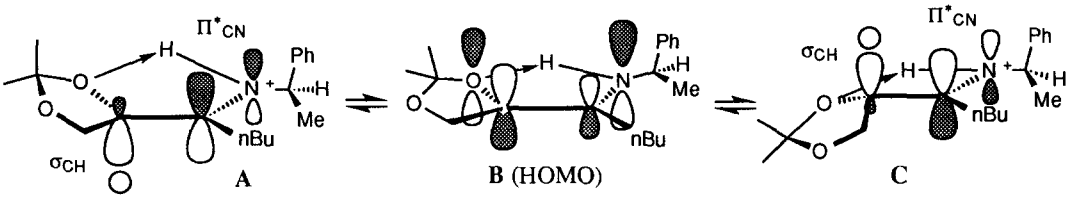
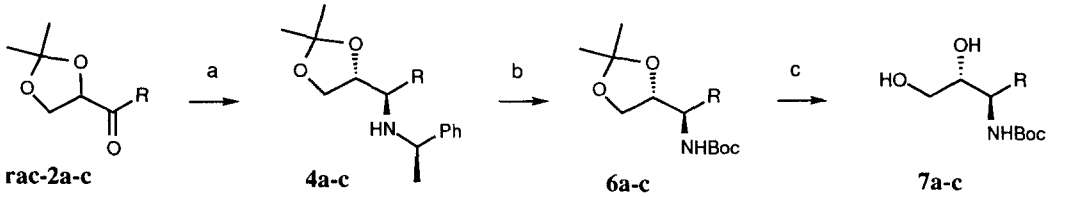


Figure 1

We thought that this epimerisation could be exploited to prepare 3-amino-1,2-diols in high enantiomerical purity from racemic 2,3-dialkoxyketones. As expected, the reductive amination of different ketones **rac-2**, using (*R*)-α-methylbenzylamine, afforded the major diastereomer **4** (Table 1).



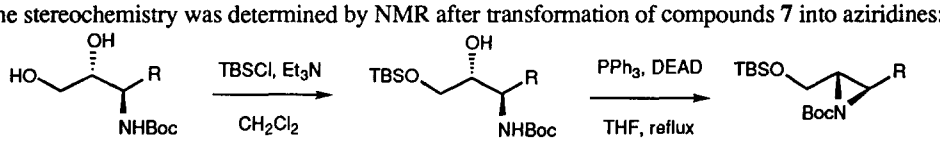
Scheme 4. Reaction conditions : a) TABH (2.5 eq), (*R*)-α-methylbenzylamine (1.3 eq), AcOH (1.3 eq), $(ClCH_2)_2$, 4Å sieves, rt, 65-68 h ; b) H_2, $Pd(OH)_2$ cat., Boc_2O, EtOH, rt, 18-24 h, 80-90% ; c) CF_3COOH, $MeOH/H_2O$, 15-18 h, 80-85%.

The isolation of this isomer was facilited by the fact that, in all cases, it was eluted in first, an event which allowed to easily isolate it in high optical purity[16]. The cleavage of the methylbenzylamine moiety by catalytic hydrogenation followed by the removal of the ketal protection led to the enantiomerically pure 3-amino-1,2-diols **7**. Of course, using (*S*)- instead of (*R*)-α-methylbenzylamine allowed the access to the 3-amino-1,2-diols **ent-7** in identical yields and optical purities.

In conclusion, the reductive amination of protected 2,3-dihydroxyketones in the presence of α-methylbenzylamine allowed us the access to *anti* aminodiols in high enantiomerical purities via a partial dynamic resolution.

References and notes:

1. Kempf, D.; Sham, H. *Curr. Pharm. Des.* **1996**, *2*, 225-246.
2. Peterson, M.A.; Polt, R *J.Org. Chem.* **1993**, *58*, 4309-4314 and references cited herein
3. for some recent syntheses, see: Overhand, M.; Hecht, S.M. *J. Org. Chem.* **1994**, *59*, 4721-4722; Veith, U.; Schwardt, O.; Jäger, V. *Synlett*, **1996**, 1181-1183; Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron:Asymmetry* **1996**, *7*, 1169-1180; Hümmer, W.; Dubois, E.; Gracza, T.; Jäger, V. *Synthesis*, **1997**, 634-642; Du Bois, J.; Tomooka, C.S.; Hong, J.; Carreira, E.M. *J. Amer. Chem. Soc.* **1997**, *119*, 3179-3180.
4. For a review, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599-619.
5. Rayner, C.M. *Synlett*, 1997, 11-21.
6. Yamamoto, Y.; Komatsu, T.; Maruyama, K. Matsumoto, T.; Kobayashi, Y.; Takemoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 930-931; Clark, R.D.; Jahangir; Souchet, M.; Kern, J.R. *J. Chem. Soc., Chem. Commun.* **1985**, 814-815; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175-4176; Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, *Tetrahedron Lett.* **1991**, *32*, 2967-2970; Franz, T.; Hein, M.; Veith, U.; Jäger, V.; Peters, E.M.; Peters, K.; von Schnering, H.G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1298-1301; Cativiela, C.; Diaz-de-Villegas, M.D.. Galvez, J.A. *Tetrahedron Lett.* **1995**, *36*, 2859-2862; Solladié-Cavallo, A.; Bonne, F. *Tetrahedron:Asymmetry* **1996**, *7*, 171-180; Razavi, H.; Polt, R. *Tetrahedron Lett.* **1998**, *39*, 3371-3374.
7. Kim, S.; Oh, C.H.; Ko, J.S.; Anh, K.H.; Kim, Y. *J. Org. Chem.* **1985**, *50*, 1927-1932; Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* **1990**, *31*, 5595-5598 and references cited herein.
8. Pégorier, L.; Petit, Y.; Larchevêque, M. *J. Chem. Soc., Chem. Commun.* **1994**, 719-720.
9. Haddad, M.; Dorbais, J.; Larchevêque, M. *Tetrahedron Lett.* **1997**, *38*, 7783-7786.
10. Petit, Y.; Larchevêque, M. *Synthesis* **1986**, 61-64.
11. Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Amer. Chem. Soc.* **1988**, *110*, 3560-3578.
12. Veith, U.; Leurs, S.; Jäger, V. *J. Chem. Soc., Chem. Commun.* **1996**, 329-330.
13. The stereochemistry was determined by NMR after transformation of compounds **7** into aziridines:



14. Knupp, G.; Frahm, A.W. *Chem. Ber.* **1984**, *117*, 2076-2098; Lauktien, G.; Volk, F.J.; Frahm, A.W. *Tetrahedron:Asymmetry* **1997**, *8*, 3457-3466; Bisel, P.; Breitling, E.; Frahm, A.W. *Eur. J. Org. Chem.* **1998**, 729-733.
15. **A**, **B**, and **C** were minimized using AM1 semi-empirical method and Polak-Ribiere algorithm (conjugate gradient) as released in Hyperchem 2.0 with a RMS gradient of 0.02 kcal/(mol.Å)
16. The enantiomerical purities were measured after transformation into the protected aminodiols **6** by chiral GC using a 25m ChirasilVal® column (Chrompack). They were found in all cases identical to the optical purity of the α-methylbenzylamine used. **7a** : $[\alpha]_D^{20}$ 12.8 (c = 1.48, MeOH); **7b** : $[\alpha]_D^{20}$ 22.1 (c = 4.03 , $CHCl_3$); **7c** : $[\alpha]_D^{20}$ 17.0 (c = 4.35, $CHCl_3$).