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# Double Stereodifferentiation in the "Acetate-Type" Aldol Reaction with Garner's Aldehyde. Stereocontrolled Synthesis of Polyhydroxylated γ-Amino Carbonyl Compounds

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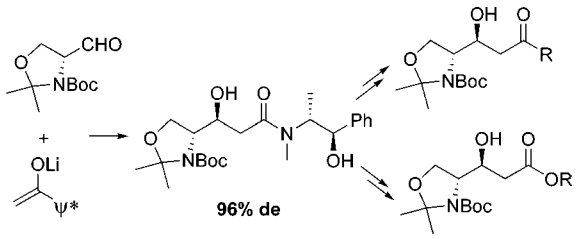
## ABSTRACT

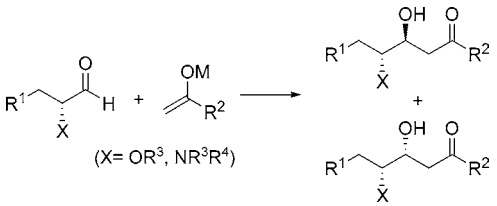



**The aldol reaction of acetamide enolates with protected chiral α-amino-β-hydroxy aldehyde 1 (Garner's aldehyde) has been performed in a stereocontrolled way under double stereodifferentiation conditions using pseudoephedrine as the additional chiral information source attached to the enolate reagent. In addition, the obtained adduct has been transformed into other valuable chiral building blocks such as γ-amino-β,δ-dihydroxy acids, esters, and ketones.**

The stereoselective construction of molecules containing sequences of contiguous heterosubstituted stereocenters is a challenging task for the synthetic organic chemist. The significance of this structural motif relies upon the fact that it is widespread in natural products and synthetic drugs.

An easy and direct approach to some of these targets consists of the nucleophilic addition of different nucleophiles to α-heterosubstituted chiral aldehydes, in which the chiral information present at the aldehyde should exert the required degree of stereocontrol.[1] In this context, many differently protected α-amino and α-alkoxy aldehydes have been tested in reactions with several nucleophiles, normally proceeding with good levels of diastereoselection.[2] Despite this, the particular case in which an α-unsubstituted enolate is subjected to addition to this kind of aldehydes, also known as "acetate-type" aldol addition (Scheme 1), has not attracted so much attention, mainly because of the low diastereoselectivities usually obtained,[3] although in some particular

**Scheme 1.** Diastereoselective "Acetate-Type" Enolate Addition on α-Heterosubstituted Chiral Aldehydes




(1) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. See also: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

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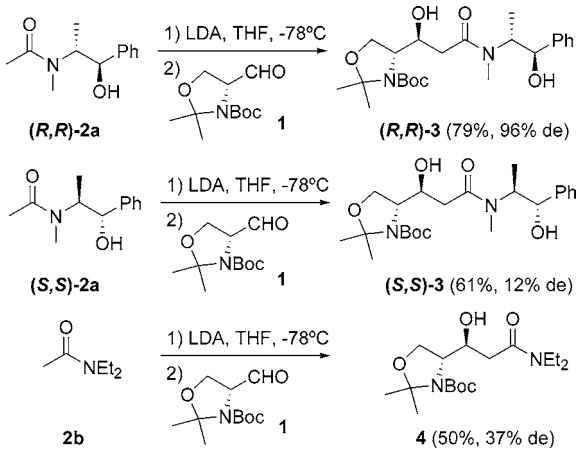
cases this problem has been circumvented by protective group tuning.

In this context and in connection with our ongoing program directed toward the development of new procedures for the asymmetric synthesis of natural products and new drugs, we have been pursuing a procedure for the stereocontrolled synthesis of polyhydroxylated amino acids and ketones. In particular, the asymmetric synthesis of $\gamma$-amino-$\beta$-hydroxy acids is of key relevance because they are peptide components that act as protease inhibitors of aspartic acid,[4] which activity has been shown to be highly dependent upon the configuration of the stereogenic centers present in the molecule.[5]

An easy and direct approach to these targets (Scheme 2)

**Scheme 2.** Diastereoselective Addition of Acetamide Enolates on Chiral Aldehyde **1**




consists of the nucleophilic addition of enolates to an α-heterosubstituted chiral aldehyde 1,1-dimethylethyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate, **1** (also known as Garner's aldehyde),[6] which is commercially available in highly enantioenriched form and configurationally stable. Although this reaction has been studied by some groups, in the particular case of α-unsubstituted enolate nucleophiles, it is difficult to find examples in which the reaction proceeded with a complete degree of diastereoselection, and mixtures of the two possible diastereoisomers have been usually obtained. In fact, only two papers can be found in the literature for this reaction, both reporting moderate diastereoselectivities.[7] A convenient way of resolving this problem in other cases has consisted of the introduction of additional chiral information, under typical double stereodifferentiation conditions.[8] However, as far as we know, this approach has never been applied to the acetate aldol reaction with aldehyde **1**.

With these precedents in mind we thought about the possibility of carrying out this "acetate" aldol reaction under double asymmetric induction conditions using the chiral amino alcohols (*S*,*S*)-(+)- or (*R*,*R*)-(−)-pseudoephedrine incorporated at the enolate reagent as second stereodifferentiating chiral component (Scheme 2). This amino alcohol has been successfully used by our group in aldol reactions with substituted enolates (propionamide enolates).[9] Remarkable features of the use of this auxiliary rely upon the fact that it is a cheap reagent, commercially available in both enantiomeric forms. Additional advantages of the use of this auxiliary are related to the unique reactivity of the amide function present in the obtained adducts, which allows the preparation of a wide range of other interesting chiral building blocks.[10]

We therefore subjected aldehyde **1** to aldol addition with the lithium enolate of (*R*,*R*)-(−)- and (*S*,*S*)-(+)-pseudoephedrine acetamides **(*R*,*R*)-2a** and **(*S*,*S*)-2a** (Scheme 2), obtaining the expected $\beta$-hydroxyamide adducts **(*R*,*R*)-3** and **(*S*,*S*)-3** in good yields and in 96% and 12% de, respectively.[11] To test the degree of simple asymmetric induction exerted by the aldehyde, we also tested the reaction using *N*,*N*-diethylacetamide **2b** as the enolate source. As expected, the diastereoselectivity observed was much lower in this case (see Scheme 2). These results indicate that a double asymmetric induction process was operating, allowing us to establish that **(*R*,*R*)-2a** and aldehyde **1** constitute the *matched*

(2) For some reviews, see: (a) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (d) Juczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(3) Reviews on the asymnetric aldol reaction: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 37. (c) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (e) Arya, P.; Quin, H. *Tetrahedron* **2000**, *56*, 917. (f) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (g) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 997. (h) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (i) Braun, M. In *Stereoselective Synthesis, Houben-Weyl*; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. E21/3, p 1603. (j) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. For an excellent discussion about the problems of the acetate-type aldol reaction, see: (k) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. See also ref 3a and b.

(4) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. See also: (b) Cooke, J. W. B.; Davies, S. G.; Naylor, A. *Tetrahedron* **1993**, *49*, 7955 and references cited therein.

(5) Liu, W.-S.; Smith, S. C.; Glover, G. I. *J. Med. Chem.* **1979**, *22*, 577.

(6) Review: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136. Some additional examples from past years: (b) Nakagawa, M.; Uchida, H.; Ono, K.; Kimura, Y.; Yamabe, M.; Watanabe, T.; Tsuji, R.; Akiba, M.; Terada, Y.; Nagaki, D.; Ban, S.; Miyashita, N.; Kano, T.; Theeraladanon, C.; Hatakeyama, K.; Arisawa, M.; Nishida, A. *Heterocycles* **2003**, *59*, 721. (c) Starkmann, B. A.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 725. (d) Ma, D.; Yieng, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706

(7) Acetate aldol additions with aldehyde **1**: (a) Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294. (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. For other examples of acetate aldol addition to *N*-Boc α-amino aldehydes, see: (c) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Pazos, R.; Odriozola, J. M.; Bañuelos, P.; Tello, M.; Linden, A. *J. Org. Chem.* **2004**, *69*, 4126 and references therein.

(8) Reviews: (a) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.

(9) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489. (b) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754.

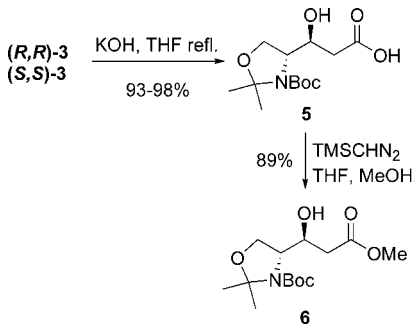
(10) See, for example: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. See also ref 9b.

(11) Diastereomeric excesses were determined by HPLC analysis of crude reaction mixtures (see Supporting Information).

combination of reagents and **(*S,S*)-2a** and **1** are the *mismatched* couple.

We proceeded next to the transformation of the obtained enantiopure adducts into the target $\gamma$-amino carbonyl compounds. The first transformation performed was the removal of the chiral auxiliary by base hydrolysis, which proceeded in excellent yield and no racemization, regardless the configuration of the auxiliary (Scheme 3). Remarkably, both

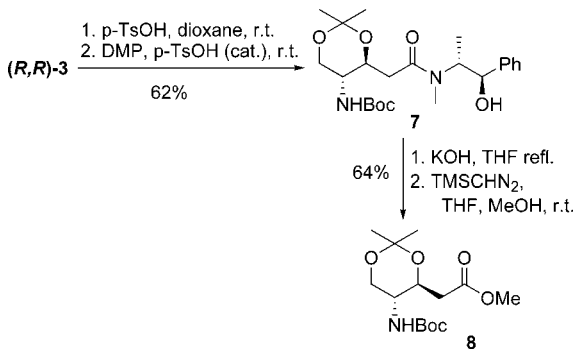
**Scheme 3**




chiral auxiliaries (*S,S*)-(+) and (*R,R*)-(−)-pseudoephedrine could be easily recovered after this hydrolysis step by standard acid−base workup, which allowed their recycling for further uses. Next, the acids **5** were esterified with $TMSCHN_2$,[12] furnishing methyl esters **6**.

At this point, to determine the absolute configuration of the new stereogenic center created in the aldol addition step, we converted amide **(*R,R*)-3** into the cyclic derivative **7** by first performing a selective *N,O*-acetal cleavage followed by protection of the diol moiety in the form of a cyclic acetal (Scheme 4). Unfortunately, NMR spectra of cyclic derivative

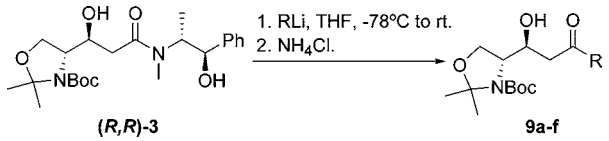
**Scheme 4**




**7** was too complicated for any structural elucidation experiment because of the presence of the amide moiety, and therefore this derivative was subjected to a hydrolysis/esterification sequence in order to afford the ester **8**. NOESY experiments on this derivative indicated the *anti* relative configuration of the $\beta$-hydroxy-$\gamma$-amino moiety.

One of the most significant features of pseudoephedrine amides is that the amide moiety is able to undergo fast and clean 1,2-addition of organolithium reagents, affording the corresponding ketones after aqueous workup.[13] This moiety has shown a behavior comparable in this context to that of Weinreb amides. Therefore, we proceeded to apply these conditions to the adduct (Scheme 5), observing that, to our

**Scheme 5**




delight, this densely highly functionalized compound behaved as we expected, thus opening a direct way for the preparation of many enantiopure $\gamma$-amino-$\beta$,$\delta$-dihydroxy ketones **9**, in excellent yields (Table 1).

**Table 1.** Synthesis of $\gamma$-Amino-$\beta$,$\delta$-dihydroxy Ketones **9a**−**f**

| entry | ketone | R | yield (%)[a] |
|---|---|---|---|
| 1 | **9a** | Me | 94 |
| 2 | **9b** | Et | 88 |
| 3 | **9c** | *i*-Pr | 87 |
| 4 | **9d** | *n*-Bu | 89 |
| 5 | **9e** | *t*-Bu | 71 |
| 6 | **9f** | Ph | 68 |

[a] Yield of product after flash column chromatography purification.

As can be observed in Table 1, a wide range of organolithium reagents are acceptable regardless of their structure, and therefore primary, secondary, and even tertiary alkyllithium reagents, as well as phenyllithium, underwent clean 1,2-addition, with no evidence of competitive aldolization at the two highly acidic α-protons of the substrates under these extremely basic conditions. It has also to be pointed out that, again, the chiral auxiliary (*R,R*)-(−)-pseudoephedrine could be easily recovered after standard acid−base work up and was recycled for further uses.

In conclusion, the amino alcohol pseudoephedrine has been shown to be an excellent auxiliary for the asymmetric acetate reaction with chiral α-amino-$\beta$-hydroxy aldehyde **1** under double stereodifferentiation conditions, which otherwise furnishes low diastereoselectivities if achiral enolates are employed. We have found that (*R,R*)-(−)-pseudoephedrine amide enolate and aldehyde **1** constitute the corresponding *matched* combination of reagents, furnishing the aldol adducts in excellent yield and diastereoselectivity. In addition, the pseudoephedrine amide moiety remaining at the aldol addition product has been demonstrated to be an extremely

(12) Hashimoto, N. Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(13) See refs 9b and 10. See also Vicario, J. L.; Badia, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745.

versatile functionality for its conversion into many interesting densely functionalized chiral building blocks such as $\gamma$-amino-$\beta$,$\delta$-dihydroxy acids esters and ketones. An additional advantage of the use of this auxiliary was found in the recyclability of the amino alcohol after cleavage from the adducts.

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**Note Added after ASAP Posting.** Scheme 3 was inadvertently duplicated as Scheme 4 in the version posted ASAP July 30, 2004; the corrected version was posted August 5, 2004.

**Supporting Information Available:** Detailed descriptions of experimental procedures and characterization of $\gamma$-amino-$\beta$,$\delta$-dihydroxy amide **(*R*,*R*)-3**, acid **5**, ester **6**, and ketones **9a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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