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Diastereo and Enantioselective Entry to β-Amino Esters by Hydride Reduction of Homochiral β-Enamino Esters.

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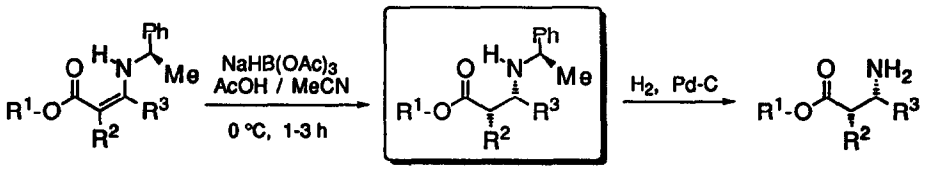
Abstract: The reduction of homochiral β-enamino esters **1** with sodium triacetoxyborohydride, which occurs with good diastereo- and enantioselectivity in the β-amino esters **2**, is described. This procedure allows a straightforward preparation of compounds with known biological activity.

The past few years have seen a growing interest in β-amino acids[1] which are important intermediates for the synthesis of compounds of pharmaceutical interest and are constituents of natural products such as terpenes, alkaloids, peptides and β-lactam antibiotics. Although several methods have been described in the literature for the synthesis of racemic compounds, only a few methods have been reported for the preparation of homochiral β-amino acids. New procedures for their enantioselective synthesis[2] have been made by the transformation of chiral pool material, the use of chiral auxiliaries in the Michael additions of homochiral lithium amides to α,β-unsaturated carboxylic acid equivalents, the additions of homochiral enolates to imines or the enantioselective hydrogenation of prochiral 3-amino acrylic acid derivatives in the presence of chiral catalyst.

In the course of our studies on the synthesis of functionalized enaminones and their reactivity,[3] we have found that the β-enamino esters can be easily reduced to β-amino esters.[4] The chemoselective reduction is realized with sodium triacetoxyborohydride in acetic acid and is highly diastereoselective in the case of α-alkylated-β-enamino esters. Now we describe the reduction of homochiral β-enamino esters **1** with the sodium triacetoxyborohydride which occurs with good diastereo- and enantioselectivity in the β-amino esters **2**.

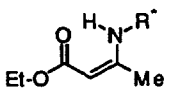
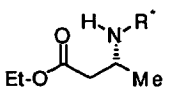
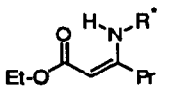
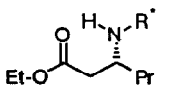
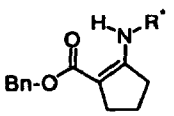
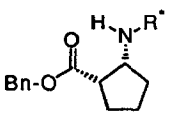
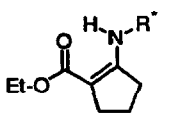
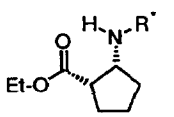
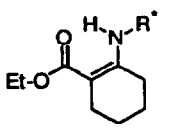
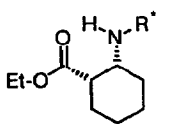
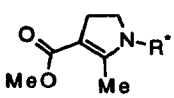
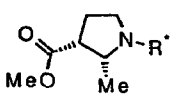
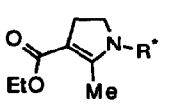
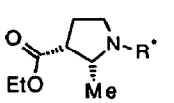


1 **2** **3**

Hydrogenolysable cheap (*R*)-α-methylbenzylamine, commercially available in both the homochiral forms, is chosen for the preparation of the starting β-enamino esters which occurs by a simple condensation with the corresponding β-keto esters.

This procedure is not applicable to β-enamino ketones which are generally resistant to these reductive conditions. In a typical procedure, a solution of sodium triacetoxyborohydride was prepared by addition of $NaBH_4$ (0.34 g, 9.0 mmol) to glacial acetic acid (5 mL) while keeping the temperature between 10-20 °C. After the H_2 evolution had ceased (30 min) CH_3CN (5 mL) was added and the temperature was lowered to 0 °C (ice bath). The β-enamino ester (3.0 mmol) was added in one portion and the reaction stirred for 1-3 hours at 0 °C. Then the reaction mixture was neutralised with Na_2CO_3 saturated aq. solution and extracted with CH_2Cl_2. The organic layer, dried and evaporated, provides a residue which is analysed by GC-MS or HPLC-MS for the determination of the yields of all the diastereoisomeric β-amino esters obtained. Pure stereoisomers were obtained by flash chromatography or by preparative HPLC with silica gel (10-20 % ethyl acetate on hexane as

Table1. Reduction of homochiral β-enamino ester **1** to β-amino ester **2**.

Entry		Substrate [a]		Product [a]	*d.e.* [b] (*cis*/*trans*)	Isolated Yield (%) [c]	$[\alpha]_D^{20}$ [d]	Config.
1	**1a**		**2a**		58	61	+45 (c=2, PhH)	(*R*) [5]
2	**1b**		**2b**		39	56	+46 (c=4)	(*R*) [9]
3	**1c**		**2c**		67 (>50)	71	+73 (c=2)	(1*S*, 2*R*) [6]
4	**1d**		**2d**		85 (>50)	66	+101 (c=6)	(1*S*, 2*R*) [9]
5	**1e**		**2e**		81 (28)	73	+59 (c=6)	(1*S*, 2*R*) [7]
6	**1f**		**2f**		74 (12)	72	+27 (c=3)	(*R*,*R*) [8]
7	**1g**		**2g**		71 (14)	71	+31 (c=4)	(*R*,*R*) [9]

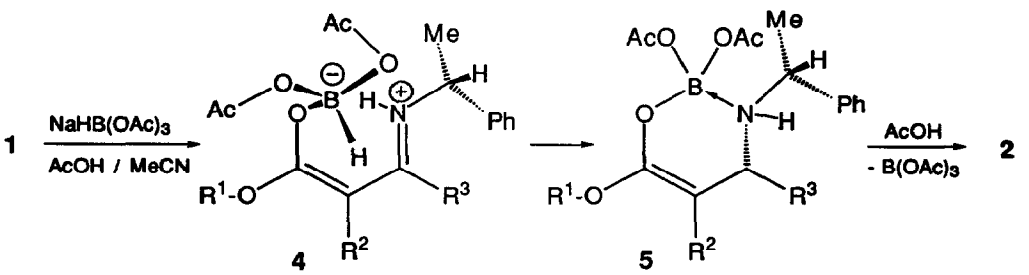
[a] R* = (*R*)-1-Phenylethyl. [b] Determined by GC-MS or HPLC-MS on the mixture reaction before purification. [c] Yields refer to pure isolated compounds. [d] All $[\alpha]_D^{20}$ were measured for solution in 95% ethanol unless otherwise stated.

eluent). Yields of isolated pure β-amino esters are reported in the table. All the compounds show analytical and spectroscopic data in agreement with the structure reported and with the literature data. The attribution of the absolute configuration for the new β-amino esters is made converting them to derivatives whose absolute configuration is known in the literature and by the comparison of the $[\alpha]_D^{20}$, as reported in the respective notes.

This procedure allows good yields in the isolated homochiral β-amino esters by simple chromatographic separation of the reaction mixture (see Table 1) although moderate asymmetric inductions (*d.e.*) were observed for this reaction. The reduction is fast in spite of the mild reaction conditions, easy to perform, inexpensive and the readily available reagents and starting materials, in both the homochiral forms, provide a convenient asymmetric entry to β-amino esters.

It is noteworthy that this procedure allows the convenient preparation of compounds of known biological activity as the homochiral pyrrolidines **2f,g** which present insecticidal properties.[8] The cispentacin [(1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid], with a powerful antifungal properties,[6] can be directly obtained by the hydrogenolysis of the enantiomer of the β-amino ester **2c** obtained in the entry 3.

As explained in a previous article[4] the reduction proceeds through an enolester-diacetoxyboroydride complex **4**. The asymmetric induction, observed for the substrates examined, can be rationalised examining the more stable conformer for the supposed enolester-diacetoxyboroydride complex intermediate **4** which is depicted in the following scheme. The intramolecular reduction of the immonium function of the intermediate **4** from the front side (the less hindered diastereotopic face) affords the β-amino enolester-borane complex **5** which upon acidolysis (AcOH) gives the β-amino ester **2**.



In conclusion a new convenient procedure for the stereoselective reduction of β-enamino esters to homochiral β-amino esters is reported. Work is now in progress to a better understanding of the mechanism and the study of the potentialities of this reaction.

References and Notes

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6. The hydrogenolysis of the β-amino ester **2c** with $Pd(OH)_2/C$ gives directly the pure (*1S,2R*)-2-amino-1-cyclopentanecarboxylic acid $[\alpha]_D^{20}$ = +8.2 (c=2.3, H_2O) [lit $[\alpha]_D^{20}$ = -8.8 (c=1.0, H_2O) for the (*1R,2S*)-2-amino-1-cyclopentanecarboxylic acid (cispentacin) (Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett*, **1993**, 461)].
7. The absolute configuration of the β-amino ester (*1S,2R*)-**2e** was ascertained by epimerization of this to (*1R,2R*)-**2e** {$[\alpha]_D^{20}$ = -72 (c=2.1, EtOH)} which by hydrogenolysis give ethyl (*1R,2R*)-2-amino-1-cyclohexanecarboxylate $[\alpha]_{578}^{20}$ = -52.9, $[\alpha]_{365}^{20}$ = -112.2 (c=2.7, EtOH) {lit $[\alpha]_{578}^{20}$ = -42.6, $[\alpha]_{364}^{20}$ = -119 (c=1.08, EtOH) (Armarego, W. L. F.; Kobayashi, T. *J. Chem. Soc. (C)*, **1970**, 1597); ethyl (*1S,2S*)-2-amino-1-cyclohexanecarboxylate $[\alpha]_{578}^{20}$ = +56.3 (c=0.266, EtOH) (Armarego, W. L. F.; Kobayashi, T. *J. Chem. Soc. (C)*, **1969**, 1635)}.
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9. The absolute configuration of the β-amino esters **2b,d,g** was ascertained by comparison of spectroscopic data of confrontable β-amino esters of known configuration.

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