Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8511-8514, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10301-X

Chiral Cyclic β-Amino Esters. Part II : Synthesis by Diastereoselective Reduction of Enamino Esters.

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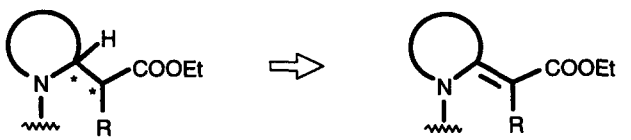
Abstract : Catalytic and chemical reductions of chiral pyrrolidine β-enamino esters provides corresponding β-amino esters with good to moderate diastereomer excesses. The unexpected major diastereomer **5** comes from a reduction process which amounts to an *anti* hydrogen addition. © 1997 Elsevier Science Ltd.

In *Part I* we described the synthesis of pyrrolidine β-amino esters **A** by reduction of the corresponding trisubstituted enamino esters followed by alkylation[1]. Such compounds, which are useful intermediates in alkaloid synthesis, could also be obtained directly by reduction of tetrasubstituted β-enamino esters **D**.



A **D**

Scheme 1

The reduction of the prochiral exocyclic double bond plays generally a major role in the route to natural product[2-4], as two stereogenic centers are created simultaneously. The use of a chiral auxiliary which induces a facial differenciation during the reduction and the stereospecificity of this reaction may enhance the diastereoselectivity of this step in order to obtain the desired stereochemistry of the asymmetric centers of a given alkaloid. Recently we used α-methylbenzylamine as chiral source in the synthesis of disubstituted pyrrolidines[5] and (-)isoretronecanol[6] by *syn* reduction of an endocyclic double bond.

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We report herein our results dealing with the reduction of chiral pyrrolidine β-enamino esters with a tetrasubstituted exocyclic double bond either in a catalytic or a chemical way, using different reducing agents.

Chiral β-enamino esters **2** were easily prepared by modified Eschenmoser coupling reaction[7] of *S*-1-(1-phenylethyl)-pyrrolidin-2-thione[1,8] with a series of commercial secondary α-bromo esters. All compounds **2** were obtained as a mixture of *E/Z* diastereomers in 75/25 ratio[9a] excepted for **2a** (R = CH_3) (90/10).

Theoritical calculations were carried out in order to predict the major conformation of enaminoester **2a**(*E*) : Molecular Modelling studies were performed by way of SYBYL 6.03[10] software on this compound. All the generated geometries were minimized using the Tripos force-field and optimized using AM1[11] calculations. Conformational space of compound **2a** was explored using the SYBYL search facility. The two bonds C*-N (θ_1) and C*-Ph (θ_2) were allowed to rotate respectively from 0 to 360° and 0 to 180° by 15° increments. The obtained results were analyzed by graphical representation in three dimensions (E, θ_1, θ_2). Its two dimensional projection (E, θ_1) showed a single deep minimum with a high energetical barrier of 68.4 kJ.mol^{-1} . Consequently only one conformer of **2a** (*E*) is present. In this preferred conformation, in which nitrogen atom is plane, (Fig.1) one face of the molecule is overcrowded by the bulky phenyl group. Therefore a very high stereospecificity can be predicted for the hydrogenation reaction and, in particular, for the creation of the stereogenic center **C-2'** with a ***R*** configuration.

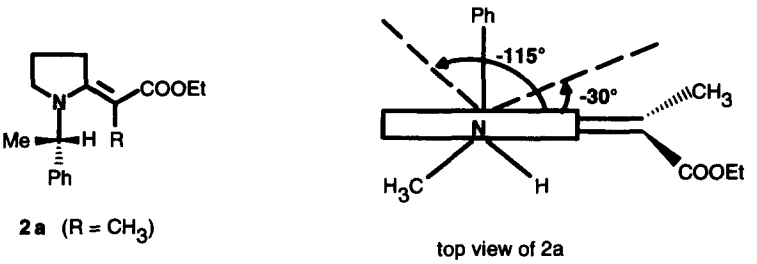


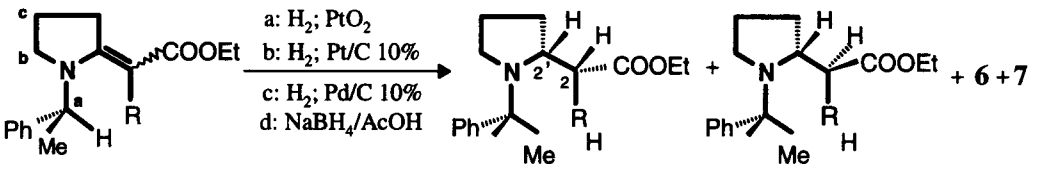
Figure 1

All reductions of compounds **2a-d** were carried out directly on the *E/Z* mixture which could not be separated. Hydrogenations were performed in ethanol, using PtO_2, 10% Pt/C and 10% Pd/C as catalysts; chemical reductions were realized with sodiumborohydride in acetic acid[12].

Chiral β-amino esters were obtained in good yields (80-98%) as a mixture[9b] of three or four diastereomers, **4**, **5**, **6**, **7** inseparable by chromatography. Two diastereomers (**4** and **5**) are generally detected in higher proportion and represent about 85 to 90% of the mixture: the percentage of **6** never exceeds 5% and **7** varies between 5% and 15%. In most cases, the major diastereomer is **5** (60-70% with $NaBH_4$; 70-80% with Pt/C; and 85-90% with Pd/C) and not the expected stereomer **4**, resulting from a *syn*

hydrogenation of enaminoester **2**(*E*). Diastereomer **4** is the major one only for **2a** (R=Me) and **2c** (R=Pr) reduced with PtO_2 (respectively 44% and 56%). For all compounds **2a-d**, the highest diastereoselectivity was achieved with 10% Pd/C (de 68 to 84%).

X-ray cristallography, carried out on **5a** (R=Me) as its picrate, showed ***2S***, ***2'R*** absolute configurations (*anti* relationship), while **4a** has been shown to have ***2R***, ***2'R*** configurations[1].



2 **4** *(2'R,2R)* **5** *(2'R,2S)*

Scheme 2

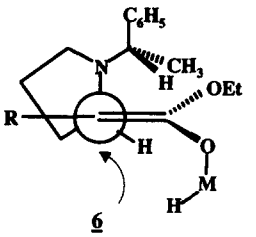
The same absolute configurations can be respectively assigned to stereomers **5** and **4** issued from **2b**, **2c** and **2d.** These attributions were based on a comparison of chemical shifts in ^{13}C NMR of three significant carbon atoms of these compounds with **5a** and **4a** whose structures are known (Table 1).

Table 1 : ^{13}C NMR (62.5 MHz) data for C_a, C_b, C_c of β-amino esters **4** and **5** (δ ppm).

Carbon	C_a		C_b		C_c	
Diast.	**4**	**5**	**4**	**5**	**4**	**5**
a ; R = Me	58.6	57.0	47.9	46.7	24.1	23.4
b ; R = Et	58.7	56.6	47.5	46.8	24.1	23.2
c ; R = Pr	58.6	56.8	47.5	46.6	24.1	23.2
d ; R = Bu	58.7	57.1	47.6	46.8	24.1	22.8

The ***R*** configuration at **C-2'** of compounds **4** and **5,** which represents more than 80% of the reduction product, is in agreement with the prediction based on Molecular Modelling studies and with the results observed for reduction of enamino esters endocyclic tetrasubstituted double bond[5,6,12] or exocyclic trisubstituted one[8].

It is noteworthly that **5** is mainly obtained (≥85%) whereas the *syn* hydrogenation of the major diastereomer *E* in the mixture of **2** would afford to **4**. The presence of both *syn* and *anti* addition products is often explained by a double bond migration during the reduction course[13-15]. An other example about some enamino esters has recently been reported[16]. In our case, the formation of the major diastereomer **5** could be explained by an oxallylic intermediate[17] like **6**, in which 1,3-allylic strain were minimized (Scheme 3).



6

Scheme 3

In this work, the satisfactory diastereoselectivity observed, particularly in the catalytic hydrogenation using 10% Pd/C, allows us to use now functionnalized β-enamino esters as precursors of pyrrolizidine and indolizidine alkaloids. In conclusion, enantiopure β-amino esters with *syn* or *anti* relationship between **C-2** and **C-2'** can be easily prepared either by a reduction-alkylation sequence[1] or by a direct reduction of tetrasubstituted β-enamino esters.

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(*Received in France* 20 *August* 1997; *accepted* 2 *October* 1997)