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A Facile and Stereocontrolled Synthesis of *syn*-α-Alkyl α–Hydroxy β-Amino Acids

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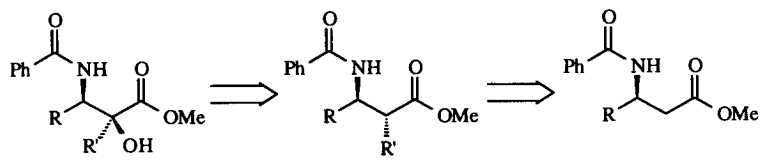
Abstract: The diastereoselective synthesis of *syn*-α-alkyl α–hydroxy β-amino acids **4a-h** was easily accomplished by reaction of the sodium dianion of the corresponding *anti* α-alkyl β-benzoylamino acid methyl esters with iodine. The intermediate α-iodo derivatives spontaneously afforded *cis*-oxazolines which, upon hydrolysis, provided the desired products, with diastereoselectivities up to 99:1. © 1999 Elsevier Science Ltd. All rights reserved.

The synthesis of polysubstituted amino acids is of great importance for the design and preparation of unnatural polypeptides containing a rigid frame which can be the promoter of a constrained conformation of the whole peptide.[1] Thus development of facile synthetic methods for the preparation of such molecules is highly desirable. Furthermore, α,α-disubstituted α-hydroxy β-amino acids are constituents of biologically active compounds, such as some highly active derivatives of Taxol.[2]

We have recently reported the preparation of α-alkyl α-hydroxy β-amino acids by the formation of *trans*-oxazolines,[3] which are alkylated at C-5 in high yields and then hydrolysed under mildly acidic conditions, affording the corresponding hydroxy amides in quantitative yield. This method gave *anti* isomers with good to high diastereoselectivity.

In this paper we describe a straightforward synthesis which affords *syn* α-alkyl α-hydroxy β-amino acids in a few steps; thus this method is complementary to the preceeding one. In order to obtain the C-2 epimer, a variation of the strategy was adopted: the α-alkyl group was introduced first, then the α-hydroxy group was added to the β-amino acid with high diastereoselection (Scheme 1).

Scheme 1.



Reactions were performed on racemic 3-aminobutanoic acid (R = Me), which is commercially available, and 3-phenyl-3-aminopropanoic acid (R = Ph), which was readily obtained on a multigram scale through a

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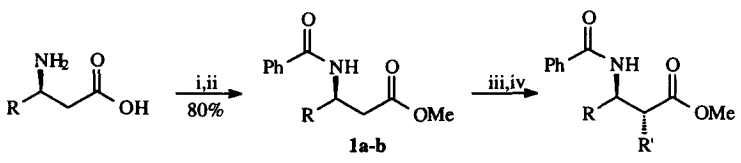
known procedure.[4] It is well known that the β-amino acids can be obtained in the enantiomerically pure form by kinetic resolution of their phenylacetamides with penicillin G amidase,[5] so, by using enantiomerically pure starting material, this method affords enantiomerically pure compounds. The β-amino acids were transformed into their benzamido methyl esters **1a** and **1b**, then alkylated following a known procedure [6] (Scheme 2). The esters **1a** and **1b** were treated with LiHMDS (2.2 equiv.) then the appropriate alkylating agent was added at low temperature: the reactions proceed with high yields and diastereoselectivity.

Scheme 2.



1a-b **2a-h**

a: R = Me, R' = Me; **b**: R = Me, R' = Et; **c**: R = Me, R' = allyl; **d**: R = Me, R' = CH_2Ph; **e**: R = Ph, R' = Me; **f**: R = Ph, R' = Et; **g**: R = Ph, R' = allyl; **h**: R = Ph, R' = CH_2Ph.

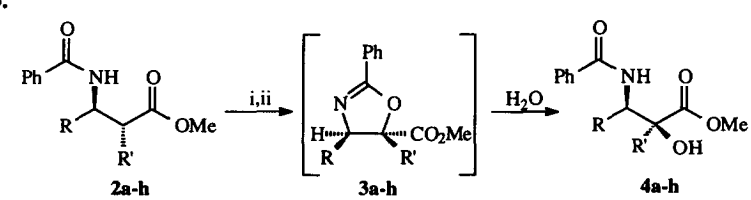
yield 70-99%
diastereomeric ratio > 99:1

Reagents and conditions: i: PhCOCl (1.1 equiv.), Et_3N (2 equiv.); ii: MeOH, $SOCl_2$ (2 equiv.); iii: LiHMDS (2.2 equiv.), THF, 0 °C, 5 h; iv: alkylating agent (1.2 equiv.), -60 °C to r.t. for R = Me and -30 °C to r.t. for R = Ph; 14 h.

The low temperature for the alkylation reaction is required more in order to obtain high yields than diastereoselectivities; indeed if the alkylation reaction is performed at higher temperature (i.e. 0 °C), worse yields are obtained: on the other hand in the following steps, the stereogenic centre at C-2 is temporarily destroyed, owing to the formation of an intermediate carbanion.

Then our goal was the introduction of hydroxyl group at C-2 with high diastereoselectivity on a very hindered carbon atom. From known methods used to introduce a "positive" hydroxyl group on a carbanion [7] we choose to react the sodium dianions of **2a-h** with iodine (Scheme 3), as we had successfully used in the synthesis of (2*R*,3*S*)-*N*-benzoylphenylisoserine methyl ester [8] and methyl (2*R*,3*S*)-3-benzoylamino-2-hydroxybutanoate.[3] Following this route, the 4,5,5-trisubstituted oxazolines **3** should be formed and should furnish the desired products **4** after mild acidic hydrolysis.

Scheme 3.



2a-h **3a-h** **4a-h**

Reagents and Conditions: i: NaHMDS (2.2 equiv.), dry THF, r.t.; ii: I_2 (2.4 equiv.), dry THF, r.t.

We obtained exclusively the 2-hydroxy derivatives **4** with good diastereoselectivity and with the desired *syn* configuration. No trace of the intermediate oxazoline **3** was observed. The results are reported in Table 1.

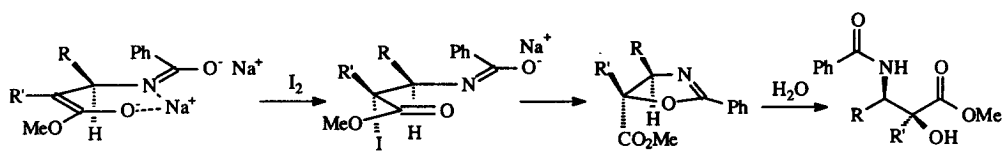
Table 1. Chemical yields and Diastereomeric Product Ratios for the Cyclisation of Amidoesters **2a-h**.

Reagent	R	R'	Time (h) of NaHMDS	Time (h) of I_2	Yield of **4** (%)	*syn*/*anti* ratio of **4**
2a	Me	Me	5	16	50	68:32
2b	Me	Et	16	24	20	68:32
2c	Me	Allyl	7	16	30	>99:1
2d	Me	CH_2Ph	16	24	50	75:25
2e	Ph	Me	16	24	75	60:40
2f	Ph	Et	16	24	50	>99:1
2g	Ph	Allyl	16	24	77	76:24
2h	Ph	CH_2Ph	16	24	99	70:30

The yields are modest to good and the diastereomeric ratios are modest to excellent. In no case was the oxazoline **3** isolated, even if the cyclisation was performed for a shorter time.[9] However, it is reasonable to think that the 2-hydroxy derivatives **4a-h** are products of hydrolysis of the oxazolines **3a-h** during the reaction work-up.[10] The observed stereochemistry was determined by comparison of the ^1H NMR of the products with authentic samples.[3][11]

The hypothesis of participation of a heterocycle accounts for the observed *syn* diastereoselectivity. The sodium dianion should react with iodine, forming an intermediate *anti* 2-iodo derivative,[12] which is transformed into the corresponding heterocycle and hydrolysed (Scheme 4). The presence of a substituent at C-3 (a methyl or a phenyl group) accounts for the good diastereoselectivity, whilst the presence of a substituent at C-2 (a methyl, ethyl, allyl or benzyl group) determines the yield, which is never quantitative. Indeed in the absence of a substituent at C-2, better yields were obtained.[3][8] The best diastereoselectivities (reagents **2c** and **2f**) were associated with modest yields, perhaps, due to incomplete formation of the α-iododerivative, albeit with high diastereoselectivity.

Scheme 4.



In conclusion, we have developed a straightforward synthetic method which gives *syn* α-alkyl α-hydroxy β-amino acids from β-amino acids with good to high diastereoselectivity. These highly functionalised molecules are of great interest both in the synthesis of modified peptide chains and in the preparation of new biologically active molecules, such as new members of the Taxol family.

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(9) In a typical procedure, NaHMDS (0.44 mmol, sol. 1M in THF, 0.44 mL) was added to a stirred solution of **2a-h** (0.2 mmol) in dry THF (5 mL) and the mixture was stirred at room temperature for the scheduled time (see Table 1). Then iodine (0.48 mmol, 0.12 g) in dry THF (10 mL) was added and the mixture was stirred at room temperature for the additional time reported in Table 1. Then an aqueous saturated solution of ammonium chloride was added, THF was eliminated under reduced pressure and replaced with ethyl acetate. The organic layer was washed twice with a saturated solution of sodium thiosulphate, dried over sodium sulphate and concentrated. The residue was chromatographed on silica gel (cyclohexane: ethyl acetate in 8:2 ratio as eluant).

(10) Several attempts to detect the presence of the oxazoline were fruitless: these oxazolines cannot be detected by GC-MS, furthermore the TLC analysis of the crude reaction is difficult to understand, owing to the presence of unreacted iodine. When the TLC analysis is performed after work-up with aqueous ammonium chloride and aqueous sodium thiosulphate, only the starting material and the compound **4** are present.

(11) The ^{1}H NMR of the hydroxy derivatives **4f**: ^{1}H NMR ($CDCl_3$): δ 0.79 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.33 (m, 1H, $CHHCH_3$), 1.75 (m, 1H, $CHHCH_3$), 3.68 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 5.50 (d, 1H, J = 9.5 Hz), 7.11 (d, 1H, J = 9.5 Hz, NH), 7.19-7.60 (m, 8H, Ph), 7.65-7.85 (m, 2H, Ph).

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