Tetrahedron: Asymmetry Vol. 1, No.6 , pp.371-374 , 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF α,γ-DIAMINO-β-HYDROXY AMINO ACID ESTERS: A NEW CLASS OF AMINO ACIDS

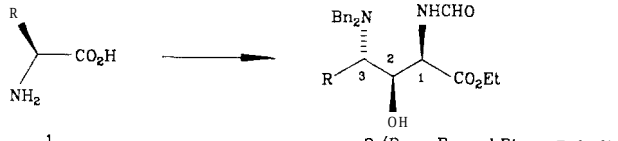
M.T. Reetz*, T. Wiinsch and K. Harms

Fachbereich Chemie der Universitaet, Hans-Meerwein-Str., 3550 Marburg, FRG

(Reccivcd 15 May 1990)

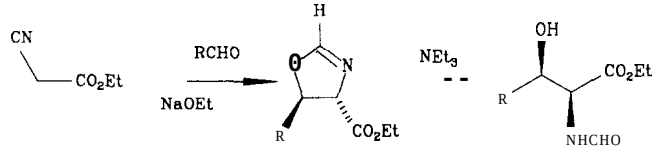
Abstract: Isocyano-acetic acid ethylester 3 undergoes a base catalyzed aldol-type addition to N,N-dibenzylamino aldehydes 6 to form oxazolines 7 stereoselectively; these can be ring-opened with NEt_3, affording α,γ-diamino-β-hydroxy amino acid esters 2.

The synthesis of unnatural amino acids is of considerable current interest, primarily due to their observed or potential biological activity as such or as components of larger molecules (e.g., peptides)[1]. In this communication we report the stereoselective synthesis of α,γ-diamino-β-hydroxy amino acid derivatives of the type 2 starting from a-amino acids 1:



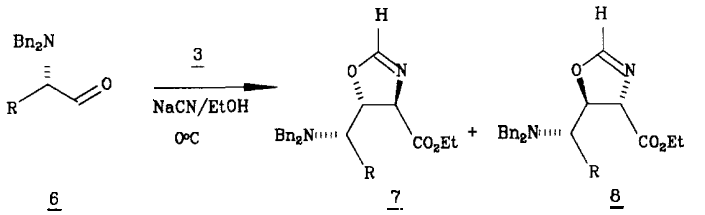
1 2 (Bn = Benzyl;Et = Ethyl)

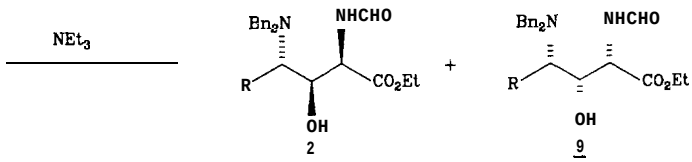
Retrosynthetic analysis of 2 points to an aldol-type addition of a glycine enolate or equivalent to N,N-dibenzylamino aldehydes 6 derived from 1. Indeed, previous studies have shown that simple ester enolates add to 6 with a high degree of non-chelation control[2], which corresponds to the relative stereochemistry at C2/C3 in the present target molecules 2. Since glycine enolates or equivalents are prochiral, simple diastereoselectivity at C1/C2 in 2 is also relevant. Such syn-selectivity was reported by Schollkopf in the base-catalyzed addition of isocyano-acetic acid ester 3 to simple aldehydes, the oxazolines 4 having the thermodynamically controlled (racemic) trans stereochemistry[3]. These undergo stereospecific ring opening with NEt_3/H_2O to form racemic amino acid derivatives 5[3]:



3 4 (rac) 5 (rac)

Using this methodology, we reacted the amino aldehydes 6[2] with 3. Indeed, only two of the four possible diastereomers 2/9 were observed, the desired stereoisomer 2 predominating[4]:





a) R = CH,	84	16 (62%)
b) R = $PhCH_2$	84	16 (58%)
c) R = $(CH_3)_2CH$	81	19 (73%)
d) R = $(CH_3)_2CHCH_2$	67	13 (51%)

The configurational assignments were made by NMR-spectroscopy and x-ray structural analysis, for example, of the major product 2b[5]:

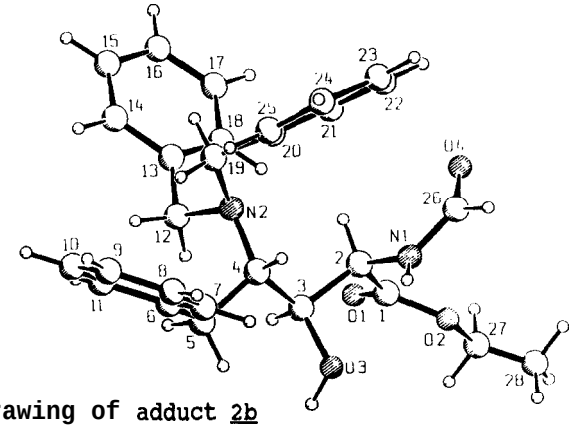
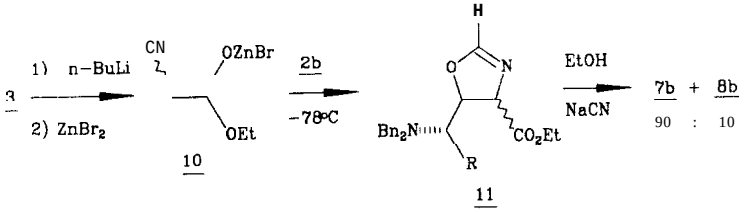


Fig. 1. SHAKAL-drawing of adduct 2b

The results show that thermodynamically controlled simple diastereoselectivity (syn at C1/C2) is > 98 % and that kinetically controlled diastereofacial selectivity in favor of non-chelation amounts to 81-87 %. This is

an interesting case in which kinetic and thermodynamic control are both operating at two different centers in one molecule. In order to show that no racemization at Cl of the starting aldehydes 6 occurs, the adducts 2 were examined with an optically active HPLC column. Using a ChiraSpher^{R} column[6], no appreciable racemization was detected as shown by the analysis of 2d and its racemic form.

In order to increase diastereofacial selectivity, the lithium enolate of the ester 3 was prepared followed by Li/Zn exchange[7]. The resulting Zn-enolate 10 was added in situ to the aldehyde 6b (R = $PhCH_2$), affording a mixture of four oxazolines 11 (7b/8b and the corresponding two cis-forms). The crude product was subjected to cis/trans-equilibration using weakly basic NaCN/EtOH to form a 90 : 10 mixture of 7b/8b. Recrystallization from ethanol resulted in an 81 % yield of pure 7b (R = $PhCH_2$). This procedure[8] may be the method of choice, especially since separation of diastereomers in the final stage, i.e., of 2/9 is not uniformly easy.



In summary, we have devised a simple method for the stereoselective synthesis of a new class of amino acid esters 2 having differently protected amino groups. Such regiospecific protection may be of utility in further reactions. Since many amino acids 1 are also available in the D-form, the enantiomers of the products 2 are also accessible.

Acknowledgement: We thank the Deutsche Forschungsgemeinschaft (SFB 260 and Leibniz Programm) and the Fonds der Chemischen Industrie for support.

References and Notes:

1) See for example: R.M. Williams, "Synthesis of Optically Active Alpha-Amino Acids", Pergamon Press, Oxford 1989.
2) M.T. Reetz, M.W. Drewes, A. Schmitz, Angew. Chem. 99 (1987) 1186; Angew. Chem. Int. Ed. Engl. 26 (1987) 1141. Review of chelation and non-chelation controlled reactions of alkoxy carbonyl compounds: M.T. Reetz, Angew. Chem. 96 (1984) 542; Angew. Chem. Int. Ed. Engl. 23 (1984) 556.
3) D. Hoppe, U. Schöllkopf, Liebigs Ann. Chem. 763 (1972) 1.

4) Typical procedure: The mixture of the ester 3 (0.22 ml, 2.0 mmol) and NaCN (12.5 mg, 0.3 mmol) in 30 ml of ethanol is stirred at room temp. for I5 min, cooled to 0°C and treated with 2.0 mmol of an aldehyde 6[2] in 5 ml ethanol. After 0.5 h the temp. is raised to 23°C, the mixture stirred for another 0.5 h and then worked up by addition of sat. NH_4Cl. Following several extractions with ether the combined org. phases are washed with NaCl-soln. and dried over $MgSO_4$. The solvent is removed and the brown oil is dissolved in 20 ml of ethanol. Several drops of NEt_3 and 2 ml H_2O are added and the mixture is heated under reflux for 6 h. The mixture is diluted with H_2O, extracted with ethyl acetate and dried over $MgSO_4$. Removal of solvents followed by flash chromatography (pet ether/ethyl acetate 1 : 1) on SiO_2 affords 2/9.

5) Details of the crystal structure are available from the Cambridge Crystallographic Date Centre, University Chemical Lab., Lensfield Road, Cambridge CB2 1EW, U.K. Request should be accompanied by a full literature citation for this communication.

6) ChiraSpher^R is commercially available from Merck (Darmstadt, FRG) and is based on a Blaschke column: G. Blaschke, W. Broker, W. Fraenkel, Angew. Chem. 98 (1986) 808; Angew. Chem. Int. Ed. Engl. 25 (1986) 830.

7) Zn-enolate of N,N-diethyl glycine ester: J.T.B.H. Iastrzebski, F.H. van der Steen, G. van Koten, Recl. Chim. Pays-Bas 106 (1987) 516.

8) The solution of the ester 3 (0.22 ml, 2.0 mmol) in 30 ml of dry THF is treated with 2.0 mmol of n-butyllithium in hexane at -78°C. A solution of $ZnBr_2$ (473 mg, 2.1 mmol) in 10 ml THF is added dropwise and the mixture is stirred for 0.5 h. The aldehyde 6b in 10 ml THF is added and the mixture is stirred for 17 h at -78°C. sat. NH_4Cl is added, the mixture is extracted with ether, the combined org. phases are washed with NaCl-soln. and dried over $MgSO_4$, and the solvents are removed. The crude product is dissolved in 50 ml of abs. ethanol, two crystals of NaCN are added and the soln. is stirred at room temp. for 2 h. Water is added, the mixture is extracted with ether, the combined org. phases are washed with NaCl-soln. and dried over $MgSO_4$, and the solvents are removed. The crude product is recrystallized from ethanol to afford 717 mg (81%) of pure 7b having a m.p. of 84°C. ^{13}C-NMR ($CDCl_3$): δ = 14.2, 32.1, 54.1, 61.8, 62.2, 71.7, 80.9, 126.2, 127.0, 128.2, 128.3, 128.8, 129.5, 139.0, 139.6, 156.2, 170.7 ppm. The product can be transformed into 2b by treatment with NEt_3/H_2O[4]. ^{13}C-NMR ($CDCl_3$) of 2b: 14.0, 32.4, 53.8, 54.5, 60.6, 61.7, 72.7, 126.1, 127.0, 128.3, 129.1, 129.5, 139.1, 141.1, 162.0, 171.4 ppm.