Tetrahedron Letters, Vol. 33, No. 33, pp. 4743-4746, 1992
Printed in Great Britain

0040-4039/92 $5.00 +
Pergamon Press Ltd

A New Chiral Glycine Synthon. Synthesis, X-Ray Structure of (-).(2S,4R)-2-Ethoxycarbonyl-4-phenyl-1,3-oxazolidine and Diastereoselective Nucleophilic Ring Opening to (R)-Ethyl α-Amino Carboxylates.

Celia Andrés,[a] Alfonso González,[a] Rafael Pedrosa,[a]* Alfonso Pérez-Encabo,[a] Santiago García-Granda,[b] M. A. Salvadó,[b] and Fermín Gómez-Beltrán.[b]

[a]Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Dr. Mergelina s/n, 47011-Valladolid. Spain.
[b]Departamento de Química Física y Analítica, F. de Química, Universidad de Oviedo, Julián Claverías s/n, 33006-Oviedo. Spain

Key words: Chiral Oxazolidines, alpha-amino Esters, Chiral Glycine Synthon, Ring Opening, Asymmetric Synthesis

Abstract. Condensation of (R)-N-benzyl-2-phenylglycinol **1** with the methyl hemiacetal of ethyl glyoxylate leads to (2S,4R)-2-ethoxycarbonyl-4-phenyl-1,3-oxazolidine **2** as the major product, obtained as a pure enantiomer after column chromatography. Compound **2** is stereoselectively cleaved by dialkylzinc reagents, prepared from alkylmagnesium iodides and $ZnCl_2$, with moderate to good d.e.'s (72-94 %). These compounds, after separation by column chromatography and debenzylation by hydrogenolysis in the presence of 10% Pd on carbon, lead to enantiomerically pure ethyl α-amino carboxylates with good chemical yields.

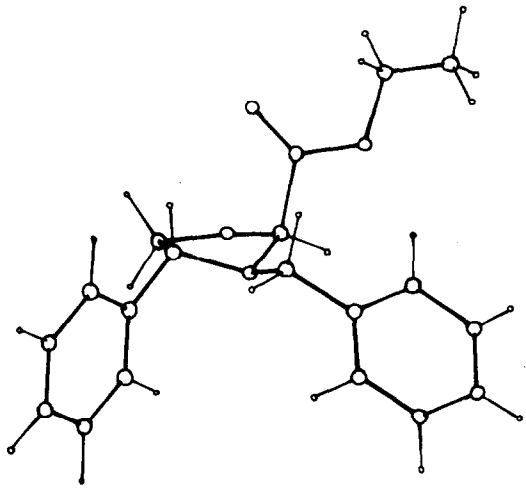
Recently, considerable attention has been drawn to the stereoselective synthesis of nonproteinogenic and natural and non natural proteinogenic α-aminoacids, owing to their biological interest.[1] Some recent methodological advances in this field are the electrophilic alkylation of bislatim ethers,[2] alkylation on chiral glycine enolates derived from oxazinones,[3] imidazolidinones,[4] and oxazolidinones;[5] reaction of nucleophiles with electrophilic chiral glycinates,[6] and asymmetric alkylation of N-acylpyrrolidines,[7] N-acyloxazolidones,[8] and N-(cyanomethyl)oxazolidines.[9]

On the other hand, chiral cyclic N,O-acetals have been used widely as chiral adjuvants,[10] but the nucleophilic ring opening of these heterocycles in asymmetric synthesis is only restricted until now to the preparation of chiral amines.[11]

As a part of our work on stereoselective nucleophilic ring opening of chiral 1,3-oxazines,[12] we wish now to report on a short and efficient route to ethyl α–amino carboxylates, starting from 2-ethoxycarbonyl-1,3-oxazolidine **2**.

The condensation of (-).(R)-N-benzyl-2-phenylglycinol **1** with the methyl hemiacetal of ethyl glyoxylate, in refluxing CH_2Cl_2 and mol. sieves for 2 h, gave a mixture (83:17) of epimeric 2-ethoxycarbonyl-1,3-oxazolidines **2** and **3** (95% chemical yield). The mixture was separated by column chromatography on silica gel (hexane/ethyl acetae 15/1 as eluent) giving, by the order of elution pure **2**, as a white solid (m.p. 55-56°C from pentane), and **3**, as a colorless oil (b.p. 221-223°C/2 Torr), in 66 and 10 per cent total yield respectively.[13]

Owing to the controversial stereochemical assignment of the 2-phenylglycinol-derived oxazolidines,[14] and that any further rationalization on the stereochemical course of the reactions will be associated with the geometry of this substrate, we have established the absolute configuration of the compound **2** by a single-crystal X-ray determination.[15] In contrast with 2-alkyl-4-phenyl-1,3-oxazolidines, the phenyl group at C-4 and the ethoxycarbonyl at C-2 have a *trans* relationship in the major diastereomer 2, while the benzyl substituent on the nitrogen is *cis* with respect to the substituent at C-2. Then, the absolute stereochemistry for compound **2**, derived from (R)-N-benzyl-2-phenyl glycinol will be 2S,4R, whereas the stereochemistry for the minor diastereomer **3** is assigned as 2R,4R.



PLUTO plot for Compound 2

(2S,4R)-2-Ethoxycarbonyl-1,3-oxazolidine **2** was recovered unchanged after stirring for 4h with 4 eq. of a solution of diethylzinc in hexane, but it does react with dialkylzinc regents, prepared from alkylmagnesium iodides and zinc chloride,[16] in diethyl ether at 0°C for 2-3h,[17] leading to the ring opening compounds **4** and **5** with good diastereoselectivity.The same results are obtained by reaction of **2** with 4 eq. of a mixture of commercial Et_2Zn and MgI_2 (1/1). Moreover, diastereomers **4** and **5** were obtained as pure compounds from the reaction mixtures by flash chromatography on silica gel using hexane/ethyl acetate 8/1 as eluent. The mixture

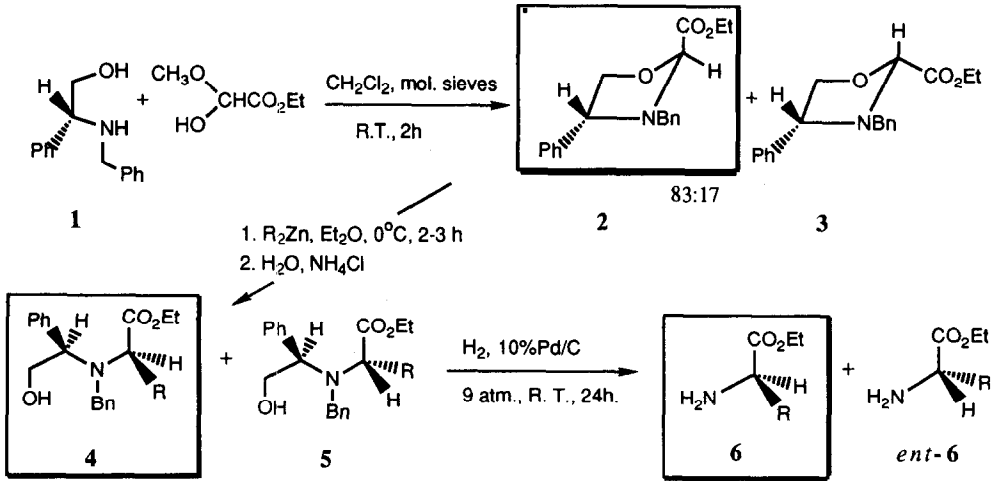


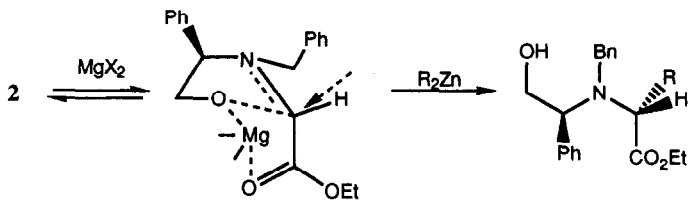
Table 1. Diastereoselective Ring Opening of Compound **2** by Dialkylzinc reagents, in Et_2O at 0°C.

Entry	R	Time(h)	Molar Ratio (**4**/**5**)[a,b]	Debenzylated mixtures e.e.[c]	Chemical Yield(%)[d]	Conf.[e]
a	Me	2	86/14 (>98/2)	72 (>98)	(**6a**)45	R
b	Et	2	87/13 (>98/2)	74 (>98)	(**6b**)42	R
c	Pr	2.5	88/12 (>98/2)	76 (>98)	(**6c**)47	R
d	i-Pr	2	97/3 (>98/2)	94 (>98)	(**6d**)56	R
e	n-Bu	2	92/8 (>98/2)	84 (>98)	(**6e**)54	R
f	i-Bu	3	89/11 (>98/2)	78 (>98)	(**6f**)47	R

[a]Measured by ^{13}C-NMR on the reaction mixture. [b] Numbers in parenthesis refer to the ratio after separation of diastereomers by column chromatography. [c]Measured by G.C.on a Chirasil-val column derivatized as trifluoroacetamides, in parenthesis are given the e.e. for **6** after purification of compounds **4**. [d]Numbers refer to the total chemical yields from **2** of the isolated pure amino esters **6**. [e]The given configurations correspond to the major isomer formed in the reaction.

of diastereomers were bis-debenzylated by hydrogenolysis, at room temperature using 10% Pd on carbon as catalyst, to a mixture of **6** and *ent*-**6**, maintaining their stereochemical integrity,[18] while debenzylation of diastereomers **4** purified by chromatography allowed to obtain (R)-ethyl α-aminocarboxylates **6** with excellent e.e. (>98%) (table).

The sense of the asymmetric induction in the ring opening of **2** can be explained, by analogy to the behaviour of chiral acetals.[19] Taking into account that the dialkylzincs only react with **2** in the presence of a Lewis acid (in our case the magnesium halides formed in the preparation of the zinc derivatives) we propose, as the first step of the reaction, the formation of a chelate ion pair **7**, followed by a rapid capture by the nucleophile from the nitrogen side of the heterocycle.



7 **4**

In summary, (2S,4R)-2-ethoxycarbonyl-4-phenyl-1,3-oxazolidine **2** has been shown as a convenient homochiral glycine synthon equivalent in its diastereoselective ring opening by zinc derivatives. Enantiomerically pure (R)-ethyl α–amino carboxylates are easily prepared from **2**, in two steps, in good chemical yields. At the present we are working on the exploitation of **2** in different asymmetric transformations.

Acknowledgements

Authors are indebted to the Spanish DGICYT for the finnancial support of this work (Project PB89-0356). One of us (A. P.-E.) thanks to the Ministerio de Educación y Ciencia for a predoctoral fellowship (PFPI)

References and notes.

(1) Williams, R. M. *The Synthesis of Optically Active a-Amino Acids.* Pergamon Press: Oxford, **1989**.

(2) Schöllkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1989**, *44*, 5293-5305.

(3) (a) Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916-3926. (b) Ornstein, P. L. *J. Org. Chem.* **1989**, *54*, 2251-2253. (c) Dellaria, J. F.; Santarsiero, B.D. *Tetrahedron Lett.* **1988**, *29*, 6079

(4) Fitz, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277-5292.

(5) Blaser, D.; Ko, S. Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230-6233.

(6) (a) O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389-5401. (b) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103-1104. (c) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723-3728.

(7) Ikegami, K.; Uchiyama, H.; Hayama, T.; Kasuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333

(8) (a) Evans, D. A.; Britton, T. C.; Dorow, R. L;Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525-5540. (b) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881-6883.

(9) (a) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814-2820. (b) Marco, J. L. *Heterocycles* **1987**, *26*, 2579-2584

(10) (a) For a recent review on 1,3-oxazolidines see: Scolastico, C. *Pure and Appl. Chem.* **1988**, *60*, 1689-1698. (b) For an example on 1,3-perhydrobenzoxazines see: Eliel, E. L.; He, X.-C. *J. Org. Chem.* **1990**, *55*, 2114-2119. He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979-4987.

(11) (a) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340-1344. (b) Takahashi, H.; Hsieh, B.-C.; Higashiyama, K. *Chem. Phar. Bull.* **1990**, *38*, 2429-2434. (c) Alberola, A.; Andrés, C.; Perosa, R. *Synlett* **1990**, 763-765.

(12) Andrés, C.; Maestro, A.; Pedrosa, R.; Pérez-Encabo, A., Vicente, M. *Synlett* **1992**, 45-47.

(13) Both diastereomers were fully characterized by their analytical and spectral data. The optical rotations are as follows: For **2**, $[\alpha]_D^{25}$ = -139.9 (c = 1.6, $HCCl_3$). For **3**, $[\alpha]_D^{25}$ = -30.8 (c = 1.8, $HCCl_3$).

(14) Arséniyadis, S.; Huang, P. Q.; Morellet, N.; Beloeil, J.-C.; Husson, H.-P. *Heterocycles* **1990**, *31*, 1789-1799, and references therein

(15) *Crystal data for compound* **2**: M_r = 311.38, monoclinic, space group $P2_1$, a = 16.75 (1), b = 5.763 (1), c = 19.08 (1) Å, β = 111.59 (7)°, V = 1713 (2) $Å^3$, Z = 4, D_x = 1.21 g cm^{-3}. MoK_α radiation (graphite crystal monochromator, λ = 0.71073 Å), μ (MoK_α) = 0.76 cm^{-1}, F (000) = 664, T = 293K. Final conventional R-factor = 0.043 for 2047 "observed" reflections and 454 variables. The structure was solved by Direct Methods and Fourier synthesis. Distances and angles are normal.

(16) Kusama, F.; Koive, D. *J. Chem. Soc. Japan* **1951**, *72*, 871-874

(17) A typical experimental procedure is as follows: A solution of Me_2Zn (8 mmol) in 20 mL. of Et_2O was prepared by stirring anhydrous $ZnCl_2$ (1.088 g, 8 mmol) in 12 mL of Et_2O and 8 mL. of 1M solution of MeMgI under nitrogen. To this mixture, cooled to 0°C, was added a solution of **2** (622 mg, 2 mmol) in 10 mL of Et_2O, and stirred for 2 h under nitrogen. The reaction was quenched with a sat. NH_4Cl solution (5 mL), decanted, and the aqueous layer extracted with Et_2O (2x 20 mL). The organics were dried over anhydrous $MgSO_4$, the solvent was evaporated under vacuum and the products were isolated by column chromatography.

(18) The e.e.'s were determined by G.C. on a Chirasil-val column, derivatized as trifluoroacetamides.

(19) (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107-6115. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458-6467. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485-6487. (d) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074-7075.

(Received in UK 28 May 1992)