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Diastereoselective Synthesis of Functionalized 2,4-Diamino-3-hydroxyglutaric Acid Derivatives of Potential Biological Interest from Glycine Derivatives

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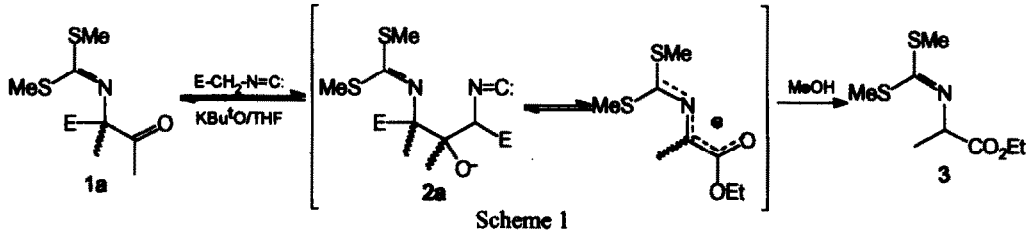
Abstract: Two out of the four possible diastereomers of *C*- and *N*-protected 2,4-diamino--3-hydroxyglutaric acid derivatives **6a-c** were obtained with diastereomeric excesses of 9:1 to 1:1. The compound **6b** was converted into two lactam derivatives of 2,4-di(N-methylamino)-3-hydroxy-3-phenylglutaric acid diethyl ester with retention of configuration.

More than 700 unusual aminoacids have already been found in nature, and there is an evergrowing interest in the synthesis, pharmacology, and conformational properties of these compounds due to their biological activities as antibiotics, metal chelators, neurotoxins, and enzyme inhibitors.[1] Thus, α,α-disubstituted-α-amino acids,[2] β- or γ-hydroxy-α-amino acids,[2,3] and bis-α-amino acids[4] have been the subject of numerous studies over recent years. In particular, 2,4-diamino-3-hydroxyglutaric acid derivatives have turned out promising in the development of new antitumoral agents.[5] Nevertheless, most syntheses thus far developed for these compounds usually use 1,3-diamino-2-propanol as starting material, therefore involving rather cumbersome transformations to complex diastereomeric mixtures.

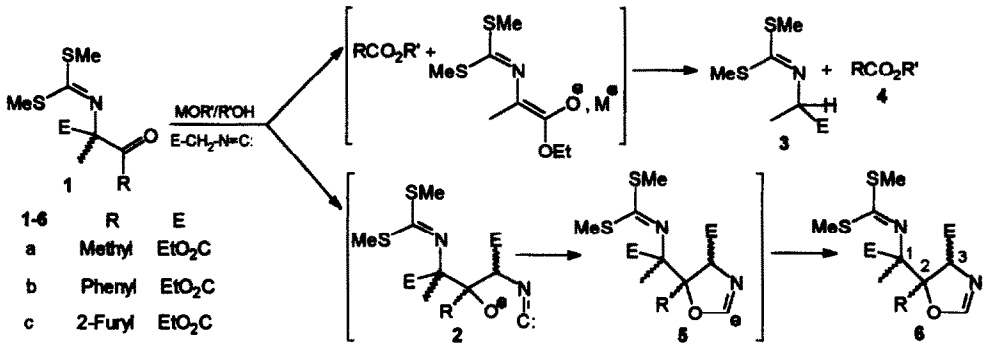
On the other hand, kinetically controlled aldol addition of α-metallated isocyanides to simple carbonyl compounds provides an useful route to β-amino alcohols.[6] Therefore, this methodology should allow for the diastereoselective synthesis of the 1,3-diamino-2-propanol moiety from suitable functionalized *N*-protected α-amino ketones. However, metalation of ethyl isocyanoacetate with KO^{t}Bu in THF at -78°C followed by treatment with ketones **1a** and **1b**[7] under standard reaction conditions[6a] did not produce the expected oxazolines (synthetic equivalents of 2,4-diamino-3-hydroxyglutaric acid derivatives) (Scheme 1), but *N*-bis(methylthio)-methylene alanine ethyl ester **3** was instead isolated after methanolic quenching, probably as a consequence of the low activation energy for the retro-aldol reaction[8] promoted by the high stability imparted to the extruded fragment by aza-allylic anion resonance[9], as well as steric compression in aldolates **2**.



Scheme 1

However, oxazolines **6** were obtained upon treatment of equimolecular amounts of ethyl isocyanoacetate and ketones **1** with metal alkoxides under protic conditions (Scheme 2; Table 1). In this media, the retro-Claisen reaction in this case responsible of the formation of **3** and the corresponding ester derivative of the acyl

fragment in the substrate **4** (isolated for **1b** and **1c**) was inhibited at the expense of the diastereoselective synthesis of oxazolines **6**. It has to be pointed out that, whereas the choice of the alkoxide/alcohol system had scarce influence on the **3**:**6** ratio in the case of lithium alkoxides, a marked dependence on this parameter was noticed in the case of potassium alkoxides (Table 1; runs 1-4).



Scheme 2

On the other hand, when the temperature was increased (runs 5-7) a decrease of **3**:**6** ratio was observed. Both these statements are in agreement with the minor activation energy needed for the aza-allyl anion **3** extrusion *versus* aldol reaction. Kinetic control was also observed in the diastereomeric reaction pathway to **6** *via* the adduct intermediate **2** (Scheme 2) since neither epimerization nor deuterium incorporation were observed when diastereomeric mixtures of oxazolines **6** were treated with $KMeO/CD_3OD$ under standard reaction conditions.

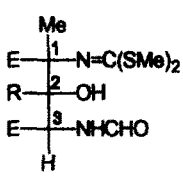
Table 1. Reaction of Ethyl Isocyanoacetate with Ketones 1 Under Protic Conditions[10]

Run	Ketone	MR'O	R'OH	t(°C)	**3**:**6** ratio	(1*R*,2*S*,3*S*:1*R*,2*S*,3*R*) ratio[11]
1	**1a**	Li^{t}BuO	^{t}BuOH	25	45:55	50:50
2	**1a**	LiMeO	MeOH	25	37:63	66:34
3	**1a**	K^{t}BuO	^{t}BuOH	25	45:55	59:41
4	**1a**	KMeO	MeOH	25	13:87	84:16
5	**1a**	NaEtO	EtOH	-23	16:84	82:18
6	**1a**	NaEtO	EtOH	0	5:95	80:20
7	**1a**	NaEtO	EtOH	25	5:95	80:20
8	**1a**	TlEtO	EtOH	25	18:82	83:17
9	**1b**	KEtO	EtOH	25	9:91	90:10
10	**1c**	KEtO	EtOH	20	20:80	88:12
11	**1c**	Li^{i}PrO	^{i}PrOH	20	15:85	70:30

Out of the four possible diastereomers for **6**, only two of them were obtained. The diastereoselectivities observed were subject to metal tuning, and the highest diastereomeric excesses were found with the use of potassium alkoxides (Table 1; run 4 for **1a**; run 9 for **1b**, and run 10 for **1c**).

Several attempts to hydrolyze the oxazolines **6b** were unsuccesful because a retroaldol fragmentation of β-hydroxyformamides **7**, which were originated by oxazoline ring opening, was the principal reaction pathway.[12] However, albeit oxazolines **6a** did scarcely undergo this retroaldol reaction, cyclization to single

diastereomeric **8a** and **9a** was obtained,[12] instead of the expected 2,4-diamino-2,3-dimethyl-3-hydroxyglutaric diethyl ester. It has to be pointed out that full epimerization to (1*R*,2*S*,3*R*:1*S*,2*R*,3*S*)-**7a** and (1*R*,2*S*,3*S*:1*S*,2*R*,3*R*)-**7b-7c** was observed for **6a** and **6b-c**, respectively, on comparing the ^{1}H-NMR (300 MHz) spectra of quenched reaction mixtures before the equilibrium was reached.



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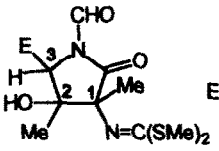
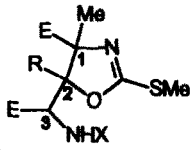
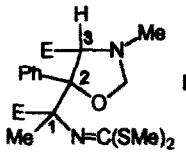


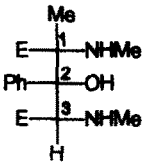
8a



9 (X:CHO)
10 (X:Me)



11b



12b

On the other hand, methylation of oxazoline **6b** followed by $NaBH_4$ reduction gave rise to oxazolidine **11b**, which upon oxalic acid hydrolysis cyclized to 2-methylthiooxazoline **10b** with good chemical yield. In this case, no epimerization of C-3 was observed. Repetition of the *N*-methylation/$NaBH_4$ reduction/oxalic acid hydrolysis[13] sequence on **10b** afforded the mixture of the two monolactam derivatives of **12b**. Therefore, the herein described methodology provides an access to symmetrical and unsymmetrical *N,N'*-difunctionalization of the 1,3-diamino-2-propanol core unit.

Stereochemical and structural control in the hydrolysis, new functionalization reactions, and the application of this aldol methodology to an enantioselective synthesis of bis-α-amino acid derivatives are in progress.

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REFERENCES AND NOTES

1. a) Weinstein, B. *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Marcel Dekker: New York. 1983; Vol. VII, pp. 267-357; b) Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Eng.* **1983**, *22*, 816-828c) Enders, D.; Jegelka, U.; Dücker, B. *Angew. Chem.. Int. Ed. Eng.* **1993**, *32*, 423-425; d) Wittenberger, S.J.; Baker, W. R.; Donner, B. G. *Tetrahedron*, **1993**, *49*, 1547-1556.
2. For a review on the synthesis of α,α-disubstituted and β-hydroxy-α-amino acids see: Williams, R.M.; *Synthesis of Optically Active α-Amino Acids*; Pergamon Pres:: Oxford. 1989 and references cited therein.
3. Recent references: a) Beullhausen, T; Groth, U.; Schöllkopf, U. *Liebigs Ann. Chem.* **1992**, 523-526; b) Zanbergen, P.; Brussee, J.; van der Gen, A.; Kuse, Ch. G. *Tetrahedron Asymmetry*, **1992**, *3*, 769-774; c) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, F. L. *Tetrahedron Asymmetry*, **1992**, *3*, 1127-1130; d) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360-366 and references cited therein.
4. a) Kunieda, T.; Ishizuku, T.; Iguchi, T.; Hiroe, M. *J. Org. Chem.* **1988**, *53*, 3381-3383; b) Bold, G.; Allmendinger, T.; Herold, P.; Moesch, L.; Schörr, W-. P.; Duthaler, R. O. *Helv. Chim. Acta*, **1992**, *75*, 865-882.
5. a) Sasamori, H.; Hori,C.; Chiba, K. *Jpn. Kokai Tokkyo Koho Jp* 02,223,591; *CA* **1991**, *115*, 84232; b) Sasamori, H.; Hori, C.; Niitsuma, S.; Chib, K.; *Jpn. Kokai Tokkyo Koho Jp* 03,127,796; *CA* **1991**, *115*, 293683.
6. a) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemann, K. H.; Eilers, E.; Blume, E. *Liebigs Ann. Chem.* **1976**, 183-202; b) Schöllkopf, U.; Gerhart, F.; Schröder, R.; Hoppe, D. *Liebigs Ann. Chem.* **1972**, 116-129.

7. Ketones **1** were synthetized from *N*-bis(methylthio)methylene alanine ethyl esther and the corresponding acyl halides as electrophiles, following literature conditions: Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066-2075.
8. Arnett, M. E.; Fischer, F. T.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1989**, *111*, 748-749.
9. Hoppe, D. *Angew. Chem, Int. Ed. Eng.* **1975**, *19*, 424-426.
10. To a suspension of MR'O (0.38 mmol) in R'OH (0.35 mL) under Ar atmosphere, a solution of ethyl isocyanoacetate (0.38 mmol) and **1** (0.38 mmol) in R'OH (0.7 mL) was added. The reaction mixture was stirred for 15 minutes at the given temperature, quenched with water, and extracted with CH_2Cl_2. The analysis by ^{1}H-NMR (300 MHz) of the reaction crudes showed in all cases a net conversion of initial ketone. (1*R*,2*S*,3*S*:1*R*,2*S*,3*R*) Oxazoline diastereomeric ratios were determined by ^{1}H-NMR from the reaction crude before their purification by flash chromatography on silica gel.
11. The major oxazoline was isolated in all cases to allow (1*R*,2*S*,3*S*) racemate configurational assignement . X-Ray determination for **6c**[14] is in agreement with the results obtained from NOE experiments on the mixtures of oxazoline **6c**. The generalization of this procedure to oxazolines **6a** and **6b** allowed the establishment of an identical relative configuration for the major isomers of these ones. These results can be justified on the basis of a geometrical minimization of the diastereomeric oxazolines with the MM2 force field[15] (results to be published). Minor oxazolines were in all cases the (1*R*,2*S*,3*R*) epimeric racemate.
12. Reaction conditions:[16] **1a**→**7a** (yield: 40%)(AcOH (1.8 M)/H_2O-EtOH, 20°C, 100 min); **6a**→**8a** (36%) + **9a** (47%) (AcOH (1.8 M)/H_2O-EtOH, pH=5-6, 50°C, 20 h.).
13. Reaction conditions:[17] **6b**→**11b** (yield: 85%): i) MeOTf, 2 eq. (2h, r.t.); ii) $NaBH_4$, 2 eq. (THF/MeOH: 4/1 v/v; 30 min., 0°C). **11b**→**10b** (yield: 86%):iii) oxalic acid, 5 eq. (THF/H_2O: 1/1 v/v, 64 h.,55°C). **10b**→**12b**(as a mixture of the two monolactam derivatives) (as i, ii, iii; yield: 65%). Structural and relative configuration of all these compounds were tested by ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz), and combustion analysis after purification by silica gel flash chromatography.
14. Crystal data for **6c**: $C_{18}H_{24}N_2O_6S_2$, monoclinic, a=10.538(6), b=11.356(3), c=18.213(7)Å, α=90°, β=104.23(3)°, γ=90°, V=2113(1)Å^3, Z=4, D_c=1.34 g.cm^{-3}, F(000)=904, μ(Mo-K_α)=2.74 cm^{-1}. Diffraction data were measured on an Enraf-Nonius CAD4 diffractometer operating in the ω-2θ mode with graphite-monochromated Mo-K_α radiation (λ=0.71069 Å) up to Θ=30° from a crystal of size 0.4x0.4x0.3 mm. 6128 Unique reflexions were scanned and 2140 with I>2σ(I) were considered and used in the analysis. The intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods and Fourier synthesis using the Multan 80[18] and the X-Ray 80[19] systems and refined by least squares. The R and R_w factors were of 0.078 and 0.074.
15. Molecular mechanic calculations were carried out using PCMODEL 4.0 software (Serena Software, Inc., Bloomington, IN, U.S.A.).
16. Schöllkopf, U.; Gerhart, F.; Schröder, R.; Hoppe, D. *Liebigs. Ann. Chem.* **1972**, 116-129.
17. a) Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098-7102; b) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A. *J. Am. Chem. Soc.* **1988**, *110*, 4611-4624.
18. Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. *MULTAN80*, University of York, England and Louvain, Belgium, **1980**.
19. Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. *X-Ray 80 System*, Computer Science Center, University of Maryland, College Park, **1985**.

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