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A Highly Diastereoselective Synthesis of 4-Alkyl *Threo* Glutamic Acids

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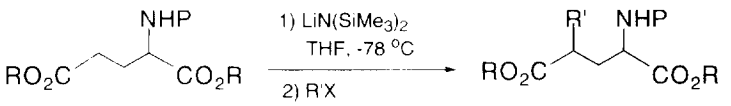
Abstract: Treatment of *N*-*p*-nitrobenzoyl *L*- or *D*-glutamic acid diester with lithium bis(trimethylsilyl)amide generates a chelated γ-enolate which reacts with alkyl halides to give (2*S*,4*S*)- or (2*R*,4*R*)-4-alkylated glutamic acid derivatives with very high diastereoselectivity.

Asymmetric synthesis of 4-substituted glutamic acids has generated extensive interest in recent years owing to the ease with which they can be further transformed into a variety of natural and unnatural amino acids.[1] Furthermore, some glutamic acid analogs have been reported to interact with glutamate receptor complex, and have exhibited potential as agents to modulate the function of glutamate receptors.[2] As part of a continuing research program we required enantiomerically pure 4-substituted glutamic acid derivatives. Although ample precedents for the preparation of 4-substituted glutamic acid via dianion mechanism have been reported, the main obstacle in these alkylation methods is the lack of diastereoselectivity. Rapoport *et al.* had developed an route to prepare 4-substituted glutamic acid derivatives through alkylation of glutamic acid diester with a 9-(9-phenylfluorenyl) as amine protecting group. They successfully demonstrated that the steric bulk amine protecting group prevented racemization at the α-center. However, the diastereomeric ratio (erythro:threo) of the alkylation products varied very little, only from 2:3 to 1:3 depending upon the electrophile used.[3] Hanessian *et al.* have reported that reaction of *N*-Cbz protected glutamate enolate with oxaziridine gave the γ-hydroxyglutamic acid with fairly good diaseteroselectivity (10:1).[4] More recently, North *et al.* reported that alkylation of *N*-Cbz protected glutamate enolate afforded a mixture of diastereoisomers at the γ-carbon with ratio about 2:1.[5] These results prompt us to report our own recent results on the alkylation of the γ-enolate of *N*-*p*-nitrobenzoyl protected glutamic acid diester with very high diastereospecificity.

Scheme 1



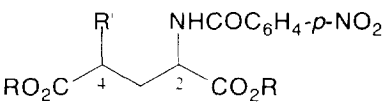
(*L*) or (*D*)

(2*S*, 4*S*) or (2*R*, 4*R*)

P = COC_6H_4-*p*-NO_2
R = Me or Et

Herein, we utilize the *p*-nitrobenzoyl as amine protecting group that electronically prevent α-deprotonation by acidifying the adjacent NH. Lithium bis(trimethylsilyl)amide is the choice of base for the reactions is due to its relative hinderness which may contribute to the diastereoselectivity. Thus, *N*-*p*-nitrobenzoyl *L*- or *D*-glutamic acid diester was treated with lithium bis(trimethylsilyl)amide (2.2 equiv.) in THF at -78 C for one hour to generate γ-enolate and an alkyl halide electrophile (3 equiv.) was then added (Scheme 1). The reaction mixture was stirred for an additional 2 to 3 hours at -78 °C (monitored by TLC) and then quenched with acetic acid. The 4-substituted glutamic acid products were obtained as single isomer in moderate to good yields (Table 1) accompanied by various amounts of unreacted starting materials. No attempt was made to optimize the yield of the alkylation products.

Table 1 Diastereoselective Synthesis of *Threo* 4-Alkylated Glutamic Acids.



Entry	Protected Glutamate	R	R'	Product (*threo*)	Isolated Yield (%)
1	*L*	Et	Me	2*S*,4*S*	65
2	*L*	Et	Et	2*S*,4*S*	56
3	*L*	Et	CH_2=$CHCH_2$	2*S*,4*S*	49
4	*L*	Et	$PhCH_2$	2*S*,4*S*	52
5	*D*	Me	Me	2*R*,4*R*	54
6	*D*	Me	Et	2*R*,4*R*	45
7	*D*	Me	CH_2=$C(CH_3)CH_2$	2*R*,4*R*	39
8	*D*	Me	$PhCH_2$	2*R*,4*R*	59

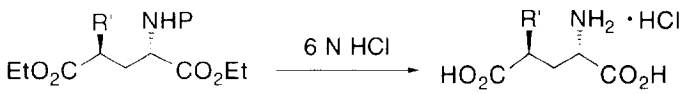
TLC analysis of the reaction mixtures in different solvent systems indicated the presence of single product. The proton and carbon-13 NMR analyses of the crude reaction mixtures showed the formation of a single diastereoisomeric product[6] along with various unreacted starting material and a trace seemed to be impurity, which may be the other diastereoisomer. In the case of 4-methyl substituted glutamic acid, a mixture of the racemates of two diastereomers was prepared via literature procedure[7] and then converted to the corresponding *N*-*p*-nitrobenzoyl 4-methyl glutamic acid dimethyl ester. Comparison of these NMR spectra revealed that the alkylation product **1** matched one NMR pattern of this diasteroisomeric mixture of *N*-*p*-nitrobenzoyl 4-methyl glutamic acid diester, indicating only one isomer obtained in our alkylation step. Subsequently, acidic hydrolysis of compound **1** provided the fully deprotected (2*R*,4*R*)-4-methylglutamic acid which was confirmed as the *threo* isomer by comparison with literature spectroscopic data.[8]

Careful control of the reaction conditions is an important factor. Two equivalent of base was required in order to achieve reasonable yield in these dianion mechanism based alkylation reactions. Under the reaction conditions, the acidic NH group is easily deprotonated that prevent racemization occurring at the α-position via deprotonation. Generation of the γ-enolate with the second base is rather slow at -78 °C and if insufficient time is allowed for deprotonation of the γ-position prior to addition of the electrophile, the product is obtained in very low yield. It is also critical to maintain the temperature at -78 °C during the reaction, because allowing the temperature to rise results in the other diastereoisomer to appear in various ratios along with a cyclized product.

Presumably, the stereochemical outcome in these alkylations is due to the formation of a chelated dianion (dimetalated) transition state which may be approached by electrophile almost exclusively from one face of the enolate, thus leading to the formation of a product with very high diastereoselectivity. This dimetalated mechanism was reported previously in the alkylation of succinamides which lead to a product with high diastereoselectivity.[9] It is also observed that by using of potassium bis(trimethylsilyl)amide as a base, a diastereomeric mixture of 4-alkylated product was obtained.[10] This result supports the chelated dianion mechanism proposed above. The fact that the (2*S*, 4*S*), or (2*R*, 4*R*), product is obtained exclusively from the *L*- or *D*-glutamic acid respectively, implies that the stereo center at the α-carbon has a profound influence on the newly formed chiral center.

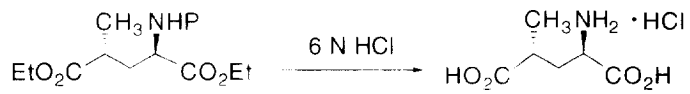
Compounds **1**, **2** and **5** were deprotected under standard acidic conditions[11] to afford the corresponding (2*S*, 4*S*)-4-methyl glutamic acid (**9**), (2*S*, 4*S*)-4-ethyl glutamic acid (**10**) (Scheme 2) and (2*R*, 4*R*)-4-methyl glutamic acid (**11**) (Scheme 3).[12] However, approximately 3% of epimerization at C-4 was observed by proton NMR at the acidic hydrolysis step. This result is similar to that reported by literature.[8] The minor diastereomer which introduced by acid hydrolysis, however, was easily removed in the final crystallization in water and acetone. The spectroscopic data for these compounds are in agreement with literature data.[8]

Scheme 2



1 R' = Me, **2** R' = Et **9** R' = Me, **10** R'=Et

Scheme 3



5 **11**

In summary, we have demonstrated a highly diastereospecific route to preparation of *threo* 4-alkylated glutamic acid derivatives via alkylation of the lithium γ-enolate of *N*-*p*-nitrobenzoyl glutamic acid diester. Utilizing *N*-*p*-nitrobenzoyl as amino protecting group proved to be effective to prevent the

isomerization at the α-position and also lead to an alkylation product with very high diastereoselectivity. The protecting groups can be easily removed under acidic conditions. Further studies to extend the application of this chemistry and to evaluate the biological activity of these compounds are currently under investigation.

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References and Notes

1. (a) Baldwin, J. E.; Flinn, A.; Moloney, M.G.; North, M. *Tetrahedron* **1989**, *45*, 1465; (b) Baldwin, J.E.; Moloney, M.G.; North, M. *Tetrahedron*, **1989**, *45*, 6319. (c) Coppola, G. M. and Schuster, H. F. Difunctional Amino Acids. In *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*; John Wiley and Sons, Inc.: New York, 1987; pp. 204-266.
2. (a) Olverman, H. J.; Jones, A. W.; Mewett, K. N.; Watkins, J. C. *Neuroscience* **1988**, *26*, 17; (b) Chamberlin, R.; Bridges, R.: Conformationally Constrained Acidic Amino Acids as Probes of Glutamate Receptors and Transporters. In *Drug Design for Neuroscience*; Kozikowski, A.P. Ed.; Raven Press, Ltd.: New York, 1993; pp. 231-260; (c) Ohfune, Y.; Shinozaki, H.: L-2-(Carboxycyclopropyl)glycines: Conformationally Constrained *L*-Glutamate Analogues. In *Drug Design for Neuroscience*, Kozikowski, A.P. Ed.; Raven Press, Ltd.: New York, 1993; pp. 261-284.
3. Koskinen, A.M.P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.
4. Hanessian, S. and Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401.
5. Johnstone, A.N.C.; Lopatriello; S.; North, M. *Tetrahedron Lett.* **1994**, *35*, 6335.
6. Selected spectroscopic data: for compound **1**, ^{1}H-NMR ($CDCl_3$): δ 8.28 (dd, 2H, J = 1.5, 6.8 Hz), 7.97 (dd, 2H, J = 1.6, 6.9 Hz), 7.02 (d, 1H, J = 8.0 Hz), 4.75 (m, 1H), 4.22 (q, 2H, J = 1.2, 8.2 Hz), 3.89-4.18 (m, 2H), 2.58 (m, 1H), 2.25 (m, 1H), 2.02 (m, 1H), 1.29 (t, 3H, J = 7.1 Hz), 1.26 (d, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$): 176.4, 171.1, 165.1, 149.7, 139.0, 128.3, 123.7, 61.9, 60.8, 51.9, 37.0, 35.1, 17.8, 14.08, 14.07. For compound **3**, ^{1}H-NMR ($CDCl_3$): δ 8.29 (dd, 2H, J = 2.0, 6.9 Hz), 7.95 (dd, 2H, J = 2.0, 6.9 Hz), 6.90 (d, 1H, J = 7.8 Hz), 5.70 (m, 1H), 5.08 (m, 2H), 4.75 (m, 1H), 3.88-4.28 (m, 4H), 2.58 (m, 1H), 2.37 (m, 2H), 2.15 (m, 2H), 1.23 (t, 3H, J = 7.1 Hz), 1.10 (t, 3H, J = 7.1 Hz). ^{13}C-NMR ($CDCl_3$): 175.2, 171.8, 165.0, 149.6, 138.9, 134.0, 128.3, 123.6, 117.8, 61.8, 60.8, 52.0, 42.2, 36.7, 32.8, 14.1, 14.0.
7. Done, J.; Fowden, L. *Biochem. J.* **1952**, *51*, 451-458.
8. (a) Righini-Tapie, A.; Azerad, R. *J. Applied Biochem.* **1984**, *6*, 361; (b) Echalier F.; Constant, O.; Bolte, J. *J. Org. Chem.* **1993**, *58*, 2747. (c) Belokon, Y. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Y. T.; Barhmutov, V. I.; Belikov, V. M. *J. Chem. Soc. Perkin. Trans. 1*, **1986**, 1865.
9. (a) Mahalanabis, K. K. and Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 3971. (b) Mahalanabis, K. K. and Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 3975.
10. Unpublished data.
11. Example of experimental condition for acid hydrolysis: 2.5 g of **1** in 60 ml of 6 N HCl was heated to reflux for 2 hours. After cooling down to room temperature, the precipitate was filtered and the filtrate was concentrated in vacuo. The oily residue was dissolved in 60 ml of distilled water which was washed with 5% trioctylamine in $CHCl_3$ (50 ml x 3) followed by $CHCl_3$ (50 ml x 3). The aqueous phase was separated and lyophilized to afford off-white powder which was subsequently crystallized from acetone and water to give compound **9**.
12. For compound **9**, $[\alpha]^{25}_D$ = +34.7 (c 0.79, 6 N HCl); ^{1}H-NMR (D_2O): δ 3.95 (dd, 1H, J = 6.4 Hz, 7.9 Hz), 2.65 (m, 1H), 1.85-2.2 (m, 2H), 1.15 (d, 3H, J = 7.1 Hz). ^{13}C-NMR (D_2O): 182.0, 174.2, 53.5, 38.3, 35.6, 19.4. Anal.Calcd. for $C_6H_{11}NO_4$·HCl: C, 36.46; H, 6.12; N, 7.08. Found: C, 36.45; H, 6.13; N, 7.08. For compound **10**, $[\alpha]^{25}_D$ = +28.4 (c 1.0, 6 N HCl); ^{1}H-NMR (D_2O): δ 3.55 (t, 1H, J = 7.6 Hz), 2.40 (m, 1H), 1.70-2.0 (m, 2H), 1.45 (m, 2H), 0.7 (t, 3H, J = 7.4 Hz). Anal.Calcd. for $C_7H_{13}NO_4$·HCl: C, 39.72; H, 6.66; N, 6.61 Found: C, 39.63; H, 6.55; N, 6.57. For compound **11**, $[\alpha]^{25}_D$ = -34.5 (c 0.87, 6 N HCl); ^{1}H-NMR (D_2O): 3.95 (dd, 1H, J = 6.4 Hz, 7.9 Hz), 2.65 (m, 1H), 1.85-2.2 (m, 2H), 1.15 (d, 3H, J = 7.1 Hz). Anal.Calcd. for $C_6H_{11}NO_4$·HCl: C, 36.46; H, 6.12; N, 7.08. Found: C, 36.48; H, 6.12; N, 7.07.

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