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1,3-Asymmetric Induction in Dianionic Allylation Reactions of Amino Acid Derivatives—Synthesis of Functionally Useful Enantiopure Glutamates, Pipecolates and Pyroglutamates.

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Abstract: Dianions derived from N-Cbz and N-Boc glutamic acid esters undergo highly stereoselective *anti* allylation reactions at C-4. The roles of protecting groups and of the electrophile were studied. Synthetic applications and potential utility in peptidomimetic design are also described.

Keyword: *Allylation; Asymmetric induction; Amino acids and derivatives; Peptide analogs/mimetics*

Glutamic acid is released as a chemical messenger in most of the excitatory synapses of the mammalian CNS.[1] Excessive activation or disturbance of glutamate receptors has been linked to a variety of acute and chronic neurodegenerative disorders related to the CNS.[2] Both ionotropic (iGluRs) and metabotropic (mGluRs) glutamate receptors have been identified and investigated to delineate the structural and conformational requirements of agonist and antagonist interactions.[3] The conformational flexibility of glutamic acid[4] has led to the synthesis of constrained analogs to identify and map out the roles of the different receptors.[5] In this regard, little is known about the effects of the substituted glutamates,[6] largely due to the limited variety of such compounds in enantiomerically pure form.

In the preceding Letter,[7] we reported on the highly *anti* stereoselective allylation of dianions of N-protected aspartic esters using 1,2-asymmetric induction. The orthogonally functionalized *anti* aspartates were also used for the creation of versatile constrained scaffolds. In this Letter, we describe methods for the highly stereocontrolled *anti* 4-allylation of N-substituted glutamate esters relying on 1,3-asymmetric induction.

A few examples of 1,3- and 1,4-asymmetric induction have been reported in the α-C-alkylation of γ- and δ-hydroxy carboxylic acid esters.[8] We have previously demonstrated examples of stereoselective α-alkylations[9] in dianions of γ-amino acids, of 4-hydroxylation of glutamates,[10] and α-radical allylation of β-, γ-, δ- and ω-amino acid derivatives through H-bond control.[11]

The enantiospecific enzymatic methylation at C-4 of glutamates has been described.[12] The stereoselectivities reported in the limited examples of direct chemical alkylations of glutamates

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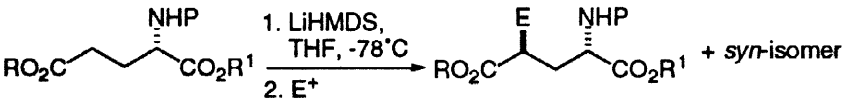
appear to differ from one alkyl halide to another[13c], or to be highly dependent on the nature of the N-substituents[13a] and the ester.[13d,e] In view of this, we deemed it of interest to extend our dienolate allylations[7] to the readily available[14] N-Boc and N-Cbz glutamates as practical prospects for 1,3- asymmetric induction, and to explore the utility of the 4-allylated products.

Table 1.



Entry	R	R^1	P	E^+	E	*Anti/Syn* ratio[a]	Yield[b] (%)
1	Me	Me	Cbz	methyl iodide	Me	>99:1[c]	73
2	Me	Me	Cbz	allyl bromide		>99:1[c]	93
3	Me	Me	Cbz	crotyl bromide		>99:1[c]	82
4	Me	Me	Cbz	methallyl bromide		>99:1[c]	82
5	Me	Me	Cbz	cinnamyl bromide	Ph	>99:1[c]	80
6	Me	Me	Cbz	cyclohexenyl bromide		75:25[d]	60
7	Me	Me	Cbz	Br, CO_2Me	CO_2Me	>99:1[c]	65
8	Me	Me	Cbz	benzyl bromide	Ph	>99:1[c]	77
9	Me	Me	Boc	allyl bromide		>99:1[c]	92
10	Me	Me	Boc	cinnamyl bromide	Ph	>99:1[c]	89
11	Me	Me	Boc	Br, CO_2Me	CO_2Me	>99:1[c]	86
12	Me	Me	Boc	benzyl bromide	Ph	>99:1[c]	75
13	Me	TMSE	Boc	allyl bromide		>99:1[c]	89
14	Me	TMSE	Boc	methallyl bromide		>99:1[c]	84
15	Me	TMSE	Boc	cinnamyl bromide	Ph	>99:1[c]	75
16	Me	TMSE	Boc	Br, CO_2Me	CO_2Me	>99:1[c]	78

a. *Anti/syn* ratios determined by ^1H NMR of the products after chromatographic purification. For a typical procedure see ref 15. b. Yield of pure isolated product after chromatography. c. Only one isomer could be detected by ^1H NMR. d. Inseparable by chromatography, see however ref. 7. The *anti*-configuration is assumed.

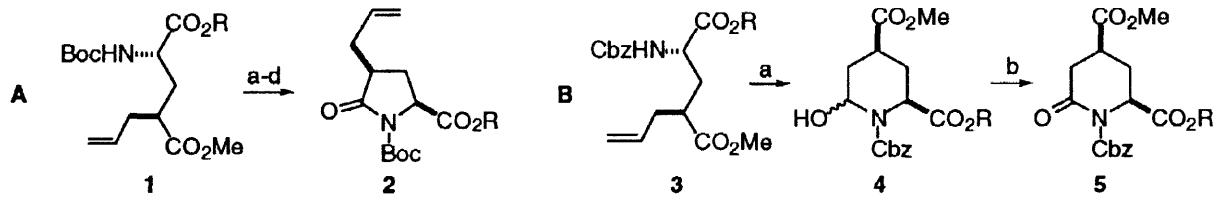
As seen in Table 1, allylation of dianions of N-Boc and N-Cbz glutamates with a variety of allylic halides[15] proceeded with remarkable stereoselectivity *in the absence of additives* to give the corresponding *anti* isomers essentially as single products. The *anti* configuration was ascertained by complete deprotection of the 4-methyl derivative (Table 1, entry 1) in refluxing 6N HCl and comparison to literature data .[13a] The result of these interesting examples of 1,3-asymmetric inductions can be rationalized by a general transition state that could involve *Z*(O) or *E*(O) enolate geometries similar to previous proposals.[9]

Complete hydrolysis of ester groups could be achieved by treatment with LiOH (3 equiv.) in THF/water, while selective cleavage of the TMSE group could be easily accomplished with TBAF/THF thus affording end-group differentiated intermediates.

Treatment of the N-Boc derivative **1** with TFA in CH_2Cl_2 followed by neutralization and heating furnished 4-*syn*-substituted pyroglutamic analog **2** acid in good overall yield (70%, Scheme 1, A). Unlike 4-*anti* alkyl derivatives of L-pyroglutamic acid which are the thermodynamic products of direct alkylations of the precursor enolates,[16] the 4-*syn*-substituted products are only available indirectly through an aldol condensation, elimination, and reduction sequence.[17] Clearly, access to synthetically useful unsaturated carbon branching (Scheme 1, A) cannot be considered by this protocol, hence the utility of the methods described herein.

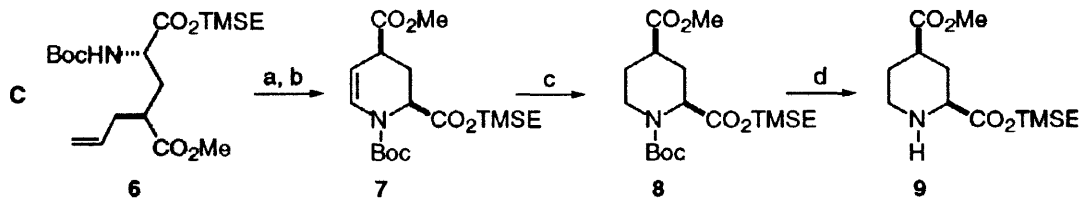
Modification of the allyl side-chain offers an easy access to 4-*syn*-methoxycarbonyl pipecolic ester derivatives.[18] For example, dihydroxylation and oxidative cleavage of the double bond of **3** furnished the versatile carbinol lactam **4**. Oxidation with the Jones reagent resulted in 6-oxo-4β- methoxycarbonyl pipecolic ester **5** in 80% overall yield (Scheme 1, B). Alternatively, dihydroxylation and oxidative cleavage of the double bond of **6** followed by dehydration with QCS[19] led to the enecarbamate **7** which was converted to the corresponding 4-*syn*-methoxycarbonyl pipecolic ester by simple hydrogenation in 64% overall yield (Scheme 1, C). N-Deprotection with TFA resulted in the constrained glutamate **9** as a single isomer.

Scheme 1



R= Me, TMSE. Conditions: a) TFA / CH_2Cl_2. b) $NaHCO_3$. c) Δ, toluene. d) $(Boc)_2O$, TEA, DMAP (cat.). (Overall 60-70%).

R= Me, TMSE. Conditions: a) OsO_4 (cat.), $NaIO_4$ (2.2 equiv.). b) Jones Oxid. (Overall 75-80%).



Conditions: a) OsO_4 (cat.), $NaIO_4$ (2.2 equiv.). b) QCS, Δ toluene. c) H_2, Pt/C 10%. d) TFA, CH_2Cl_2. (Overall 60%).

In conclusion, we have developed general and stereocontrolled syntheses C-4 *anti* allylated glutamates, which are new and versatile intermediates to functionally useful unnatural aminoacids with a wide range of applications in medicinal chemistry where glutamates[2, 3, 6, 20] are involved. The option to selectively manipulate the ester groups and to maintain the useful allyl and diversely substituted allyl functionality in constrained analogs of pyroglutamic acid is particularly noteworthy (Scheme 1, A). Access to orthogonally functionalized pipecolic acids and related motifs (Scheme 1, B and C) further highlights the utility of the methodology reported in this Letter.

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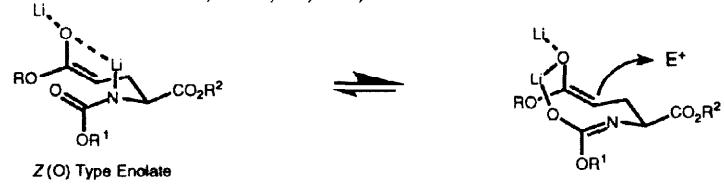

Z (O) Type Enolate

E (O) Type Enolate

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[15] **Typical procedure**: a solution of substrate (1 mmol) was dissolved in dry THF (4 ml) and added dropwise (*via cannula*) to a stirring solution of LiHMDS (2.1 mmol, Aldrich 1M in THF). After about 30 min. freshly distilled allyl iodide or bromide (3 mmol, neat) was added and the reaction mixture was stirred at -78°C until disappearance of the starting material. Quenching with 10% HCl (-78°C), work-up and silica gel flash chromatography (hexanes/AcOEt) provided the desired alkylated compound.

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