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1,2-Asymmetric Induction in Dianionic Allylation Reactions of Amino Acid Derivatives—Synthesis of Functionally Useful, Enantiopure Aspartates and Constrained Scaffolds.

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Abstract: Dianions derived from N-Cbz aspartic acid esters undergo highly stereoselective *anti* allylation reactions at the unsubstituted carbon. The roles of additives, of the cation 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*

Methodologies based on amino acids have assumed increasing importance since non-proteinogenic analogs play a determinant role in the design and synthesis of pharmacologically important molecules.[1] In this context, stereocontrolled C-C bond formation presents a challenge in synthesis, particularly in the case of acidic amino and hydroxy acids. For example, 1,2-asymmetric induction in the alkylation of malic acid[2] and aspartic acid[3] ester enolates is well documented, and some 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[4] and of γ-amino acid derivatives.[5] Previous reports on the alkylation of enolates of aspartic[3] derivatives clearly show that stereoselectivities can vary drastically with the nature of the N-substituents, the type of ester and with the reaction conditions. For example, stereoselectivities of allylation can be completely reversed simply by changing the counter cation from Li to K for one and the same aspartate derivative.[3b] Ratios of 99:1[3a] to 3:1[3e] have been reported for the same reaction from two different laboratories. The majority of the reported examples describe methylation, benzylation and allylation reactions of ester enolates.

We have previously shown examples of β-hydroxylation of aspartates.[6] More recently, we have demonstrated the successful α-radical C-allylation of β-, γ-, δ- and ω-amino acid derivatives through H-bond control.[7] We now report a general method for the *anti* allylation of dianions of N-protected aspartates capitalizing on 1,2-asymmetric induction. The required amino acid derivatives were prepared by literature protocols.[8] Treatment of N-Cbz dimethyl or mixed methyl and 2-(trimethylsilanyl)-ethyl (TMSE) esters with 2 equivalents of base in the presence of 15% of HMPA or DMPU in THF followed by different allylic type electrophiles led to β-allyl derivatives with a preponderant *anti* selectivity as shown in Table 1.[9]

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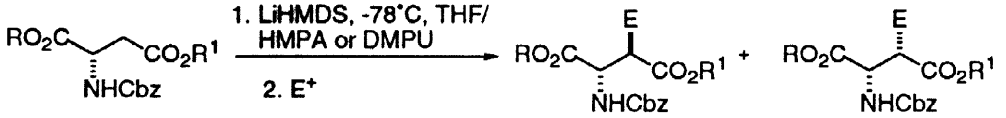
Table 1.



Entry	R	R^1	E^+	E	*Anti/Syn* ratio[a]	Yield[b] (%)
1	Me	Me	allyl iodide		93:7	84
2	Me	Me	allyl iodide[c]		97:3	85
3	Me	Me	crotyl bromide		90:10	85
4	Me	Me	methallyl bromide		>99:1[e]	77
5	Me	Me	cinnamyl bromide		75:25	76
6	Me	Me	cyclohexenyl bromide[d]		75:25	45
7	Me	Me			85:15	87
8	TMSE	Me	allyl iodide		>99:1[e]	80
9	TMSE	Me	crotyl bromide		>99:1[e]	85
10	TMSE	Me	methallyl bromide		>99:1[e]	78
11	TMSE	Me	cinnamyl bromide		>99:1[e]	75
12	TMSE	Me	cyclohexenyl bromide[d]		75:25	63
13	TMSE	Me			75:25	85
14	Me	TMSE	allyl iodide		>99:1[e]	80
15	Me	TMSE	crotyl bromide		>99:1[e]	75
16	Me	TMSE	methallyl bromide		>99:1[e]	74
17	Me	TMSE	cinnamyl bromide		>99:1[e]	74
18	Me	TMSE	cyclohexenyl bromide[d]		75:25	58

a. *Anti/syn* ratios determined by ^{1}H NMR of the products after chromatographic purification. For a typical procedure see ref 9. b. Yield of pure isolated product after chromatography. c. LiCl (6 equiv.) instead of HMPA. d. Possible mixture of diastereomers at the cyclohexenyl carbon. e. Only one isomer could be detected by ^{1}H NMR.

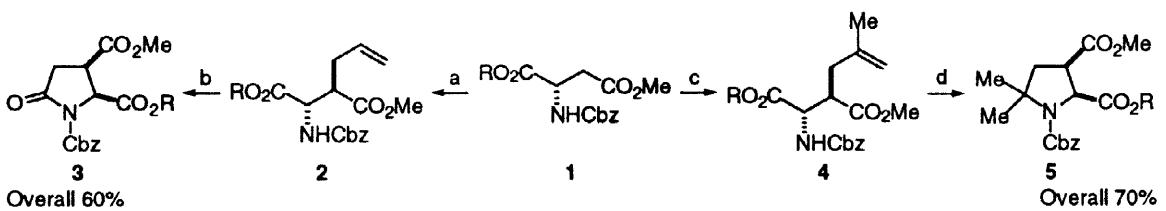
The absolute configuration of the products was determined by chemical transformation to cyclic analogs and detailed NMR analysis, as well as by X-ray crystallography. Interestingly, the combination of a methyl and a TMSE protecting group produced a dramatic enhancement of the stereoselectivity of alkylation with the exception of cyclohexenyl bromide and methyl-2-(bromomethyl)-acrylate (Table 1, entries 6, 7, 12, 13, 18). Preliminary studies with N-Cbz dimethyl aspartate and allyl iodide, showed that the configuration of the newly created asymmetric center was highly dependent on the counter cation and the presence of additives.[10] The highest diastereoselectivities were obtained in the presence of HMPA or DMPU (15%), or LiCl (6 equiv.) in conjunction with LiHMDS as base. The use of sodium and potassium HMDS and lesser quantities of HMPA (1-5%) resulted in significant erosion of selectivity.

Previous models proposed for the alkylation of aspartates are related to a monoanion of an *N,N*-disubstituted derivative.[3b] Chamberlin *et al.*[3b] have shown that the stereochemistry of enolates of aspartates differs from that of ordinary enolates.[11] Although the result of our highly *anti*-selective allylation can be rationalized based on possible transition states that could involve *Z*(O) or *E*(O) enolates,[12] the possibility of doubly charged open transition states in the presence of HMPA cannot be excluded. Furthermore, the additives have a beneficial effect of disrupting aggregation,[13] while accelerating the reaction time and ensuring excellent diastereoselectivity in most cases.

Complete hydrolysis of ester groups could be achieved by treatment with LiOH (3 equiv.) in THF/water. Interestingly, hydrolysis of the mixture of 2-cyclohexenyl derivatives (Table 1, entry 5) resulted in the selective deprotection of the α-amino ester group. Selective cleavage of the TMSE group could be easily achieved with TBAF/THF thus affording end-group differentiated intermediates, useful in further transformations.

Modification of the C-3 unsaturated side-chain in our allylated derivatives provides a facile access to a variety of 2,3-*cis* substituted pyrrolidines and pyrrolidinones,[14] which represent interesting examples of functionally useful constrained amino acid analogs.[15] For example, dihydroxylation and oxidative cleavage[3a] of the mixed ester derivative **2** afforded the corresponding pyrrolidinone **3** in 60% overall yield (Scheme 1). Imidocyclization of **4** in the presence of mercury acetate[16] followed by demercuration led to the 5,5-dimethyl pyrrolidine diester **5** in 70% overall yield. These reactions were also possible with the corresponding dimethyl esters. The alternative route consisting of ozonolytic cleavage of the allyl group in **2**[17] followed by hydrogenation and heating, led to the des-Cbz analog of **3** in modest overall yield. The *cis*-substitution pattern was ascertained from 2D ^{1}H NMR and n.O.e studies.[3a,b]

Scheme 1.



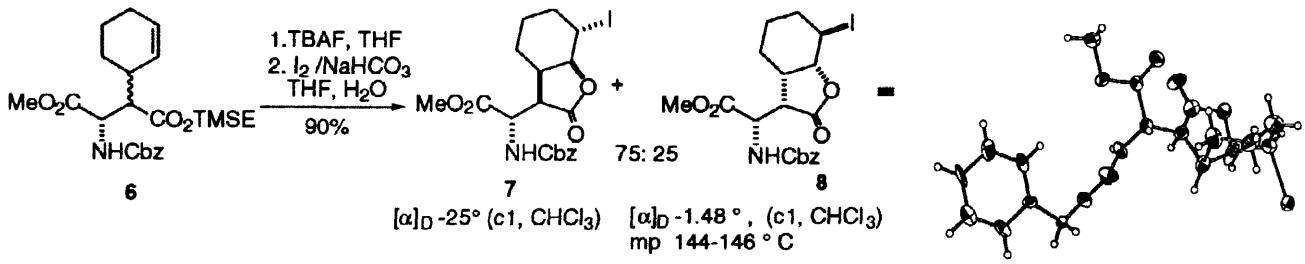
R= Me, TMSE. Conditions: a) LiHMDS, THF / HMPA, -78°C then allyl iodide. b) OsO_4 (cat.), $NaIO_4$, then Jones oxid. c) LiHMDS, THF / HMPA, -78°C then methallyl bromide. d) $Hg(OAc)_2/Hg(OCOCF_3)_2$, then $LiBH_4$, THF.

Although the stereoselectivity of cyclohexenylation is comparatively modest (Table 1, entries 6, 12, 18) the products offer synthetic possibilities of interest.[18] For example iodolactonization of the *anti/syn* mixture of **6** led to iodolactones **7** and **8**, which could be easily separated (Scheme 2). The absolute configuration of the minor product **8** was secured by X-ray crystal structure analysis. Reduction of **7** with tributyltin hydride gave the corresponding bicyclic lactone in quantitative yield.

In conclusion, we have developed general and stereocontrolled syntheses of *anti* C-substituted allylated aspartates. The resulting unnatural amino acid derivatives are new and versatile intermediates possessing orthogonally functionalized substituents with a wide range

of applications in medicinal chemistry where aspartates[19]are involved. The obvious applications in the synthesis of constrained analogs of proline and related motifs[15] are added amenities that should heighten interest in this methodology.

Scheme 2.



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[9] **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) and HMPA or DMPU (1 ml). After about 45 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 allylated compound.

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