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Stereoselective Synthesis of β-Substituted Aspartic acids *via* Tetrahydro-1,3-Oxazin-6-ones

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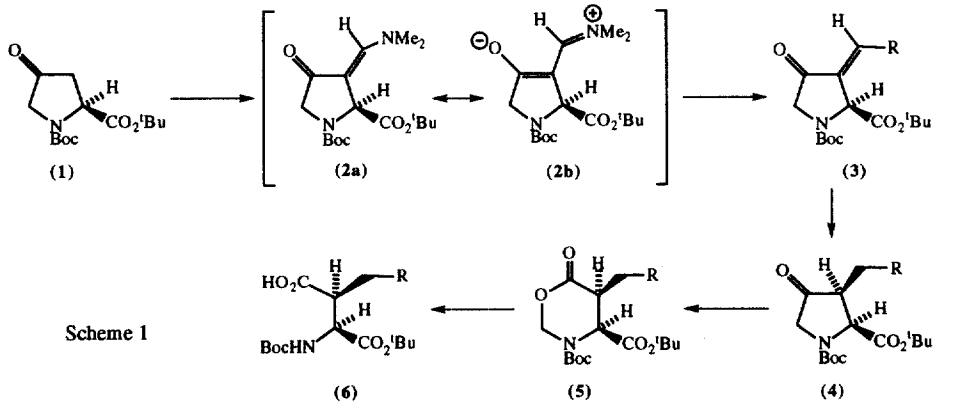
Abstract : Oxazinones have been synthesised and used as chiral templates in the synthesis of β-substituted aspartic acids. Use of a Bredereck's reagent/Grignard/hydrogenation strategy gave *cis*-oxazinones with complete stereoselectivity, whereas an alkylation strategy, although *trans*-selective, gave mixtures of isomers. The oxazinones could be converted to β-substituted aspartic acids and to regioselectively protected β-substituted aspartic acids without loss of stereochemistry at either centre.

Stereospecifically β-alkylated aspartic acids are of great interest as starting materials for the preparation of natural products. Direct alkylation of aspartic acid derivatives was first reported by Seebach in 1981,[1] and later by Baldwin and other workers.[2-10] Except for reports of stereospecific allylation,[9,10] these reactions gave mixtures of diastereoisomers. Single diastereoisomeric β-alkylaspartates have however been obtained by alkylation of chiral β-lactam esters *trans* to the ester group.[11-14]

We have developed a stereoselective method of preparing 4-alkylpyroglutamates[15] and have applied the method to protected 4-ketoprolines such as **(1)** to prepare the *cis*-alkyl compounds **(4)**. This involves preparation of the enaminone **(2)**, followed by reaction with a suitable Grignard reagent to yield the enones **(3)**. Addition of hydrogen from the less hindered side of **(3)** then gives the *cis*-isomer **(4)** as shown in Scheme 1.[16] If the compounds **(4)** could be converted to oxazinones such as **(5)** by an appropriately regiospecific Baeyer-Villiger process, then hydrolysis would lead to a new and stereoselective route to β-substituted aspartic acids **(6)**. The method should lead stereoselectively to epimers of the compounds prepared by alkylation of β-lactam esters.



Scheme 1

We have prepared **(4, R = Me)** and **(4, R = Ph)** as single stereoisomers by the above route[16] and, although these compounds proved prone to epimerisation even on chromatography on silica gel, we were in a

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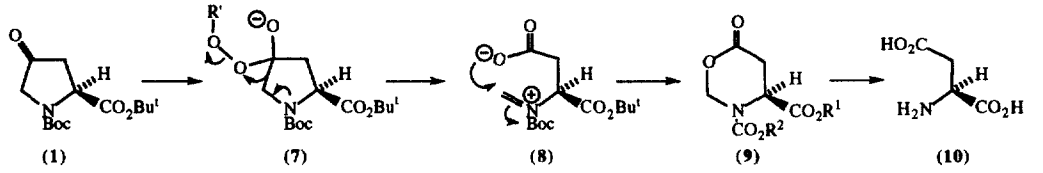
position to study the Baeyer-Villiger reaction. Treatment of the unsubstituted ketone (**1**) with *meta*-chloroperbenzoic acid or with pertrifluoroacetic acid failed to elicit any reaction. However, when a catalytic amount of copper(II) acetate was added,[17] reaction with *meta*-chloroperbenzoic acid at room temperature gave a 79% yield of the tetrahydro-1,3-oxazin-6-one (**9**, $R^1 = R^2 = {}^tBu$), mp 84 - 85 °C, $[\alpha]_D^{25}$ -120.1 (c 1, $CHCl_3$).† The regiospecificity of the reaction was proved by hydrolysis of the product to (S)-aspartic acid (**10**), the specific rotation of which indicated that no racemisation had occurred at the α-centre during the reaction. The most likely explanation for the regiospecificity of the Baeyer-Villiger reaction would be intermediacy of the acyclic compound (**8**) as suggested in Scheme 2 below.

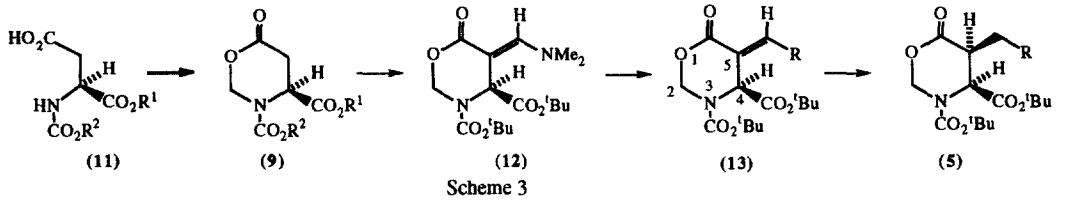


(1) (7) (8) (9) (10)

Scheme 2

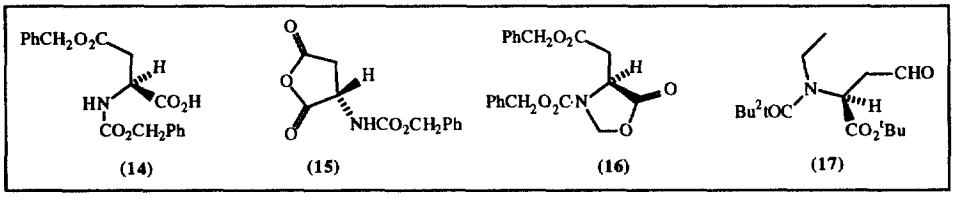
When the reaction was examined using the *cis* 3-ethyl derivative (**4**, **R = Me**), the expected oxazinone (**5**, **R = Me**), mp 67 - 68 °C, $[\alpha]_D^{20}$ +107.8 (c 1, $CHCl_3$),† was obtained in only 12% yield at room temperature together with a 2% yield of the corresponding *trans* isomer. The yield was improved on heating to reflux but epimerisation at the β-centre was exacerbated.

Although there are obvious problems in accessing stereospecifically alkylated aspartic acids from 3-ketoproline derivatives, the possibility of using the oxazinones (**9**) directly as chiral templates in their synthesis remained attractive. It was also of interest to examine the possibility of preparing the tetrahydro-1,3-oxazinones by an alternative and more straightforward method than our Baeyer-Villiger approach. We therefore prepared the aspartate α-ester urethanes (**11**, $R^1 = R^2 = {}^tBu$)[18] and (**11**, $R^1 = PhCH_2$, $R^2 = {}^tBu$)[19] by literature methods and (**11**, $R^1 = R^2 = PhCH_2$) as a 3 : 1 mixture with the β-ester (**14**) by reaction of the anhydride (**15**) with benzyl alcohol. These were then reacted with an excess of paraformaldehyde in refluxing toluene with 4Å molecular sieves to yield the corresponding oxazinones (**9**)† in good yields. The mixture of the benzyl esters (**11**, $R^1 = R^2 = PhCH_2$) and (**14**) was resolved at this stage by chromatographic separation of (**9**, $R^1 = R^2 = PhCH_2$)† from the oxazolone (**16**).



(11) (9) (12) (13) (5)

Scheme 3



(14) (15) (16) (17)

When the oxazinone (**9**, $R^1 = R^2 = {}^tBu$) was reacted with Bredereck's reagent, the enaminone (**12**)† was obtained in 70% yield as the single E-isomer as shown by a nOe of the α-hydrogen, H-4, when the NMe_2 resonance was irradiated. Reaction of the enaminone (**12**) with MeMgBr in THF gave the E-isomer (**13**, **R = Me**)† in 46% yield accompanied by a by-product with the spectral characteristics of the aldehyde (**17**),† presumably originating by reaction of the Grignard reagent with the oxazinone or its ring opened form

corresponding to **(8)** followed by hydrolysis of the enaminone and decarboxylation of the resultant β-aldehydo acid in the work up. A similar by-product was not evident when the enaminone was reacted with PhMgBr, an 88% yield of the E-isomer **(13, R = Ph)**† being obtained. Hydrogenation of the enones **(13)** in ethyl acetate using palladium on carbon as catalyst gave single isomers **(5)**† in nearly quantitative yields. As the NMR spectra were complicated by rotational isomerism, the stereochemistry of **(5, R = Me)**† was proved by a single crystal X-ray structure determination[20] (Figure 1) which showed the oxazine ring to be in a boat conformation and the side chain at C-5 to be *cis* to the ester at C-4. The stereochemistry of **(5, R = Ph)**† followed from the single crystal X-ray structure of the *trans*-epimer[21] **(18, R = Ph)** (Figure 2) whose synthesis is reported below.

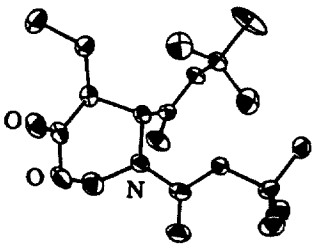


Figure 1: X-ray crystal structure of the substituted oxazinone **(5, R = Me)**

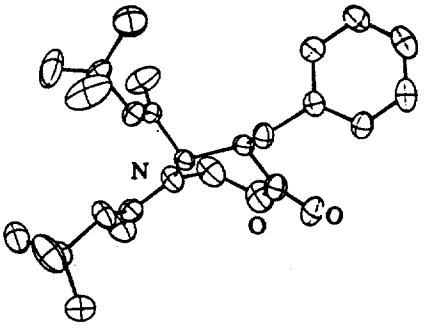
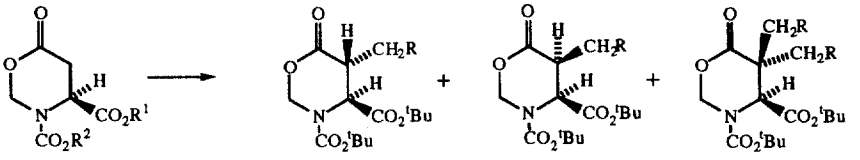


Figure 2: X-ray crystal structure of the substituted oxazinone **(18, R = Ph)**

As our Bredereck/Grignard/hydrogenation sequence had been so successful in obtaining single stereoisomers, it was of interest to study stereoselectivity in alkylation of the oxazinone **(9, $R^1 = R^2 = {}^tBu$)**. This gave mixtures of monoalkylated and dialkylated products as shown in Table 1. The stereochemistry of the products was indicated by nOe experiments and confirmed by an X-ray structure determination of the *trans*-benzyl derivative **(18, R = Ph)**.[21] The stereoselectivity in the monoalkylation reaction proved to be *trans*.



Scheme 4

Table 1 Alkylation of the oxazinone **(9, $R^1 = R^2 = {}^tBu$)** at -72 °C

Reaction	Electrophile	Base	Yield (18) + (5)	Ratio (18) : (5)	Yield (19)
1.	MeI (5 equ)	LiHMDS (2.2 equ) THF (to -20°C)	52%	1.3 : 1	28%
2.	MeI (3 equ)	LiHMDS (2.2 equ) THF/HMPA	33%	1 : 1.2	-
3.	MeI (3 equ)	KHMDS (1.8 equ) THF	38%	3.9 : 1	17%
4.	$PhCH_2Br$ (4 equ)	NaHMDS (2.2 equ) THF	25%	4.0 : 1	14%
5.	$PhCH_2Br$ (4 equ)	LiHMDS (2.2 equ) THF/HMPA	33%	4.4 : 1	11%

Having achieved synthesis of 5-alkyloxazinones, it was now of interest to examine their conversion to aspartic acid derivatives. Treatment of the *trans*-methyloxazinone **(18, R = H)** with 6N HCl at room temperature gave (2S,3R)-3-methylaspartic acid $[\alpha]_D^{25}$ +29.7° (c 1, 5N HCl) {lit.[14] +32.9°} as a single isomer in 80% yield. Since it is synthetically more useful to prepare products which retain regioselective protection, we

examined alternative methods. Use of strong base caused epimerisation, but when the oxazinone (**18, R = H**) was reacted with one equivalent of aqueous LiOOH in THF then *tert*-butyl (2S,3R)-N-*tert*-butoxycarbonyl-3-methylaspartate was obtained in 40% yield as a single stereoisomer. This isomer was also obtained pure in 56% yield on reaction of (**18, R = H**) with 4:1 acetic acid : water at 45 °C and the pure (2S,3S)-epimer (**6, R = H**)† was obtained in 53% yield from (**5, R = H**) using these conditions. Reaction of (**5, R = Ph**) under these conditions gave (2S,3S)-3-benzyl-N-*tert*-butoxycarbonylaspartic acid (**6, R = Ph**)† in 51% yield.

Acknowledgements

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20. **Crystal data for (5, R = Me)** : $C_{16}H_{27}NO_6$, hexagonal, $P6_5$ (No. 170), a = 10.468 (1), c = 29.581 (5) Å, z = 6, R1 = 0.041 for 1083 reflections with $I>2\sigma(I)$. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre (see ref 21).
21. **Crystal data for (18, R = Ph)** : $C_{21}H_{29}NO_6$, monoclinic, $P2_1$ (No. 4), a = 5.767 (2), b = 20.214 (5), c = 9.370 (4) Å, β = 90.48 (3) °, z = 2, R1 = 0.051 for 1525 reflections with $I>2\sigma(I)$. The atomic coordinates are available on request from The Director, Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

† These compounds had the expected analytical and spectroscopic properties and an acceptable specific rotation. Variable temperature and saturation transfer NMR experiments were performed on compounds whose spectra were complicated by rotational isomerism.