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A SIMPLE SYNTHESIS OF γ AND δ-KETO α-AMINO ACID DERIVATIVES

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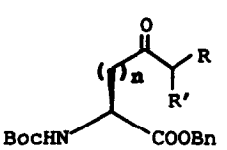
Summary: The γ and δ-keto α-amino acid derivatives **1a** and **1b** were prepared from L-aspartic and L-glutamic acid respectively *via* alkylation of the corresponding ß-ketoesters **3a** and **3b** followed by subsequent ester cleavage and decarboxylation.

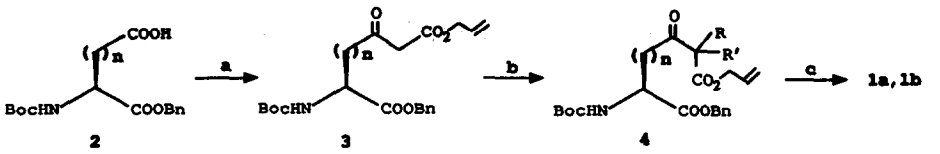
The preparation of chiral non proteinogenic α-amino acid derivatives has become an area of great interest especially with the advent of peptide-derived chemotherapeutics[1]. In this regard, we wish to report a simple synthesis of γ and δ-keto α-amino acid derivatives **1a** and **1b**[2]. Our strategy for the preparation of these compounds relies on creating an active methylene center by converting commercially available protected aspartic or glutamic acid into a ß-ketoester derivative. Subsequent anion formation and alkylation would be predicted to occur regioselectively under mild conditions to provide after a simple decarboxylative process the γ or δ-keto derivatives **1**.

The ß-ketoester derivatives **3a** and **3b** were prepared from N-Boc-L-aspartic and glutamic acid α-benzyl esters **2a** and **2b** in 88% yield using the Masamune protocol[3] (see scheme). The introduction of various alkyl groups was best accomplished by treatment of **3** with Na_2CO_3 and the appropriate alkyl iodide in DMF at 60°C to give compounds **4** (Table). In addition to the desired C-alkylated product varying amounts of O-alkylated material were also obtained (10-30%). However this byproduct could easily be separated by silica gel chromatography. Several reaction conditions were investigated in order to suppress O-alkylation (solvent polarity, cation effects, phase transfer catalysis, etc...) but none proved to be better than Na_2CO_3 in DMF. Removal of the allyloxycarbonyl moiety was readily achieved with pyrrolidine and a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile[4] to give the desired keto derivatives **1** in 70-90% yield[5].



1a n=1
1b n=2

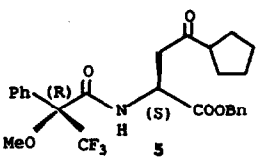
Scheme



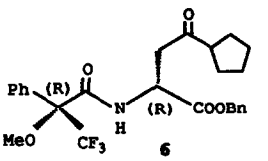
Reagents and conditions: a) Im_2CO, $(C_3H_5OCOCH_2CO_2)_2Mg\backslash CH_3CN$ 25°C; b) Na_2CO_3 (3eq), RNDMF 60°C 18h; c) pyrrolidine, $Pd(PPh_3)_4$ 2.5 mole%\ CH_3CN 25°C 18h.

In order to establish that no racemization had occurred during the reaction sequence we made the Mosher amide[6] derivative **5** from **1a** (entry 3) and its antipode **6** from D-aspartic acid. Proton NMR spectroscopy indicated no observable diastereomeric contamination.

In summary, mono, di and cycloalkylated γ and δ-keto α-amino acid derivatives can easily be obtained from commercially available protected aspartic and glutamic acid respectively.



δ (MeO) =3.25ppm



δ (MeO) =3.50ppm

Table: Conversion of (3) to the keto derivatives (1)

Entry	Derivatives	R	R'	Yield % (4)	Yield % (1)	$[\alpha]_D^{27}$ (c in MeOH)
1	a	CH_3	H	58	85	-23.4 (2.14)
2	a	CH_3	CH_3	68	94	-15.9 (6.05)
3	a	$-(CH_2)_4-$		55	71	-13.1 (5.15)
4	a	$PhCH_2$	H	44	85	-10.0 (5.55)
5	a	$n-C_6H_{13}$	H	54	80	-11.8 (0.65)
6	a	$n-C_4H_9$	H	54	79	-16.1 (0.39)
7	b	$-(CH_2)_4-$		55	95	-23.3 (8.30)
8	b	$n-C_4H_9$	H	66	92	-22.3 (8.10)

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