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Asymmetric Synthesis of β-Amino Acid Derivatives by Michael Addition to Chiral 2-Aminomethylacrylates

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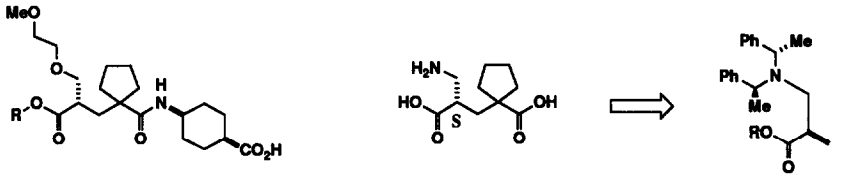
Abstract: The addition of lithium enolates to chiral aminomethylacrylates **7** and **8** proceeded with excellent diastereodifferentiation (up to 98% de) and provided an expeditious synthesis of homochiral β-aminomethylglutarates **9** and **10**, on a scale of up to 500g. The acrylates **7** and **8**, and their antipodes, should be useful synthons for the synthesis of β-amino acid derivatives.

We have reported recently a novel series of geminal-cycloalkylglutaramide derivatives which are potent inhibitors of neutral endopeptidase 24.11.[1] Candoxatril **1** is an orally active prodrug of a member of this inhibitor series, candoxatrilat **2**, which potentiates the natriuretic actions of the peptide hormone, atrial natriuretic factor (ANF), in animals and man, and is currently under clinical evaluation.[2] Further exploration of the structure activity relationships in this novel glutaramide series[3] necessitated efficient syntheses of derivatives of the β-aminomethylacrylate **3**. Importantly, since the enzyme inhibitory activity of candoxatrilat resides primarily in the (S)-enantiomer, a route was sought which provided derivatives of **3** in homochiral form.

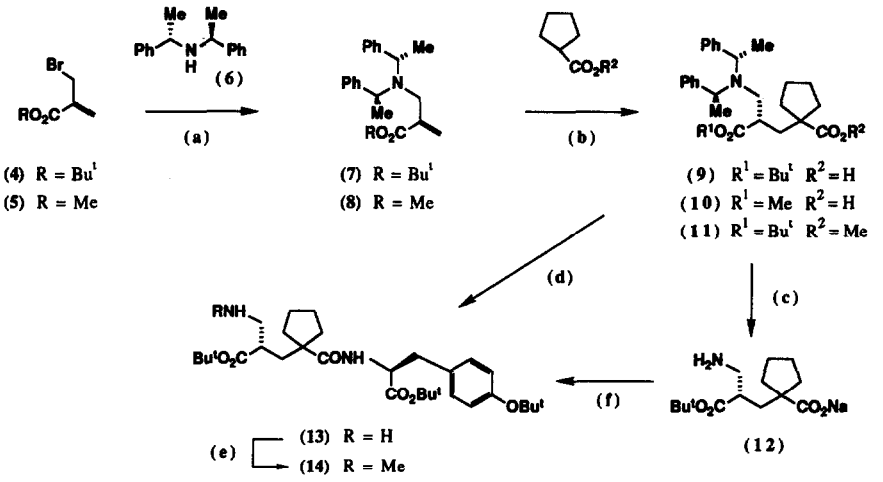


(1) R = 5-indanyl: candoxatril **(3)**

(2) R = H: candoxatrilat

Although the preparation of β-aminoacid esters *via* Michael addition of a chiral amine has been reported recently by Davies,[4] Seebach[5] and Hawkins,[6] these methods provide concise routes to compounds with chirality at the β-position but not the more labile α-centre. We now report methodology which successfully addresses this problem. Our strategy is based upon 1,4-addition of enolates to chirally protected 2-aminomethylacrylates, whereby the stereochemical outcome of the reaction is governed by the chirality of the protecting groups. We selected the C_2-symmetrical (S,S)-bis(α-methylbenzyl) system as the amino protecting group, in view of its stability to basic reaction conditions, ready removal under hydrogenolytic conditions, and potential stereochemical influence on the reaction outcome. *Scheme 1* depicts the successful realisation of this strategy.

Scheme 1



(a) K_2CO_3 (1.2 eq), **(6)** (1.1 eq), CH_3CN 60-70°C, 18h; yields 83% of **(7)**, 94% of **(8)**.

(b) For **(9)** and **(10)**: cyclopentanecarboxylic acid + LDA (2.2 eq) 0°C (1h) then cool to -50°C. Add acrylate (1 eq) -50 to -20°C (6h).Quench into ice cold ether / 1M HCl. For **(11)** use 1.1 eq LDA.

(c) Add NaOH (1 eq) aq / EtOH and hydrogenate: 60 psi, 20% $Pd(OH)_2$ / C, rt, 18h (95%).

(d) (i) **(9)** (1 eq), 1-hydroxybenzotriazole (1.2 eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.4 eq), (S) t-butyl *O*-t-butyltyrosine (1.1 eq), CH_2Cl_2, 0°C to RT, 18h; 60% yield. (ii) H_2, 20% $Pd(OH)_2$/C, ethanol, RT, 60 psi, 18h; 77% yield.

(e) (i) **(13)** (1 eq), $(CF_3CO)_2O$ (1.3 eq), *N*-methylmorpholine (1.5 eq), CH_2Cl_2, 0°C, 2h; 94% yield. (ii) CH_3I (4 eq), K_2CO_3 (2 eq, anhydrous), DMF, RT, 18h; 87% yield. (iii) NaOH (aq), ethanol, 0°C, 1h; 75% yield.

(f) (i) **(12)** (1 eq), $PhCH_2OCOCl$ (1.2 eq), Na_2CO_3 (2 eq), dioxan/water (1:1), 1.5 hr, 25°C. (ii) 1-hydroxybenzotriazole (1.2 eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.4 eq), (S) t-butyl *O*-t-butyltyrosine (1.1 eq), CH_2Cl_2, 0°C, 2.5 hr. (iii) H_2, Pd/C (10%), EtOH/H_2O (9:1), 60 p.s.i., 2 hr.

The 2-bromomethylacrylates **4** and **5** (prepared in 3 steps by standard literature procedures[7]) were condensed with the commercially available, C_2 symmetrical amine **6**[8] in acetonitrile at 60-70°C, in the presence of potassium carbonate (1.2 eq.), to give the chiral acrylates **7** and **8** in 83 and 94% yield respectively.[9] *When a solution of the t-butyl ester 7 was added to a solution of the lithiodianion of cyclopentanecarboxylic acid in THF, followed by quenching into aqueous HCl, the (S,S,S)-glutarate* **9** *was formed with excellent (99:1) diastereoselectivity,*[10] *in 83% yield.* A similar result was obtained using the methyl acrylate **8**, to yield the glutarate **10**. The Michael addition of the lithium enolate of methyl cyclopentanecarboxylate to acrylate **7** gave the glutarate diester **11** in lower yield and 80% de. The results of these asymmetric Michael addition reactions are summarised in *Table 1*:

Table 1: Asymmetric Michael Additions to Aminomethyl-acrylates[11]

Acrylate	Enolate	Glutarate	% Yield	Diastereo-selectivity SSS/SSR	$[\alpha]_D^{22}$ (*c* 1% MeOH)
7	Di-lithio cyclopentanecarboxylate	**9**	83	99:1	-19.9°
8	Di-lithio cyclopentanecarboxylate	**10**	86	97:3	-10.8°
7	Mono-lithio methyl cyclopentanecarboxylate	**11**	50	90:10	-24.1°

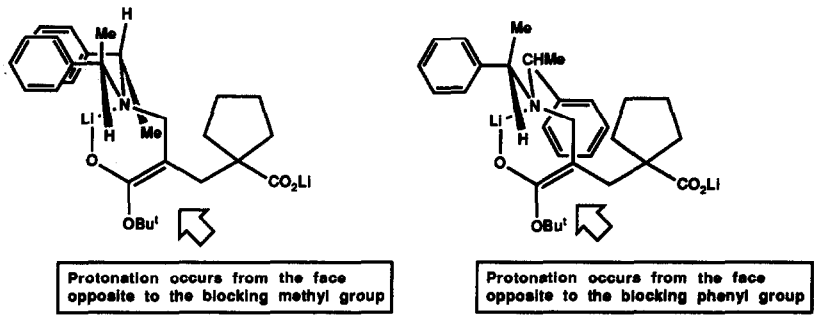
A sample of the (S,S,R)-diastereoisomer of **9** was prepared by partially epimerising the all S-product under thermodynamic conditions (KO^{t}Bu (2.5 eq.), t-BuOH, Δ, 30h) which gave an 8:5 mixture of (S,S,S/S,S,R)-**9** in 80% yield. The diastereoisomers were then readily separated by column chromatography.[12] The stereochemistry of the (S,S,S)-isomer **9** was proven by conversion to a crystalline (S)-tyrosine derivative derivative **14** (*scheme 1*), whose structure was determined by X-ray crystallography[13], and the (S)-stereochemistry of the newly formed centre correlated to the (S)-tyrosine residue.

Preparation of the primary amine **12** ($[\alpha]_D$ -3.0 (c 1% MeOH)) was achieved by hydrogenolysis of the sodium salt of **9** over Pearlman's catalyst ($Pd(OH)_2/C$). This procedure avoided lactamisation and gave the sodium salt of the amine **12** in 95% yield. It was not possible to confirm the enantiomeric purity of **12** directly by chromatographic or spectroscopic means. Accordingly, it was converted to the (S)-tyrosine derivative **13**, direct, quantitative t.l.c. analysis of which[14] confirmed >98% diastereoisomeric purity.

The sequence described above thus constitutes a short and highly stereoselective construction of the target compounds. The highly stereoselective 1,4-addition reaction described is particularly noteworthy, both for its efficiency and because the event determining the stereochemistry of the newly formed centre is apparently protonation of the intermediate enolate ester (*Scheme 2*). This suggests a conformation of the lithium enolate which facilitates transmission of stereochemical information present in the (S)-α-methylbenzyl protecting groups to the newly developing carbon-hydrogen bond. Two conformations consistent with this assumption are depicted in *Scheme 2*. In each case, the lithium counter-ion is complexed between the enolate oxygen and the β-nitrogen atom in a six-membered ring chelate. Preliminary modelling experiments suggest that the conformations depicted are of low energy, and furthermore, that in each case the resultant faces of the enolate are readily distinguishable by an incoming electrophile, the more favoured approach yielding the observed (S)-stereochemistry[15]. More detailed discussions of these results will be reported in due course.

In conclusion, the addition of lithium enolates to chiral acrylate synthons **7** and **8** results in efficient, stereoselective formation of β-aminoacid esters, which are useful intermediates in the construction of neutral endopeptidase inhibitors. The key reaction involves a remarkably stereoselective protonation of an intermediate ester enolate. Synthons **7** and **8** should find further use in stereoselective construction of β-aminoacid esters.

Scheme 2



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9 Detailed experimental procedures are described in *European Patent* A-0432898, James, K. and Barnish, I.T., *Chem Abs.*, **1991**,*115*, 256639.

10 Diastereoisomer ratios were assigned by ^{1}H nmr.

11 All new products gave microanalytical and spectroscopic data consistent with their structures. Rotations in Table 1 are of the diastereoisomer mixture.

12 Chromatography on silica eluted with ethyl acetate:dichloromethane (3:7).

13 Compound **14** was obtained as colourless crystals m.p. 105-109°C from hexane. X-ray crystallographic analysis confers the molecular structure. Space group $P2_12_12_1$, a = 11.210(3), b = 13.071(4), c = 23.494(6)Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$. A full set of bond angles, bond lengths, atomic co-ordinates and structure factors will be deposited with the Cambridge Crystallographic Data Centre.

14 A sample of **13** was spotted on a silica gel tlc plate, eluted with a mixture of chloroform, methanol and acetic acid (200:25:5) and developed with NaOCl/starch/KI. Spot intensity was measured and compared with standards of the R,S-diastereoisomer.

15 A computer model of the chelated lithio-intermediate was constructed using the SYBYL program (Tripos Associates, St Louis, MO, USA). Conformational analysis of the (S)-α-methylbenzyl groups in this intermediate finds the conformations depicted in scheme 2 as the two lowest energy conformations. Calculation of the relative steric congestion (Wipke, W.T. and Gund, P., *J. Am. Chem. Soc.*, **1976**, *98*, 8107) indicates the face most hindered to attack.

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