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threo-Selective Michael Addition of N,N-Dibenzylglycinate and Alaninate Enolates to α,β-Unsaturated Esters. A Concise and Stereoselective Synthesis of (±)-CCG-II

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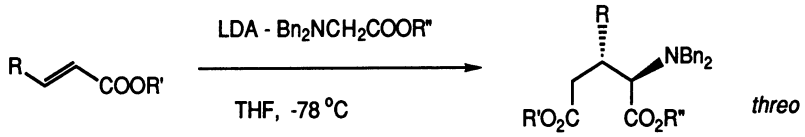
Lithium enolates of N,N-dibenzylglycinate and alaninate added to β-substituted α,β-unsaturated esters, and threo-adducts were obtained in high stereoselectivities. The reaction was employed in a concise and stereoselective synthesis of (±)-CCG-II.

The Michael type reactions of glycine enolates to α,β-unsaturated esters are one of the most convenient methods for the synthesis of glutamic acid derivatives, and several glycines with alkylidene protecting groups have been employed for this purpose.[1] In these reactions, the diastereoselective formation of two continuous asymmetric centers (erythro/threo selectivity) is an important problem, and erythro-selective reactions were recently reported by Schöllkopf[1c] and Kanemasa.[1h] During our investigations on the Michael reactions,[2] high threo-selectivities were attained by using N,N-dibenzylglycinate enolates.[3] A concise and stereoselective synthesis of (±)-CCG-II (8)[4] was also performed.

Table 1. *threo*-Selective Michael Addition of N,N-Dibenzylglycinate Enolates to α,β-Unsaturated Esters



R	R'	R"	yield/% a)
Me	Me	Et	56
	Me	tBu	84
	tBu	tBu	66 ,51 b)
n-C_4H_9	Et	tBu	62
n-C_7H_{15}	Et	tBu	68

a) The reactions were carried out with 1 mmol of lithium enolates and 0.67 mmol of unsaturated esters in THF-hexane (5+0.6 mL) at -78 °C under a nitrogen atmosphere, and isolated yields are shown. All the products gave satisfactory ^{1}H-NMR, ^{13}C-NMR, IR, MS spectra, and/or elemental analysis by HRMS. The other isomer was not detected by ^{13}C-NMR spectra. b) The reaction was carried out with 7.5 mmol of unsaturated ester and 10 mmol of glycinate.

When t-butyl crotonate was added to t-butyl N,N-dibenzylglycinate enolate generated by LDA in THF at -78 °C, the Michael addition proceeded smoothly giving glutamate as a single isomer with threo-configuration. The stereoselectivities were not affected by substituents, and several combinations of the enolates and unsaturated esters also gave the threo-adducts exclusively (Table 1). It is interesting to note that the addition of N,N-dibenzylglycinate enolates to unsaturated esters shows much higher selectivities than the addition to aldehydes.[3)]

The stereochemistry of the lithium enolate of N,N-dibenzylglycinate was known to be dependent on the solvents in which enolization was conducted: E-configuration in THF and Z- in THF-HMPA.[3a)] Actually, when the Michael addition was carried out in THF-HMPA, the product was a 2:1 mixture with the erythro-isomer predominating. Also observed was that the stereoselectivities were dependent on the bases employed. While LDA, lithium 2,2,6,6-tetramethylpiperidide, lithium diethylamide, or sec-butyllithium gave threo-adducts in THF, the use of lithium piperidide, lithium pyrrolidide, or lithium propylamide gave a 1:1 mixture of two isomers. It is presumed that the latter bases generated Z-enolates.

Comments are required concerning the stereochemical aspects of the present reactions and Kanemasa's reactions[1h)] which gave threo- and erythro-adducts, respectively (Fig. 1). At the transition state, it could be assumed that the negatively charged part of the nucleophile interacts with the electrophilic olefin of the unsaturated esters either by HOMO-LUMO attractions or charge-transfer interactions. In the present reactions, sterically favorable approach A of enolates (1-oxaallylanion) explains the formation of threo-adducts. While in the erythro-selective reactions, 2-azaallylanion moiety interacts with the olefin as indicated by the formation of cycloadducts at C-N-C part under slightly modified reaction conditions.[5)] Since E-configuration of -N=CH-COOR system is well-established,[5)] less crowded transition state C leads to erythro-isomers.

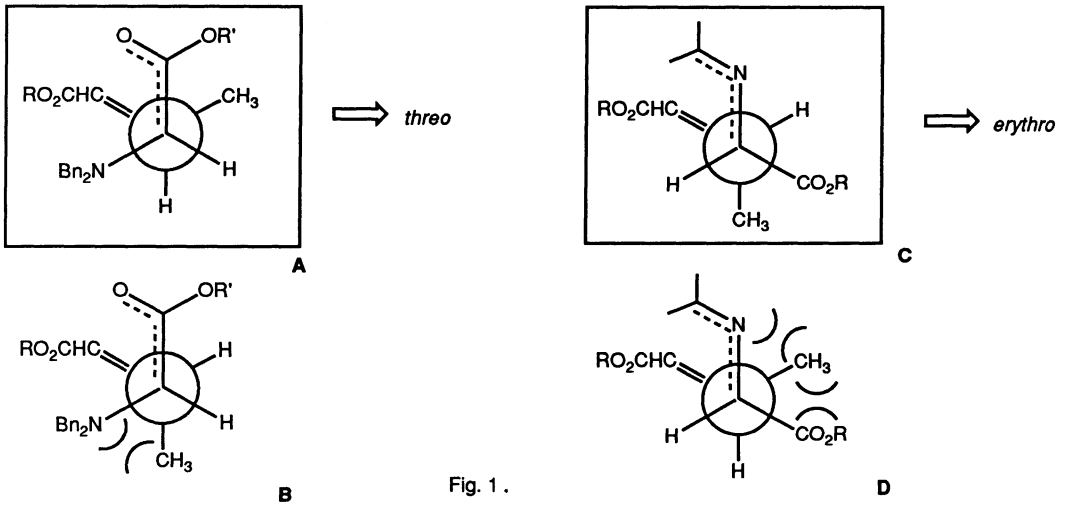
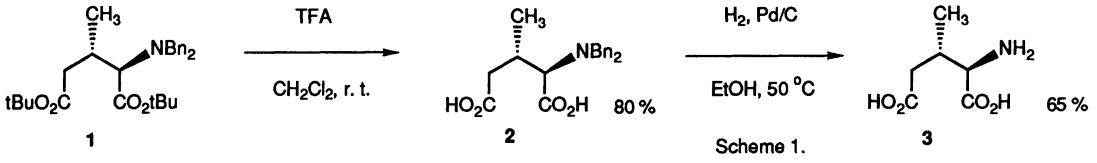


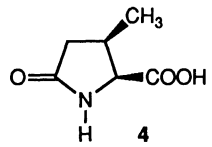
Fig. 1.

The conversion of N,N-dibenzylglutamate to glutamic acid was carried out as follows under mild reaction conditions without the formation of lactams (Scheme 1).



Scheme 1.

It is advantageous since the regeneration of glutamic acids from lactams requires strong acidic conditions.[6] A mixture of di-t-butyl ester 1 and TFA in CH_2Cl_2 was stirred for 33 h at room temperature. The solvents were removed in vacuo, and the residue was chromatographed on silica gel. The resulted TFA salt was stirred vigorously in pH 3 buffer, and the precipitate was collected to give threo-N,N-dibenzylglutamic acid 2 in 80% yield. Mp 202-203 °C (DMF-H_2O). Debenzylation[6] with H_2-Pd/C in EtOH at 50 °C for 30 min gave methylglutamic acid 3 in 65% yield. In order to determine the stereochemistry, 3 was converted to lactam 4 by heating in water, and NMR spectra agreed with the reported values.[6]



The reactions of N,N-dibenzylalaninates were carried out at -40 °C, and again the products were obtained as single isomers concerning the adjacent tertiary and quaternary carbons (Table 2). An adduct was converted to lactone 5, and cis-relation between two methyl groups was determined by NOE studies.

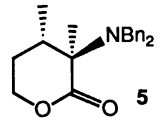
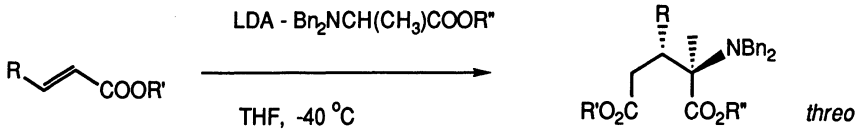


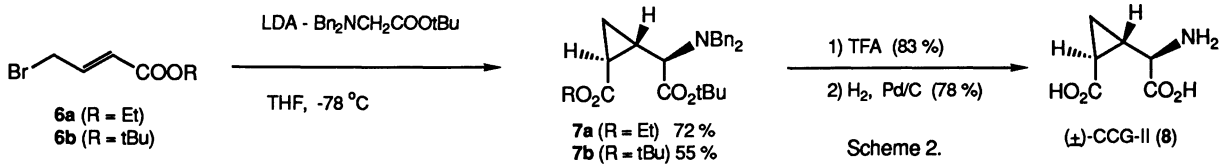
Table 2. *threo*-Selective Michael addition of N,N-Dibenzylalaninate Enolates to α,β-Unsaturated Esters



R	R'	R"	Yield/%[a]	
Me	Me	Me	72	
			69	b)
			24	c)
	Me	tBu	52	d)
	tBu	Me	53	
n-C_4H_9	Et	Me	77	
n-C_7H_{15}	Et	Me	82	

a) The reaction was carried out in 1 mmol scale, and isolated yields are shown. All the products gave satisfactory NMR, IR, MS spectra, and/or, elemental analysis by HRMS. The other isomer was not detected by ^{13}C-NMR spectra. b) A mixture of THF and HMPA (4 : 1) was used as the solvent. c) The reaction was carried out at -78 °C. d) The reaction was carried out at -20 °C.

Previously, we reported the Michael addition and intramolecular alkylation sequences to construct extracyclic chiral centers.[2a] The methodology was used here in a concise and stereoselective synthesis of (±)-CCG-II (8), a novel neuroactive glutamic acid derivative.[4] When 4-bromocrotonate 6 was reacted with t-butyl N,N-dibenzylglycinate enolate in THF at -78 °C, threo-selective Michael addition and trans-selective cyclization took place, and cyclopropane 7 was obtained in good yield (Scheme 2).[8] Deprotection of di-t-butyl ester 7b was carried out as before and NMR spectra of the product agreed with that of the authentic CCG-II.



Scheme 2.

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8) Although this approach was reported in Ref. 1g, the yield and stereoselectivity were unacceptably low.

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