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ASYMMETRIC ALKYLATIONS OF A SULTAM-DERIVED GLYCINATE EQUIVALENT: PRACTICAL PREPARATION OF ENANTIOMERICALLY PURE α-AMINO ACIDS

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Abstract: Deprotonation/alkylation of sultam-derived *N*-[bis(methyl)thiomethylene]glycinate equivalent 3 gave crystalline products 5 which on mild hydrolysis furnished α-amino acids 7 (~100% e.e.) in high overall yield.

Chiral glycine equivalents represent an attractive pivotal source for asymmetric syntheses of enantiomerically pure α-amino acids [1]. Straightforward alkylations of glycine enolate derivatives are, however, relatively scarce [2] and, despite their elegance, leave plenty of room for more practical and general alternatives.

We report here the advantageous use of the readily available and widely applicable sultam auxiliary 1 [3]. Me_3Al-mediated acylation of 1 with methyl *N*-[bis(methylthio)methylene]glycinate (2) [4] furnished, after crystallization, "glycinate" 3 (89%) [4,5] which served as a common precursor for various α-amino acids 7 (Scheme, Table).

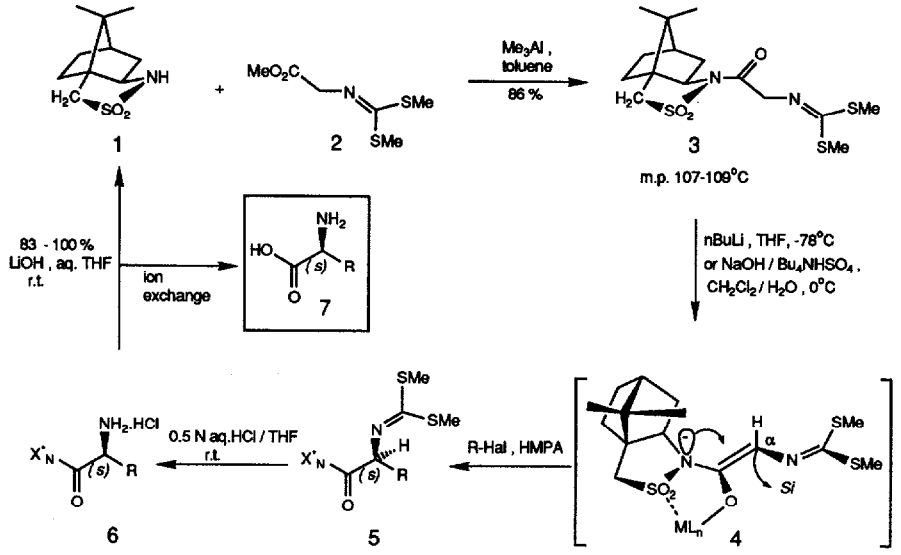

Table Preparation of Enantiomerically Pure α-Amino Acids 7 by Alkylation/Hydrolysis 3 → 5 → 7 [5]

		R	Hal	Deprotonation Conditions	Yield [%][a] 5 from 3	d.e. [%][a] 5	M.p. [°C] 5	Yield [%] 7 from 5	e.e. [%] 7
1	a	Me	I	BuLi	87[b]	>99[b] (96.4)	119-120	>99	>99.8
2	b	$PhCH_2$	I	BuLi	93 (96)	>99 (94.7)	132-133	>99	>99.8
3	c	CH_2=CH-CH_2	I	BuLi	87 (94)	>99 (96.8)	83 - 84	>99	>99.8
4	d	$tBuO_2CCH_2$[c]	Br	BuLi	96 (100)	>99 (98.4)	142-144	75[d]	>99.8
5	e	nC_4H_9	I	BuLi	86 (89)	>99 (95.6)	95 - 97	>99	>99.8
6	f	Me_2CH-CH_2	I	BuLi	85 (87)	>99 (95.6)	125-127	>99	99.5
7	g	Me_2CH	I	BuLi	95[e]	>99[e] (97.7)	-[e]	84	>99.8
8	b	$PhCH_2$	I	NaOH/PTC	- (90)	- (90.6)	-	-	-

a) Values apply to chromatographed and recrystallized (crude) 5. b) Direct crystallization without FC.
c) Alkylation in the presence of $(nBu)_4NI$. d) Treatment of 5d with CF_3CO_2H/r.t./2 h prior to hydrolysis sequence to give free (*S*)-aspartic acid. e) Chromatographed non-crystalline solid.

Successive treatment of 3 with *n*BuLi (THF, -78°C) and methyl-, benzyl-, allyl iodide or *t*-butoxycarbonylmethylene bromide/HMPA (-55°C → r.t.) provided alkylation products 5a to 5d in 94.7 to 98.4% diastereomeric excess (d.e. entries 1-4) [5]. We were pleased to find equally efficient and π-face-selective alkylations with non-activated and even secondary alkyl iodides (entries 5-7). Intriguingly, simple deprotonation/alkylation using phase transfer catalysis [6] [PTC: 10% aq. NaOH (4 mol-equiv.), Bu_4NHSO_4 (1.2 mol-equiv.), $PhCH_2I$ (1.2 mol-equiv.), stirring in CH_2Cl_2, 0°C, 24h] furnished 5b (90% yield) in 90.6% d.e. (entry 8). Products 5 could be separated from their C(α)-epimers by chromatography and, moreover, in all but one case (5g), purified (~100% d.e.) by crystallization (hexane, EtOH or MeOH). For example, pure, crystalline *(S)*-alanine derivative 5a [5] was obtained in 87% yield without chromatography. The depicted d.e. values followed directly from a comparison (GC) with 1:1-mixtures of the corresponding C(α)-epimers [7], which are also clearly distinguishable by ^{1}H- and ^{13}C-NMR. Selective *N*-deprotection of 5 by mild acidic hydrolysis (0.5N HCl, THF/H_2O 1:1, r.t., 24h) furnished amine hydrochlorides 6 which could be isolated and characterized (e.g., 6b, ~100%). In general, crude 6 was directly saponified with LiOH (4 mol-equiv., THF/H_2O 2:1, r.t., 24h). Extraction (CH_2Cl_2) gave recovered sultam 1 (83-100%). Acidification of the aq. phase (pH = 1-2) adsorption on ion exchange resin (Amberlite IR 120, H^+) and desorption with aq. NH_4OH provided ~100% enantiomerically pure *(S)*-amino acids 7 in 84 to 100% overall yield from 5. In the case of 5d the *t*-butyl ester was cleaved (CF_3COOH, r.t., 2h) prior to the usual hydrolysis sequence giving free *(S)*-aspartic acid 7d.

The *(S)*-configurations and enantiomeric purities of 7 (>99.5% e.e.) were readily determined by GC comparison (Chirasil-Val) [8] of their *N*-trifluoroacetylisopropyl esters with those of racemic and enantiomerically pure samples.

The observed topicity parallels that found on alkylation of simple *N*-acylsultams [9] and is in agreement with a kinetically controlled formation of chelated *(Z)*-enolates 4, alkylated from the C(α)-*Si*-face, opposite to the lone electron pair on the sultam-nitrogen atom.

In summary, this alkylation approach to enantiomerically pure α-amino acids compares very favorably with those previously published [2] given the easy accessibility of sultam 1 and its antipode [3], the efficient formation of crystalline alkylation products (~100% d.e., even with non-activated primary and secondary alkyl iodides), and last but not least, the mild and efficient cleavage conditions.

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