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Asymmetric Synthesis of L-Diphenylalanine and L-9-Fluorenylglycine via Room Temperature Alkylations of a Sultam-Derived Glycine Imine

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Key Words: L-diphenylalanine; L-9-fluorenylglycine; sultam-derived glycine imine; asymmetric room temperature alkylation; mild sultam deprotection.

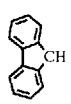
Abstract: L-diphenylalanine and L-9-fluorenylglycine were prepared from a sultam-derivated glycine imine **3** *via* room temperature-asymmetric-alkylation/hydrolysis/mild-sultam-clivage. The L-configuration was ascertained using an X-ray analysis of the alkylation product **4b**.

Models for biactive conformations of peptides have been deduced from structure-activity relationships involving local or larger-size constraints of the backbone orientation *via* the incorporation of N-methyl amino acids, proline, or cyclisation, respectively. However, to probe the relative arrangement of the side-chain of each amino acid and then generate a more precise tridimensionnal envelop representing the space-filling requirements of the bioactive conformation, topographic probes, which will stabilize one or two rotamers of the side-chain, have to be designed[1]. Diphenylalanine (Dip)[2] and 9-fluorenylglycine (Flg)[2d] were first selected, since the aromatic rings of Phe and Tyr often play crucial roles in peptide-receptor recognition. The relative orientation of the aromatic rings should be different in Dip and Flg analogues, i.e. perpendicular in Dip and equiplanar in Flg.

No preparation of these α-amino acids in their optically pure forms by using either asymmetric synthesis[3] or enzymatic methods has been reported in literature. Our first attempts at enzymatic resolution of the racemates of their N-terbutyloxycarbonyl (Boc) esters with papain or α-chymotrypsin failed (Speth *et al.* had failed, trying acylases[4]). Similarly asymmetric syntheses were inefficient, i.e. trying either asymmetric reprotonation of methyl N-(diphenylmethylene) diphenylalaninate[5], or enantioselective alkylation of methyl N-(diphenylmethylene) glycinate under phase-transfer conditions using cinchona alkaloid catalyst[6b].

These problems led us to develop a diastereoselective synthesis of Dip and Flg which is outlined in scheme.

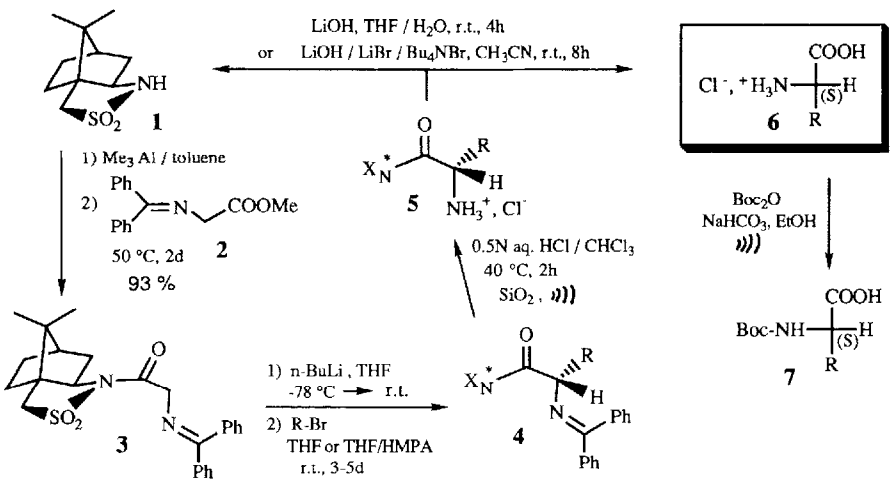
Table. Preparation of Boc-protected L-diphenylalanine and L-9-fluorenylglycine *via* alkylation/hydrolysis/N-protection.

		Yield[a] (%)				d.e. (%)	M.p.[a] (°C)			
	R	**4**	**5**	**6**[b]	**7**	**4**	**4**	**5**[c]	**6**[c]	**7**
a	$PhCH_2$	88	93	90(98)	90	> 95	219	128-129	241-243	88-90
b	Ph_2CH	68	89	76(91)	86	> 95	236-237	118-119	205-208	129-131
c		72	92	84(97)	79	> 95	> 270	149-152	> 270	206-209

a) Value apply to pure recrystallized compound. b) recovered sultam between brackets. c) Crystallized as hydrochloride.

The strong asymmetric induction observed by Oppolzer *et al.* using a sultam-derived glycinate equivalent[7a], prompted us to develop the sultam derivative of the methyl N-(diphenylmethylene) glycinate : this chiral synthon **3** was prepared *via* Me_3Al-mediated (1,2 equiv.) acylation[7a] of sultam **1**[7b-c] by methyl N-(diphenylmethylene) glycinate **2** (1,2 equiv.) [6a] (50°C, 2 days, workup, flash chromatography), yielding 93% of a foamy compound.

Scheme

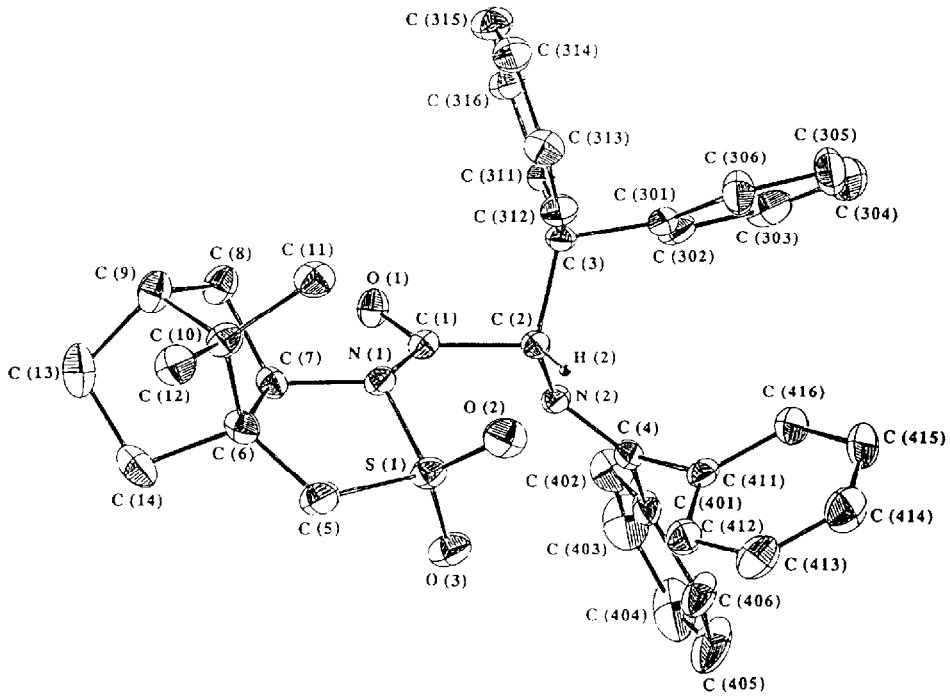


The synthon **3** was easily alkylated with benzyl bromide (n-BuLi, THF, -78°C, then electrophile/HMPA, -55°C → r.t.), to provide **4a** with yield and d.e. comparable with those obtained by Oppolzer[7a]. However bromodiphenylmethane and 9-bromofluorene did not react under such conditions. The low reactivity of these electrophiles, probably due to their steric hindrance, forced us to achieve the alkylations with a large excess of electrophile at room temperature for several days[8]. Thus bromodiphenylmethane and 9-bromofluorene afforded, after workup, crude alkylation products **4b-c** with >95% diastereoisomeric excess, which were increased to ~100% after flash chromatography over basic alumina and recrystallization (CH_2Cl_2/Et_2O) (scheme, table)[9]. Despite these long reaction times, the alkylations seem to be kinetically controlled, as suggested by the following experiment: the Schiff base **2** was alkylated with benzyl bromide, and Me_3Al-mediated coupled to sultam **1** (o-xylene, 140°C, 16h, 42%) to furnish the two diastereoisomers of sultam N-(diphenylmethylene) phenylalaninate; when this mixture (selected as representative of **4**) was added to 1 equivalent of the carbanion of **3** (in order to simulate the alkylation conditions corresponding to 50% of conversion) no evolution of the diastereoisomeric ratio was observed even after 48h at room temperature.

An X-ray analysis[10] of the L-diphenylalanine precursor **4b** unambiguously confirmed the kinetically-controlled (Si)-approach of the reactants observed by Oppolzer *et al.* on the same type of "glycinate" synthon (figure) [6a], even for bulky electrophiles.

Hydrolysis of **4** under ultrasonic irradiation (0.5N $HCl/CHCl_3$, SiO_2, 40°C, 2h, then concentration and flash chromatography) afforded the N-(α-aminoacyl)sultams **5**.

Figure. An ORTEP stereoview of **4b** with thermal ellipsoids drawn at a 30% probability level.



The next step, raised another difficulty: in fact if the cleavage of the sultam group is usually easily achieved *via* the classical method, i.e. LiOH-THF/H_2O, it was inapplicable in the case of the L-diphenylalanine precursor since only 30% **6b** and 47% **1** were obtained, together with a weight-predominant side-product[11]. This side-reaction was avoided by running the cleavage in aprotic media, with a suitable phase-transfer-catalyst (LiOH(4 equiv.)/LiBr(10 equiv.)/nBu_4NBr(0.4 equiv.), CH_3CN, r.t., 8h). Addition of water and extraction of the aqueous phase allowed sultam **1** recovery. Acidification (pH 1-2), filtration over Bio-Rex 70 (H^+ form), gave pure L-diphenylalanine **6b** and L-9-fluorenylglycine **6c** as hydrochlorides, after recrystallization[12].

These Dip and Flg derivatives were then N-protected (Boc_2O, $NaHCO_3$, EtOH,)))), 3h) to yield **7a-b**[13]. The optically pure L and the racemic amino acids, previously obtained[2e], were then introduced by solid-phase in position 8 in the sequence of Substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2). An HPLC analysis, which allowed us to distinguish the two diastereoisomers of [Flg^8]SP and [Dip^8]SP respectively, proved the enantiomeric purity of these Boc-amino acids **7** (> 98%).

In summary, we have shown that hindered aryl electrophiles can be coupled to a sultam-glycinate derivative, achieving asymmetric alkylations at room temperature for several days without apparent effect on d.e. Extension of this method to other bulky groups is currently investigated. Nevertheless it should be noted that long reaction times required for these alkylations will limit this procedure to thermally stable electrophiles.

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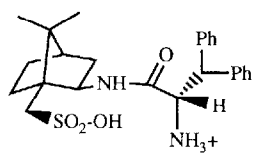
8. Alkylation under phase transfer catalysis (ref. 6b) has to be avoided due to the weak stability of these halides in aqueous media.
9. All new compounds were characterized by ^{1}H-NMR; microanalysis gave satisfactory results.

   Deprotonation/room temperature alkylation (**3b-c** → **4b-c**): 1.6 N n-BuLi (hexane, 1 equiv.) was added over 10 min to a solution of **3** (**4b**: THF, 5 ml/mmol, HMPA, 1 ml/mmol; **4c**: THF, 5 ml/mmol) at -78°C under argon. Cold bath was removed. When the mixture had warmed to r.t., addition of freshly recrystallized bromodiphenylmethane (2 equiv.) or 9-bromofluorene (1.5 equiv.) in THF (2 ml/mmol), stirring at r.t. under rigorously dry conditions, 5 days(**4b**) or 3 days(**4c**), quenching with AcOH(THF), addition of Et_2O, washing with sat. aq. NH_4Cl (4 times), afforded crude **4** which was flash chromatographied over basic alumina (**4b**: cyclohexane/AcOEt 85:15; **4c**: cyclohexane/ AcOEt 80:20) and recrystallized (CH_2Cl_2/Et_2O).

   Hydrolysis (**4** → **5**): **4** in $CHCl_3$(4ml/mmol) was adsorbed on SiO_2 (2g/mmol). After addition of 0.5 N HCl, the mixture was sonicated in a cleaning bath at 40°C for 2h. Concentration to dryness, direct flash chromatography ($CHCl_3$ → benzophenone; then $CHCl_3$/MeOH: 9:1 → **5**) gave **5**, recrystallized from CH_2Cl_2/Et_2O.

   Saponification under phase transfer conditions (**5b** → **6b**): to **5b** in acetonitrile (10ml/mmol), were added LiOH.H_2O (4 equiv.), LiBr (5 equiv) and n-Bu_4NBr (0.4 equiv.). Stirring at r.t. for 8h, concentration to dryness, addition of water and extraction with CH_2Cl_2 afforded **1**, after filtration of the organic phases over SiO_2 (to remove remaining salts). Acidification of the aqueous phase (pH 1-2), filtration over Bio-Rex 70 (H^+ form; side-product[11] kept adsorbed; it was desorbed with aq. NH_4OH), afforded **6b** after recrystallization (cf. ref.12).
10. Crystallographic data were deposited at the *Cambridge Crystallographic Data Centre* but can be obtained from us.
11. Spectral characteristics (^{1}H-NMR, CD_3OD) of this side-product are consistent with a compound resulting from an attack of LiOH on the sulfur atom of sultam, as shown below; this side-product was obtained quasi-exclusively when the reaction was performed in EtOH.



12. Observed optical rotations: **6a** (recryst. in EtOH): $[\alpha]_D^{25}$ = +43° (c 0.5, 1N HCl); **6b** (recryst. in EtOH/H_2O): $[\alpha]_D^{25}$ = -26° (c 0.5, 1N HCl); (D)-amino acids prepared from **1** antipode gave respectively -42° and +27°.
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