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Asymmetric Synthesis of the Diastereoisomers of L-1-Indanylglycine and L-1-Benz[f]indanylglycine, χ_1,χ_2-Constrained Side-Chain Derivatives of L-Phenylalanine and L-2-Naphthylalanine

Hubert Josien and Gérard Chassaing*

Laboratoire de Chimie Organique Biologique, U.A. C.N.R.S. 493, Université Pierre-et-Marie Curie, Paris, France

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Abstract: The diastereoisomers of L-1-indanylglycine and L-1-benz[f]indanylglycine, novel topographic tools and analogues of phenylalanine and 2-naphtylalanine, were synthesized from a sultam-derived glycine imine synthon alkylated by judicious electrophiles, and subsequent hydrolysis and sultam-cleavage. An X-ray analysis on one alkylation product established the β-configuration.

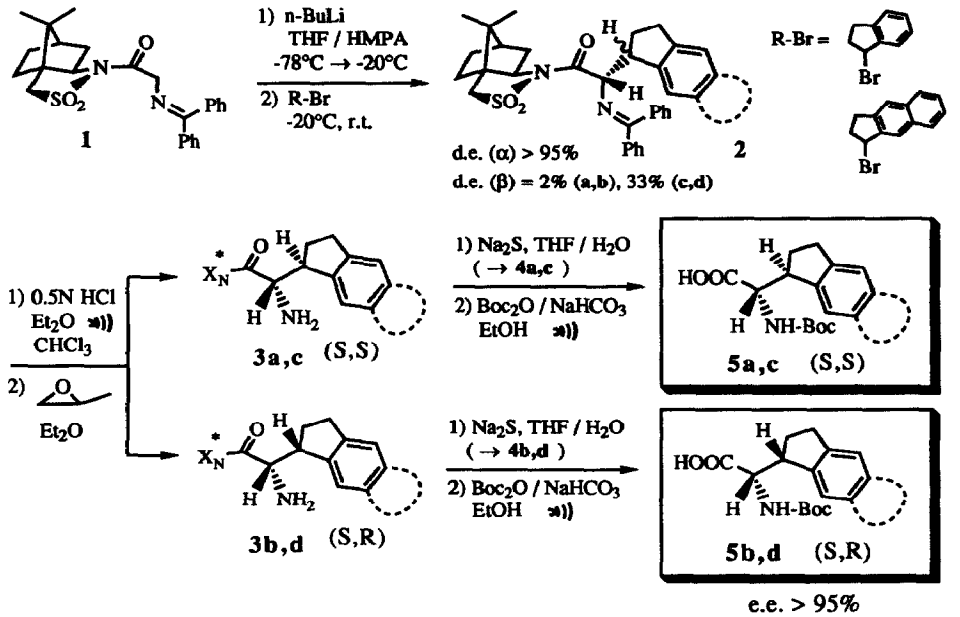
The determination of the bioactive conformation of a peptide is an important step toward the design of new pharmaceutical drugs. This analysis is usually hampered by the flexibility of the backbone and the side-chains. Thus, a general approach involves the use of conformational constraints to stabilize firstly the backbone conformation, secondly to control the side-chain orientation. The side-chain can adopt three major conformers from the α-carbon: gauche (+), gauche (-) or trans (χ_1=+60°, -60°, or 180°). We previously described the synthesis of two bis-aromatic probes, L-diphenylalanine, and L-9-fluorenylglycine[5b] which allow the simultaneous stabilization of two phenylalanine rotamers. However, to determine if one of these rotamers is favored in the receptor site, the introduction of a second chiral center on the β-carbon is necessary. This purpose was achieved by Hruby *et al.* with the diastereoisomers of β-methyl-phenylalanine[1]. We propose the synthesis of new topographic probes: the diastereoisomers of L-1-indanylglycine (Ing) and L-1-benz[f]indanylglycine (Bfi) **4a-d**, constrained side-chain derivatives of phenylalanine, and 2-naphtylalanine, respectively. These amino acids are more constrained than the β-methyl-phenylalanines: χ_1 is still controlled by the chiral center on the β-carbon, but the cyclopentene ring imposes the aromatic ring(s) orientation (diast. (2S,3S): χ_2=+60°; diast. (2S,3R): χ_2=-60°).

Ing was only synthesized in 1950 by Gagnon *et al.* as a racemic diastereoisomeric mixture[2], whereas Bfi diastereoisomers have never been prepared. The two α and β chiral centers first incited us to search for a strategy allowing α,β-stereocontrol. The method involving a β-diastereoselective 1,4-protonation of a 1-indanylenoyl sultam with L-Selectride[3a], followed by an α-stereocontrolled addition of a nitrosylchloride[3b] proved unfruitful since hydride addition resulted in sultam cleavage[3c]. In addition, attempting asymmetric alkylation of a sultam-derived glycine enolate synthon[5] with chiral 1-indanylmesylate failed due to the partial epimerization of the electrophile by the chiral Schiff base[4]. These results led us to give up β-stereocontrol and to achieve the synthesis of these amino acids *via* a route which is depicted in the scheme.

The key step of this synthesis involved an asymmetric alkylation of the sultam-derived glycinate synthon **1**[5b] with achiral 1-indanyl bromide[6a] and the novel 1-benz[f]indanyl bromide. These electrophiles were obtained quantitatively by simple hydrobromination[6b] of indene and benz[f]indene, respectively. The latter, whose preparation on a large scale was not reported until 1990[7a-b], was synthesized according to Burger's procedure[7a], except for the last step[7c]. Since these halides show a high tendency to eliminate HBr, addition reactions with them require a carbanion possessing both nucleophilic and weakly basic properties[8]. However, they occurred readily with synthon **1**, probably due to a high delocalization of the carbanion charge. Thus, deprotonation of **1** with n-BuLi (THF, -78°C) followed by the addition of electrophile (HMPA, -20°C → r.t.) afforded, after workup and

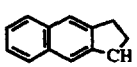
flash-chromatography over basic alumina, Schiff base **2a-d** as a (2S,3S) and (2S,3R) mixture of diastereoisomers (scheme, table)[9], whose structural features consist of a quasi-total (d.e.>95%) (S)-α-configuration and a slight β-stereocontrol, dependent on the electrophile[10].

Scheme



Hydrolysis of the imine function was carried out under ultrasonic irradiation (0.5N HCl, Et_2O, $CHCl_3$, 4h), to provide diastereoisomeric mixture of N-aminoacylsultam hydrochlorides. A smooth transformation into their free-amine counterparts with propylene oxide in diethylether allowed their separation by chromatography, to give in good yield enantiomerically pure N-aminoacylsultams (2S,3S) **3a,c** and (2S,3R) **3b,d** after recrystallization (CH_2Cl_2/Et_2O).

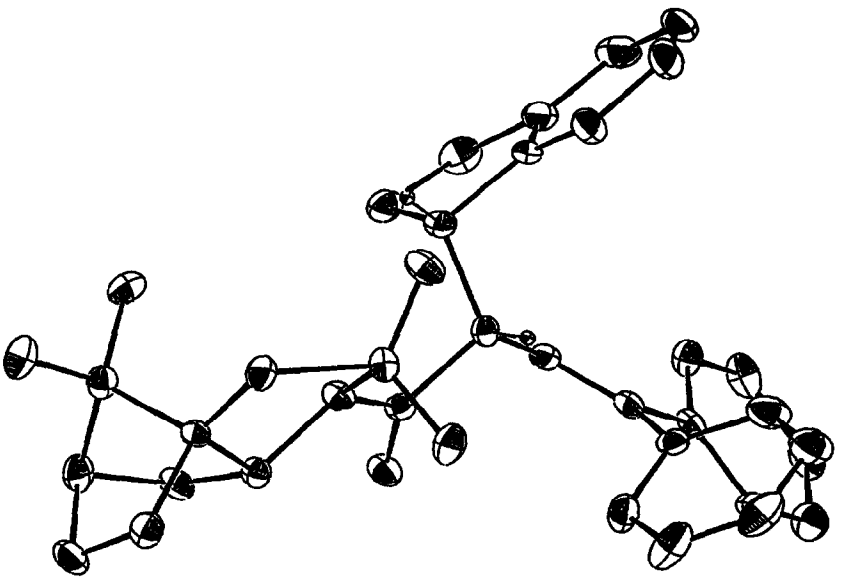
Table. Preparation of L-1-indanylglycines and L-1-Benz[f]indanylglycines **1** → **5**

	R	Config.	Yield[a] (%)			d.e. (%)		M.p. (°C)			$[\alpha]_D^{20}$	
			2	3	5	2 (α)	2 (β)	3	4[b]	5	4[d]	5[e]
a		(2S,3S)	69	83	57	> 95	2	178-180	185-188[c]	foam	+53.9	+28.6
b		(2S,3R)		83	63	> 95		150-151	227-230[c]	109-111	-9.7	+10.8
c		(2S,3S)	80	74	52	> 95	33	209-210	192-194[c]	102-106	+90.9	+112.7
d		(2S,3R)		72	62	> 95		207-208	221-225[c]	213-216[c]	-69.9	-96.2

a) Pure recristallized compound. b) HCl salts. c) Decomp. d) α_{obs} from TFA salts (c=5, AcOH) e) c=5, **a-c**: MeOH; **d**: DMF.

An X-ray analysis[11] of (2S,3R) Ing Schiff base **2b**, obtained from transimination of **3b** hydrochloride with benzophenone imine[12], allowed us to ascertain the β-configuration of the four diastereoisomer derivatives of Ing and Bfi **3a-d** (figure)[13].

Figure. An ORTEP stereoview of (2S,3R) Ing precursor **2b**



Clean removal of the sultam group proved to be highly dependent on the β-configuration: it could be accomplished readily with (2S,3R) **3b,d** compounds according to the classical method, i.e. LiOH-THF/H_2O. But an important side-reaction, involving cleavage of the sultam ring, previously encountered with L-diphenylalanine[5b], was observed in the case of (2S,3S) **3a,c** intermediates, even when phase-transfer conditions[5b] were applied. Using sodium sulfide in THF/H_2O, this side-reaction was reduced to 10-15%. The crude amino acids hydrochlorides **4a-d** were then obtained after extraction of sultam and acidification.

N-protection of these crude products under ultrasonic irradiation according to Luche's procedure[14] (Boc_2O, $NaHCO_3$, EtOH) afforded, after flash chromatography and recrystallization, Boc-amino acids **5a-d**: their high enantiomeric purity (e.e.>95%) was revealed on insertion in position 7 or 8 of the sequence of Substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2) by solid-phase synthesis followed by HPLC analysis of the resulting crude peptide. A TFA-deprotection could provide amino acids **4a-d**.

In summary, we have shown that the sultam-derived glycine synthon can be alkylated by several base-sensitive electrophiles to achieve the synthesis of four aromatic α,β-chiral side-chain constrained α-amino acids. Use of the topographic properties of these probes to model the envelope of bioactive peptide is currently underway.

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4. 1-indanylmesylate was even less reactive than 1-indanylbromide (several days were needed, at room temperature).
5. a) W. Oppolzer, R. Moretti, S. Thomi, *Tet. Lett.* , **1989**, *30*, 6009-6011; b) H. Josien, A. Martin, G. Chassaing, *Tet. Lett.*, **1991**, *32(45)*, 6547-6550.
6. a) C. Courtot, A. Dondelinger, M.A. Haller, *Comptes Rendus de l'Acad. des Sciences*, **1924**, *179*, 1168-1171; b) We also prepared quantitatively 1-indanylbromide from 1-indanol with PPh_3/Br_2.
7. a) U. Burger, P.J. Thorel, J.P. Schaller, *Tet. Lett.*, **1990**, 3155-3156 and references herein; b) L.A. Carpino, Y.Z. Lin, *J. Org. Chem.*, **1990**, *55*, 247-250; c) transformation of *endo+exo*-4,9-epoxy-3a,4,9,9a-tetrahydro-1H-benz[f]indene to benz[f]indene was achieved with 10% H_2SO_4 (reflux, 5h, 90%), i.e. same reagent used by Carpino *et al.* to deshydrate 1-benz[f]indanol.
8. These limitations might explain the low yield obtained by Gagnon *et al.*[2] in the racemic series of Ing using alkylcyanoacetic esters as carbanions. Similarly, we observed that N-acetyl sultam gave only elimination reaction with 1-indanyl bromide.
9. All new compounds were characterized by ^1H NMR; microanalysis gave satisfactory results.
   Preparation of the electrophiles: pure indene, or benz[f]indene dissolved in methylene chloride, was saturated at 0°C with HBr gas. Excess HBr was removed from 1-benz[f]indanyl bromide by concentrating to dryness its methylene chloride solution three times , and from 1-indanyl bromide by four freezing-melting cycles with liquid nitrogen *in vacuo*. These electrophiles should be used quickly.

   Alkylation (**1** → **2**): n-BuLi (1.6 N hexane, 1 equiv.) was added over 10 min to a solution of **1** in THF (4ml/mmol) and HMPA (1 ml/mmol) at -78°C under argon. Stirring the mixture to -20°C, injection at this temperature of the electrophile in THF (1 ml/mmol), then 2 h, r.t., 2 h, quenching with AcOH (THF), addition of Et_2O, washing with sat. aq. NH_4Cl, drying on magnesium sulfate, gave crude **2** which was flash-chromatographied over basic alumina (**2a-b**: cyclohexane/AcOEt 8:2 then $CHCl_3$; **2c-d**: cyclohexane/AcOEt 7:3 then $CHCl_3$) and recrystallized (CH_2Cl_2/Et_2O).

   Hydrolysis; separation of the diastereoisomers (**2** → **3**): a mixture of **2** in Et_2O (1.5 ml/mmol), $CHCl_3$ (1.5 ml/mmol), and 0.5N HCl (1.5 equiv.) was sonicated in a cleaning bath for 4 h. Concentration to dryness, trituration in Et_2O, filtration, afforded crude **3** hydrochlorides. Stirring in Et_2O with propylene oxyde, 24 h, *in vacuo* removal of solvents, chromatography over silica gel in a long column (200g for 1.5g crude; h = 1.5m; Ø = 3cm ; **3a-b**: CH_2Cl_2/AcOEt 85:15; **3c-d**: CH_2Cl_2/AcOEt 88:12) provided first (2S,3S) **3a,c**, then (2S,3R) **3b,d**, recrystallized in CH_2Cl_2/Et_2O.

   Saponification; N-protection (**3** → **4** → **5**): Na_2S (1.5 equiv.) in H_2O (3 ml/mmol) was added at 0°C to **3** in THF (3 ml/mmol). After vigorous stirring at room temperature (**3a**: 24h; **3c**: 8h; **3b,d**: 5h), addition of water, cautious extraction of sultam with $CHCl_3$, acidification of the aquous phase (pH=1-2), concentration to dryness, crude **4** was obtained. Addition of EtOH (8 ml/mmol), $NaHCO_3$ (0.40 g/mmol) and Boc_2O (1 equiv.), sonication (**5a,b**: 5h; **5c,d**: 8h), filtration over celite, flash-chromatography over silica gel (**5a-c**: CH_2Cl_2/MeOH/AcOH 95:5:0.5; **5d**: $CHCl_3$/MeOH/AcOH 90:10:0.5) and recrystallisation (**5b**: CH_2Cl_2/pentane; **5c**: Et_2O/pentane; **3d**: CH_2Cl_2/MeOH) afforded pure **5a-d**.
10. β-diastereoisomers excess was inferred from the analysis of ^1H NMR spectra which exhibited important anisotropic effects of the aromatic rings on Me (sultam), H_α, H_β (and $^3J_{\alpha\beta}$) and H_γ, particularly.
11. Crystallographic data have been deposited at the *Cambridge Crystallographic Data Centre*.
12. M.J. O'Donnell, R.L. Polt, *J. Org. Chem.*, **1982**, *47*, 2663-2666.
13. β-configurations in Bfi serie were deduced from Ing's ones by comparison of ^1H NMR spectra between all (2S,3S) and (2S,3R) **2-5** Ing and Bfi derivatives, which showed strong analogies, or identity, of the coupling constants and the chemicals schifts.
14. J. Einhorn, C. Einhorn, J.L. Luche, *Synlett.*, **1991**, 37.