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A Versatile Method for the Synthesis of (S)- or (R)-Cycloalkylglycines, (S)- or (R)-N-Heterocyclic and α,β-Unsaturated N-Heterocyclic α-Amino Acids

Régine Pauly, N. André Sasaki* and Pierre Potier

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex France

Abstract : Two different types of cyclic α-amino acids, cycloalkylglycines and N-heterocyclic α-amino acids, were prepared in optically pure form from the same chiral synthon 1-(R) (or 1-(S)) simply by altering the quantity or type of base required for anion formation. Elaboration of the heterocyclic intermediate 3 provided α,β-unsaturated N-heterocyclic α-amino acids.

Increased lipophilicity and binding affinity to receptors, improved metabolic stability or limitation of conformational mobility can be beneficial to the therapeutic usefulness of biologically relevant peptides. For example, introduction of a cycloalkyl group to the β-position of an α-amino acid and incorporation of the so-obtained cycloalkylglycine into peptides provides novel angiotensin converting enzyme inhibitors[1]. On the other hand, induction of conformational constraints into peptides by incorporating 3-substituted proline derivatives is an important tool in developing peptide-derived pharmaceutical agents[2]. Replacement of proline by its higher homologue is reported to dramatically improve pharmaceutical potency in peptide-based HIV proteinase inhibitors[3]. Although the syntheses of cycloalkylglycines and heterocyclic α-amino acids are described in the literature[4], new and general routes for the synthesis of these classes of molecules are of considerable importance[4j].

In this communication, we describe the first general method of obtaining both cycloalkylglycines and heterocyclic α-amino acids in either S- or R-configuration, as well as α,β-unsaturated N-heterocyclic a-amino acids, starting from a single chiral synthon.

We have previously demonstrated that 1-(R) and 1-(S) are readily available from N-Boc-L-serine methyl ester and can be converted to nonproteinogenic β-alkyl-α-amino acids and (Z)-β,γ-unsaturated α-amino acids in either S- or R-configuration[5].

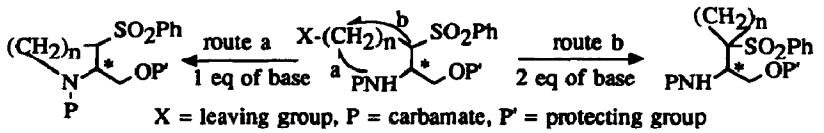
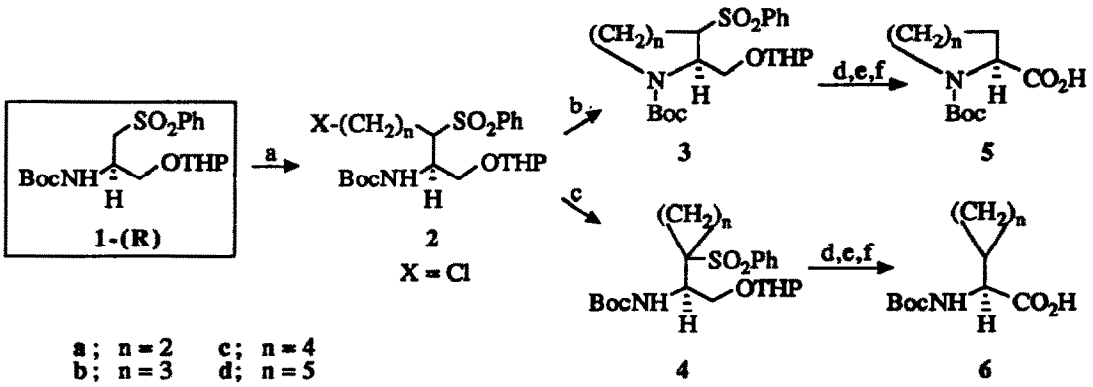


Figure 1

A notable feature of 1-(R) (or 1-(S)) is that by sequential addition of an appropriate base, it forms two distinct types of anion, i.e., carbamate and sulfonyl anions. Since a sulfonyl anion is much more reactive than a carbamate anion, creation of such dianionic species followed by addition of an α,ω-dihaloalkane would first afford monohaloalkylated 1-(R) (or 1-(S)) which could then cyclize intramolecularly either by reaction with the remaining carbamate anion to give a N-heterocylic compound (route a) or by reaction with the secondary sulfonyl anion, formed after the first alkylation by addition of one more equiv of base, to give a cycloalkyl compound (route b), as depicted in general form in Figure 1. Our synthetic strategy is shown in Scheme 1.

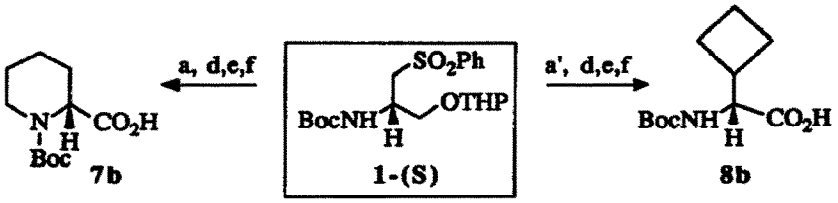


Scheme 1

Reagents and conditions: a) 2 eq n-BuLi, THF, 1.2 eq Br-$(CH_2)_n$-Cl, -78°C to 0°C; b) 1 eq of KOtBu or NaH, DMF, 0°C to rt, 2h; c) 2 eq n-BuLi, THF, -78°C to rt; d) 2 eq 6% Na-Hg, MeOH, 3 eq Na_2HPO_4, 0°C to rt, 3h; e) 0.1 eq pyridinium p-toluenesulfonate, EtOH, 50°C, 6h; f) Jones oxidation, 0°C to rt, 1h.

The starting chiral synthon 1-(R) was treated with 2 equiv of n-butyllithium in THF at -78°C. After 15 min, 1.2 equiv of bromochloroalkane (Br-$(CH_2)_n$-Cl) was added and the reaction was continued overnight at rt. In the case of n = 2, compound **3a** was obtained in 90% yield. In the case of n = 3, continuous stirring at rt for 48 h was required to furnish **3b** in 88% yield. For n = 4 or 5, the cyclization reaction did not take place. Instead, compounds **2c** and **2d** were isolated in 90% yield and 86% yield, respectively, after purification by flash chromatography (SiO_2; EtOAc/heptane = 1/3) with recovery of 3% and 10% of unreacted 1-(R), respectively. Compound **2b** could be isolated in 90% yield when the reaction mixture was quenched at -10°C. However, **2a** was never isolated under the same conditions. Treatment of **2b**, **2c** and **2d** with 1.1 equiv of KOtBu or NaH in DMF at 0°C followed by stirring at rt for 2h afforded **3b**, **3c** and **3d** in 90%, 75% and 55% yield, respectively. No contaminants other than unreacted starting materials were observed in the reaction mixtures. Separation of **2** and **3** was easily effected by flash chromatography (SiO_2; EtOAc/heptane = 1/2). In contrast, addition of one more equiv of n-BuLi at -40°C 15 min after the introduction of electrophile (step a) furnished **4** in good to excellent yield (**4a**; 90%, **4b**; 85%, **4c**; 82%, **4d**; 85%). Except for **4a**, these cycloalkyl sulfones **4** can also be prepared from **2** by treatment with 2 equiv of n-BuLi in THF at -78°C. In all cases, the yields of cyclization products were between 94 and 96%. Treatment of **4** with 6% Na-Hg provided the desulfonated products in excellent yields (94-96%), whereas **3** afforded the analogous products in 80% to 85% yields under the same conditions. Removal of THP by pyridinium p-toluenesulfonate (PPTS) was quantitative (96-98% yields) in all cases and the final Jones oxidation gave **5** and **6** in about 80 to 85% yields. In order to demonstrate the scope of

our approach, (R)-N-Boc-pipecolinic acid **7b** (enantiomer of **5b**) and (R)-N-Boc-cyclobutylglycine **8b** (enantiomer of **6b**), respectively, were prepared from **1-(S)** without isolation of the key intermediate, as shown in Scheme 2.



Scheme 2

Reagents and conditions: a') (i) 2 eq n-BuLi, THF, -78°C, Br-$(CH_2)_3$-Cl, (ii) after 0.5 h , 1 eq n-BuLi, -40°C to rt; a) 2 eq n-BuLi, THF, 1.2 eq Br-$(CH_2)_3$-Cl, -78°C to 0°C; d) 2 eq 6% Na-Hg, MeOH, 3 eq Na_2HPO_4, 0°C to rt, 3h; e) 0.1 eq PPTS, EtOH, 50°C, 6h; f) Jones oxidation, 0°C to rt, 1h.

^1H NMR analysis of Mosher amide[6] prepared from methyl ester of **6c** indicates no epimerization at the stereogenic center of **6c**.

The versatility of the present methodology was further demonstrated by the facile synthesis of α,β-unsaturated heterocyclic α-amino acids **9a** and **9b**, as illustrated in Scheme 3.

Scheme 3

Reagents and conditions: e) 0.1 eq PPTS, EtOH, 50°C, 6h; f) Jones oxidation, 0°C to rt, 1h; g) (i) CH_2N_2, (ii) 1.5 eq DBU, THF, rt, 4 h.

The yields of the final products[7] and their physical properties are summarized in theTable.

α–Amino acid	Config.	Yield % (a)	mp °C	$[\alpha]_D^{20}$ (c = 1.0, MeOH)
5a	S	67	134 (c)	- 68 (c = 1.0, AcOH) (d)
5b	S	70	116-119	- 41 (c = 0.9, MeOH)
5c	S	51	110-113	- 58
6a	S	71	108-112	+ 29
6b	S	72	76-78	+ 4
6c	S	68	58-61	- 9
6d	S	67	76-79	+ 12
7b	R	50 (b)	116-118	+ 42 (c = 0.73, MeOH)
8b	R	51 (b)	77-78	- 3
9a		70	oil	
9b		40		

Table

(a) isolated yield from 3 and 4, (b) yield from 1-(S) (4 steps), (c) lit.[8] 136-137°C, (d) lit.[8] - 60.2 (c = 2.01, AcOH).

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7. Satisfactory analytical and spectral data were obtained from all new compounds. Selected ^{1}H NMR (250 MHz, $CDCl_3$, TMS): **5b** two conformers, δ 4.98 and 4.79 (two m, 1H, C2-H), 4.03 and 3.94 (two d, 1H, J = 11 Hz, C6-Heq), 2.96 and 2.90 (two d, 1H, J = 11 Hz, 10 Hz, C6-Hax), 2.21 (m, 1H, C4-Hax), 1.45 (s, 9H), 1.20-1.84 (m, 5H, C3-H, H', C4-Heq, C5-H, H'). **5c** two conformers, 4.63 and 4.39 (two dd, 1H, J = 12 Hz, 6 Hz, C2-H), 3.98 and 3.83 (two dd, 1H, J = 14 Hz, 4 Hz, C7-H), 3.03 and 2.92 (two dd, 1H, J = 14 Hz, 10.5 Hz, C7-H'), 1.52 and 1.45 (two s, 9H), 2.28-2.48 (m) and 1.20-1.95 (m) (8H, C3-H, H', C4-H, H', C5-H, H' and C6-H, H'). **6a** 5.14 (d, 1H, J = 8 Hz, NH), 3.77 (dd, 1H, Cα-H), 1.44 (s, 9H), 1.13 (m, 1H, Cβ-H), 0.39-0.70 (m, 4H, cyclopropyl H). **6b** 5.10 (d, 1H, J = 8 Hz, NH), 4.26 (dd, 1H, J = 10 Hz, 8 Hz, Cα-H), 2.65 (m, 1H, Cβ–H), 1.72-2.10 (m, 6H, cyclobutyl H). **6c** 5.07 (d, 1H, NH), 4.26 (dd, 1H, Cα–H), 2.30 (m, 1H, Cβ-H), 1.44 (s, 9H), 1.20-1.42 (m, 8H, cyclopentyl H). **9a** 5.77 (t, 1H, J = 3.5 Hz, C3-H), 3.92 (m, 2H, C5-H, H'), 3.80 (s, 3H), 2.63 (m, 2H, C4-H, H'), 1.44 (s, 9H). **9b** 6.00 (t, 1H, J = 4 Hz, C3-H), 3.76 (s, 3H), 3.57 (m, 2H, C6-H, H'), 2.22 (m, 2H, C4-H, H'), 1.80 (m, 2H, C5-H, H'), 1.43 (s, 9H).
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