Preparation of 4-Alkylprolines by Intramolecular Radical Cyclization of Chiral Serine Derivatives

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N-Alkylation of the β-lactone derived from Boc-L-serine followed by ring opening with sodium benzeneselenoate provides chiral substrates which undergo intramolecular radical cyclization to afford *cis/trans* mixtures of 4-alkyl-L-prolines.

The use of conformationally restricted analogues of naturally occurring amino acids is finding application in the design of new drugs based on peptide structures. Such analogues of amino acids allow the probing of biologically active conformations of a peptide by restricting the number of accessible conformations or by inducing 'turns' in three dimensional structures.[1] Prolines, when incorporated into a peptide sequence are known to induce reversed turns and bends due to the rigidity of the C–N Φ angle implicated by the cyclic pyrrolidine structure.[1b,2] In conjunction with ongoing studies in our laboratories, we were interested in the use of 4-alkyl substituted prolines **1** as conformationally restricted analogues of naturally occurring amino acids as shown in Fig. 1 for L-leucine and 4-methyl-L-proline **1** (R = Me).

Asymmetric syntheses of 4-alkyl substituted prolines have been reported in the literature.[1b,3] We have developed an alternative approach to these interesting molecules which is based on the intramolecular radical cyclization of a D- or L-serine-derived substrate (Scheme 1, Table 1).[4] Readily available Boc-L-serine **2** was converted into the β-lactone **3** (72% yield).[5]† *N*-Alkylation‡ was performed by addition of an allylic halide and freshly prepared silver oxide to a slurry of the lactone **3** and

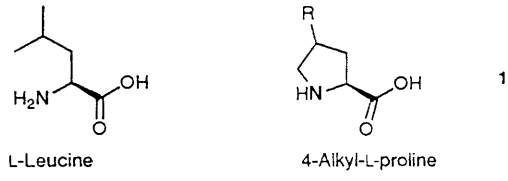


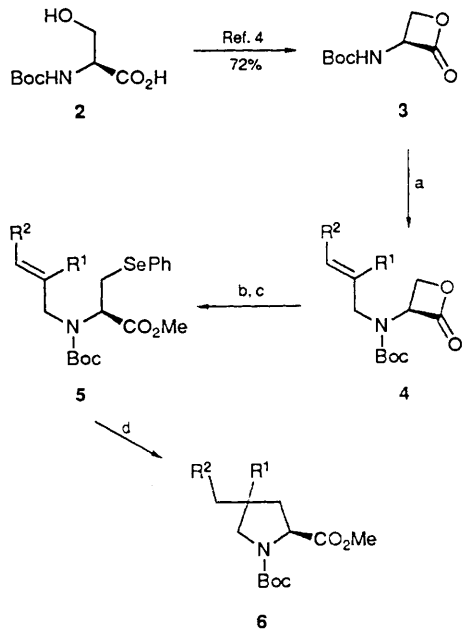
Fig. 1

Table 1

Entries	X	R^1	R^2	% Yield **4**	% Yield **5**	% Yield **6**	*cis/trans* ratio
a	I	H	H	90	89	90	62:38
b	Br	H	Me	75	84	85	60:40
c	I	H	Pr	90	90	75	60:40
d	Br	H	Ph	65	75	85	55:45
e	I	Me	H	79	84	83	—

† Satisfactory spectroscopic (IR and 200 MHz ^{1}H NMR), mass spectral and elemental C,H,N analysis data were obtained for all compounds. Throughout this communication *J* values are recorded in Hz and [α] values in 10^{-1} deg cm^2 g^{-1}.

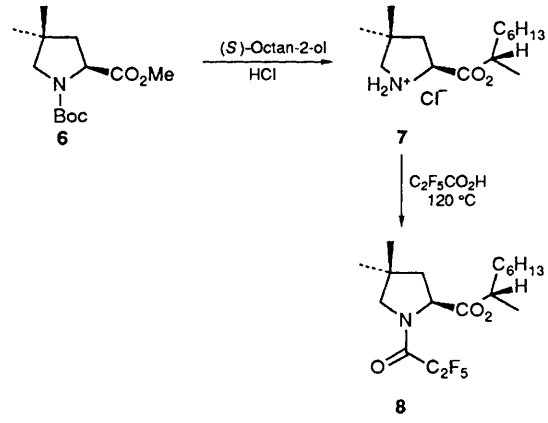
‡ *General Procedure for* N-*Alkylation of the Serine* β-*Lactone* **3**.—Powdered 4 Å molecular sieves (2–3 g) were flame-dried and cooled under nitrogen. The serine lactone **3** (0.935 g, 5.0 mmol, 1 equiv.) was added followed by anhydrous ether (50 cm^3) or THF (entry d). The slurry was stirred vigorously in the dark while freshly prepared silver oxide (2.317 g, 10 mmol, 2 equiv.) and the allylic halide (4 equiv.) were added each in 3 portions over 3–6 h. After completion, as determined by TLC, the brown slurry was filtered through a pad of Celite using ether for washings (3 × 25 cm^3). Evaporation of the solvent under reduced pressure followed by flash chromatography using hexane–ethyl acetate mixtures as eluent gave pure *N*-alkylated lactones **4** (65–90% yield).



Scheme 1 *Reagents and conditions:* (*a*) $R^2CH{=}CR^1CH_2X$ (X = Br, I), Ag_2O (2 equiv.), 4 Å molecular sieves, ether or THF (room temperature), 3–24 h; (*b*) PhSeNa (2 equiv.), DMF, room temperature 3 h; (*c*) diazomethane, ether; (*d*) Ph_3SnH (1.2 equiv.), AIBN (catalytic), benzene, reflux, 8 h

flame-dried, powdered 4 Å molecular sieves in anhydrous ether (or THF, entry d) at room temperature to give **4** (65–90% yield). Regiospecific ring opening of lactones **4**[5] at the 3-position with sodium benzeneselenoate generated under aprotic conditions (diphenyl diselenide, NaH, DMF)[6] gave after esterification with an excess of diazomethane in ether, the selenides **5** (75–90% yield). Intramolecular radical cyclization of the unsaturated selenides **5** was performed under standard conditions (Ph_3SnH, AIBN, benzene reflux)[7,*] to afford 4-alkyl-L-prolines (83–90% yield) as mixtures of *cis* and *trans* isomers with the ratios shown in Table 1.

The radical cyclization was found to be completely regiospecific for the 5-*exo* mode of ring closure. However, the degree of diastereoselectivity was poor, favouring slightly the *cis* isomer. The stereochemistry was established by comparison of physical and spectral properties to literature values.[1b,3d] Cyclization of **5e** gave L-Boc-4,4-dimethylproline methyl ester as a single enantiomer as shown by derivatization (Scheme 2), and capillary GC analysis using a chiral capillary column.† The extent of racemization was less than *ca.* 2%. This was further



Scheme 2

substantiated by preparing D-Boc-4,4-dimethylproline methyl ester starting from Boc-D-serine and comparing the final product to the L-enantiomer. The two isomers were found to be clearly distinguishable by capillary chiral GC analysis and showed equal optical rotations of opposite sign.‡ To our knowledge, this is the first report of a synthesis of chiral 4,4-dimethylproline, a potential inhibitor of collagen biosynthesis.[8]

We are currently exploring variants of this new methodology which should allow the preparation of 4-alkyl substituted L-prolines with a higher degree of diastereoselectivity. Results will be reported in due course.

* *General Procedure for Radical Cyclization of the Selenides* **5**.—The selenides **5** (1 mmol, 1 equiv.) and 2,2′-azoisobutyronitrile (AIBN) (5 mg) were dissolved in degassed benzene (25 cm^3), and the solution was brought to reflux under an argon atmosphere. Triphenyltin hydride (0.456 g, 1.3 mmol, 1.3 equiv.) in benzene (10 cm^3) was added dropwise over 1 h using a syringe pump and refluxing was continued for an additional hour or until completion as judged by TLC. After cooling and evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography using hexane–ethyl acetate mixtures as eluent to give pure proline derivatives **6** (75–90% yield).

† The protected amino acid derivatives **6** were derivatized prior to capillary GC analysis (see Scheme 2 in text). The proline derivative **6** (0.3–0.5 mg) in (*S*)-octan-2-ol (100 μl) saturated with HCl gas, was heated to 120 °C for 0.5 h. The solvent was evaporated under a stream of N_2 and the ester **7** was heated at 120 °C for 0.25 h with pentafluoropropionic acid (50 μl). After evaporation of the solvent under a stream of N_2, the residue **8** was dissolved in acetonitrile and analysed by capillary GC on a 30 m SUPELCOWAX 10 capillary column (180 °C isotherm).

‡ (*S*)-**6e**: R_f 0.27 (4:1, hexane–ethyl acetate), m.p. 57–60 °C, $[\alpha]_D^{30}$ −69 (*c* 0.98, $CHCl_3$); δ_H($CDCl_3$, 200.1 MHz), 2:1 mixture of rotamers; δ 4.33 (t, *J* 4.0, 1 H, minor), 4.27 (dd, *J* 4.5, 4.7, 1 H, major), 3.74 (s, 3 H, minor), 3.72 (s, 3 H, major), 3.28 (m, 2 H), 2.07 (dd, *J* 4.0, 1.0, 1 H, minor), 1.98 (dd, *J* 4.0, 1.0, 1 H, major), 1.76 (m, 1 H), 1.46 (s, 9 H, minor), 1.41 (s, 9 H, major), 1.13 (s, 3 H, major), 1.10 (s, 3 H, major) and 1.05 (s, 3 H); ν_{max}(Nujol)/cm^{-1} 3080–2760, 1760 and 1715; *m*/*z* (CI) (rel intensity) 258 (34, MH^+), 202 (22, MH^+ − tButyl) and 158 (100, MH^+ − Boc) (Found: C, 60.7; H, 9.05; N, 5.55. Calc. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44%).

TFA salt (30% TFA in CH_2Cl_2, 0.5 h, 0 °C) derived from (*S*)-**6e**: δ_H($CDCl_3$, 200.1 MHz) 4.65 (t, *J* 8.9, 1 H), 3.86 (s, 3 H), 3.23 (ABq, *J* 11.0, 2 H), 2.30 (dd, *J* 13.0, 8.5, 1 H), 1.97 (dd, *J* 12.8, 8.5, 1 H), 1.23 (s, 3 H) and 1.18 (s, 3 H); *m*/*z* (CI) (rel intensity) 158 (100, MH^+), 115 (80, $MH^+ - C_2H_5N$) and 98 (60, $MH^+ - HCO_2Me$).

(*R*)-**6e**. M.p. 58–60 °C, $[\alpha]_D^{30}$ +69.4 (*c* 0.84, $CHCl_3$).

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