Stereospecific synthesis of chiral alkinylogous amino acids

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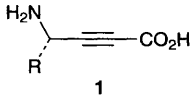
***tert*-Butoxycarbonyl (Boc)-protected α-amino aldehydes, conventionally prepared from the corresponding (*S*)-α-amino acids, are converted *via* the Corey–Fuchs reaction into the *N*-protected alkinylogous amino acids, which on deprotection yield the corresponding enantiomerically pure acids.**

The synthesis of unusual amino acids continues to be an interesting endeavour for several reasons,[1] *e.g.* the need to prepare peptidomimetic drugs.[2] In this connection the incorporation of alkinylogous amino acids **1** has not been considered to date. It can be anticipated that the presence of one or more of such units in a peptide chain may influence, *inter alia*, the secondary and tertiary structure. Indeed, preliminary molecular modelling studies show that polypeptidic forms of **1** are expected to be in an α-helical form, as in the case of normal α-amino acids, but with a considerably larger inner helix-channel.[3] Here we describe the synthesis and properties of enantiomerically pure alkinylogous amino acids **1**.[4]

Our strategy is based on the Corey–Fuchs transformation[5] of Boc-protected α-amino aldehydes **3**[6] derived from the corresponding *S*-configurated amino acids **2** (Scheme 1). The enantiomeric purity of the crude dibromides **4** was checked by removing the Boc-group and forming the corresponding (*R*)-Mosher amides.[7] HPLC analysis indicated a diastereoisomeric excess (de) for **4a**, **b**, **c** and **d** of 90, 70, >99 and >99%, respectively.[8] In the case of the alanine derivative, simple recrystallization of **4a** led to a product having 99% ee (40% yield). The synthesis of the more extensively racemized phenylalanine derivative **4b** had to be optimized by carrying out the reaction at −30 °C and recrystallizing the crude product from diethyl ether–hexane (ee = 98%; 82% yield). The use of enantiomerically pure dibromides **4** afforded enantiomerically pure derivatives of alkinylogous amino acids **1**. Thus, the *N*-protected acids **5** were converted into the corresponding methyl esters by treatment with MeI/K_2CO_3/DMF (R = Me, 78%; R = Bn, 66%; R = Pr^i, 82%; R = Bu^i, 80%), which were then deprotected at the nitrogen atom and converted into the corresponding (*R*)-Mosher amides. HPLC-analyses indicated diastereoisomeric purities of >99%, corresponding to essentially complete enantiomeric purity of the acids **5** (ee >99%).[8]

The alkinylogous amino acids **1** are white-greyish solids which decompose upon heating to 180–200 °C. In the case of **1a** suitable crystals for an X-ray structural analysis were obtained.† The results show that a three-dimensional array pertains in which the carboxylate moieties form hydrogen bonds to the NH_3^+-entities of the neighbours (Fig. 1), the same as in the crystal structure of alanine itself.[9] Thus, the acetylenic spacer not only has the effect of separating the carboxyl moiety from the NH_3^+-function, it also places the repeating hydrogen bonding units further away from one another in the crystal lattice.



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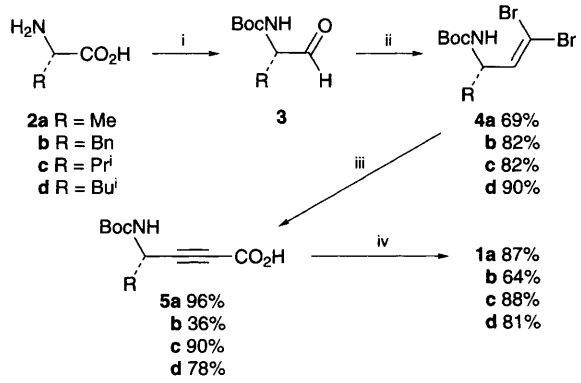
Using the classical titration method, the isoelectric points [pK_i = 1/2 (pK_S + pK_B)] of the alkinylogous amino acids **1** were determined.[8] The values turned out to be consistently lower than those of the corresponding α-amino acids (**1a**, 4.86; **1b**, 4.67;



Scheme 1 *Reagents and conditions*: i, lit.,[6]; ii, CBr_4–Zn–PPh_3, 24 h, 0 °C; **3**, 2 h, −30 °C; iii, BuLi, 1 h, −78 → −55 °C, CO_2, 2 h, → 22 °C; iv, CF_3CO_2H–CH_2Cl_2, 1 h, 22 °C

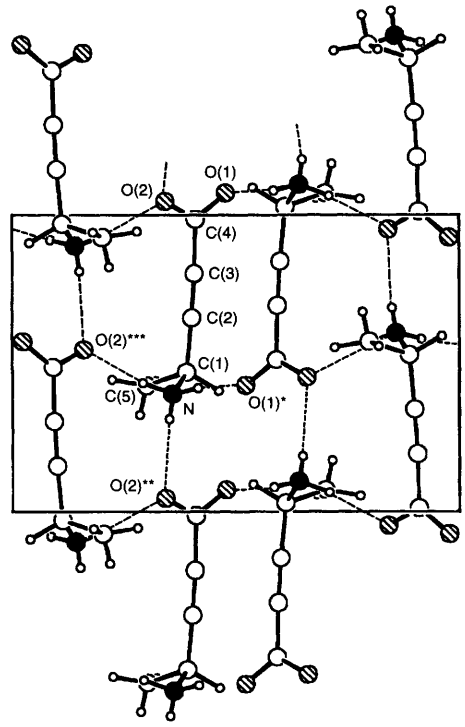
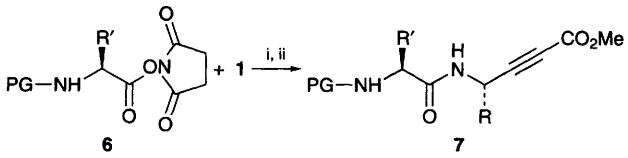


Fig. 1 Structure of the alkinylogous alanine **1a** in the crystal, showing the hydrogen bonds (symmetry related atoms denoted by *). Selected interatomic distances (Å) and angles (°): N–C(1) 1.490(2), C(1)–C(2) 1.469(2), C(2)–C(3) 1.189(2), C(3)–C(4) 1.469(2), C(4)–O(1) 1.224(2), C(4)–O(2) 1.244(1), N···O(1)* 2.718(2), N···O(2)** 2.792(1), N···O(2)*** 2.754(1), C(1)–C(2)–C(3) 178.1(1), C(2)–C(3)–C(4) 177.6(1), O(1)–C(4)–O(2) 124.2(1), N–C(1)···C(4)–O(2) (torsion) −33.4(4) [alanine N–C–C–O −18.3].



a PG = Z, R′ = Me, R = Bn, 43%
b PG = Z, R′ = Me, R = Pr^{i}, 35%
c PG = Boc, R′ = Bn, R = Bu^{i}, 57%

Scheme 2 *Reagents and conditions*: i, Et_3N in THF–H_2O (1 : 1), 1 h, 22 °C; ii, K_2CO_3, DMF, MeI, 22 °C

1c, 5.19; **1d**, 4.63 *vs.* alanine, 6.00; phenylalanine, 5.48; valine, 5.96; leucine, 6.02). This is due to the fact that compounds **1** have lower pK_S and pK_B values relative to those of the parent α-amino acids.

Preliminary attempts to incorporate **1** in dipeptides were successful. Thus, reacting the Boc- or benzyloxycarbonyl (Z)-protected active esters **6** derived from (*S*)-alanine or (*S*)-phenylalanine with the protonated form of compounds **1** followed by esterification afforded the *N*-protected dipeptide esters **7**. In a final reaction the diastereoisomeric (*R*,*S*) form of **7c** was prepared by using (*R*) phenylalanine and (*S*) **1d** (yield 57%).[8]

Initial biological screening was carried out with some of the alkinylogous amino acids **1**. For example, compound **1d** was subjected to the Ames test, which showed that it has essentially no mutagenic properties.‡ However, the biological properties of peptidic forms and of other derivatives of **1** still need to be studied.

Footnotes

† *Crystal data* for **1a**: $C_5H_7NO_2$, M = 113.1 g mol^{-1}, colourless, 0.25 × 0.25 × 0.42 mm, a = 6.7355(3), b = 7.9237(3), c = 11.6912(6) Å, V = 623.96(5) Å^3, T = 293 K, D_c = 1.20 g cm^{-3}, μ(Cu-Kα) = 0.79 mm^{-1}, F(000) = 240 e, Z = 4, orthorhombic, space group $P2_12_12_1$ [No. 19], Enraf-Nonius CAD4 diffractometer, λ = 1.54178 Å, measuring method ω-2θ, 2676 measured reflections (±h, ±k, +l), $[(\sin\theta)/\lambda]_{max}$ 0.63 Å^{-1}, 1278 independent reflections, 1247 observed reflections [$I \geq 2\sigma(I)$] for 76 refined parameters, structure solved by direct methods, non H atoms refined anisotropically, H atom positions riding, $\Sigma w(F_o^2 - F_c^2)^2$ minimized, R = 0.027, R_w = 0.081 [$w = 1/[\sigma^2(F_o^2) + 0.002p^2 + 0.036p]$ with $p = (F_o^2 + 2F_c^2)/3$, absolute structure determined [Flack 0.0(3)], final difference Fourier Δ = 0.13 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ We thank Professor Marahiel, Universität Marburg, Germany, for carrying out the test.

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