

# Stereospecific synthesis of chiral alkinologous amino acids

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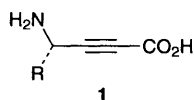
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*tert*-Butoxycarbonyl (Boc)-protected  $\alpha$ -amino aldehydes, conventionally prepared from the corresponding (*S*)- $\alpha$ -amino acids, are converted *via* the Corey–Fuchs reaction into the *N*-protected alkinologous amino acids, which on deprotection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

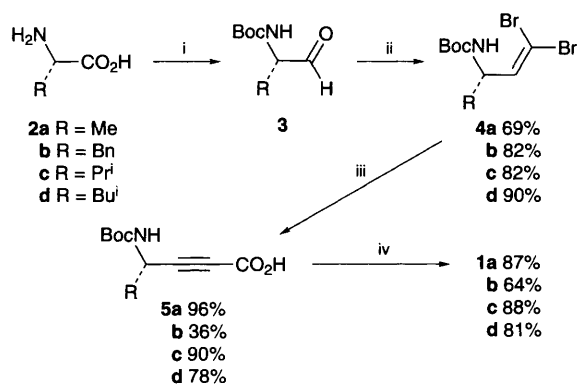
The synthesis of unusual amino acids continues to be an interesting endeavour for several reasons,<sup>1</sup> *e.g.* the need to prepare peptidomimetic drugs.<sup>2</sup> In this connection the incorporation of alkinologous amino acids **1** has not been considered to date. It can be anticipated that 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  $\alpha$ -helical form, as in the case of normal  $\alpha$ -amino acids, but with a considerably larger inner helix-channel.<sup>3</sup> Here we describe the synthesis and properties of enantiomerically pure alkinologous amino acids **1**.<sup>4</sup>

Our strategy is based on the Corey–Fuchs transformation<sup>5</sup> of Boc-protected  $\alpha$ -amino aldehydes **3**<sup>6</sup> derived from the corresponding *S*-configured 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.<sup>7</sup> HPLC analysis indicated a diastereoisomeric excess (de) for **4a**, **b**, **c** and **d** of 90, 70, >99 and >99%, respectively.<sup>8</sup> 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  $-30^\circ\text{C}$  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 alkinologous amino acids **1**. Thus, the *N*-protected acids **5** were converted into the corresponding methyl esters by treatment with MeI/K<sub>2</sub>CO<sub>3</sub>/DMF (R = Me, 78%; R = Bn, 66%; R = Pr<sup>i</sup>, 82%; R = Bu<sup>i</sup>, 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%).<sup>8</sup>

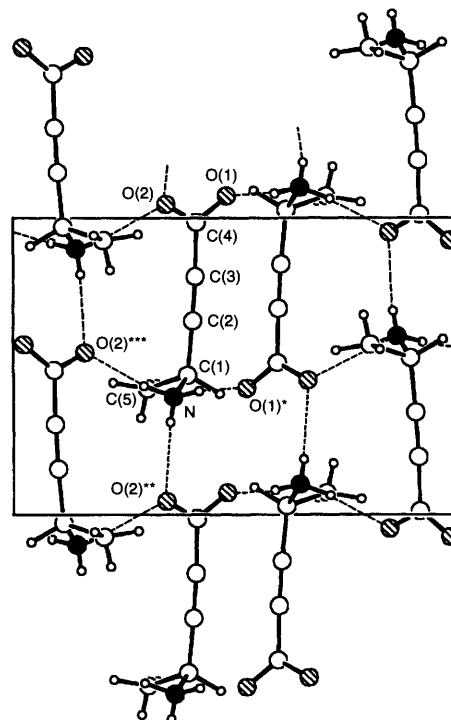
The alkinologous amino acids **1** are white-greyish solids which decompose upon heating to 180–200 °C. In the case of **1a** suitable crystals for an X-ray structural analysis were obtained.† The results show that a three-dimensional array pertains in which the carboxylate moieties form hydrogen bonds to the NH<sub>3</sub><sup>+</sup>-entities of the neighbours (Fig. 1), the same as in the crystal structure of alanine itself.<sup>9</sup> Thus, the acetylenic spacer not only has the effect of separating the carboxyl moiety from the NH<sub>3</sub><sup>+</sup>-function, it also places the repeating hydrogen bonding units further away from one another in the crystal lattice.



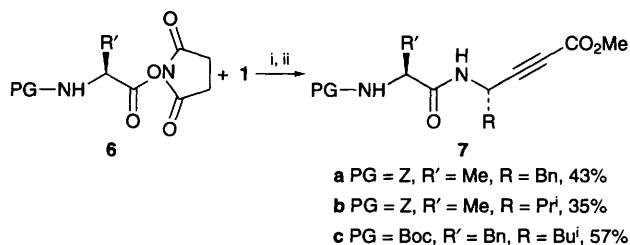
Using the classical titration method, the isoelectric points [ $pK_i = 1/2(pK_S + pK_B)$ ] of the alkinologous amino acids **1** were determined.<sup>8</sup> The values turned out to be consistently lower than those of the corresponding  $\alpha$ -amino acids (**1a**, 4.86; **1b**, 4.67;



**Scheme 1** Reagents and conditions: i, lit.<sup>6</sup>; ii, CBr<sub>4</sub>–Zn–PPh<sub>3</sub>, 24 h, 0 °C; **3**, 2 h,  $-30^\circ\text{C}$ ; iii, BuLi, 1 h,  $-78 \rightarrow -55^\circ\text{C}$ , CO<sub>2</sub>, 2 h,  $\rightarrow 22^\circ\text{C}$ ; iv, CF<sub>3</sub>CO<sub>2</sub>H–CH<sub>2</sub>Cl<sub>2</sub>, 1 h, 22 °C



**Fig. 1** Structure of the alkinologous 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  $-18.3$ ].



**Scheme 2** Reagents and conditions: i, Et<sub>3</sub>N in THF–H<sub>2</sub>O (1 : 1), 1 h, 22 °C; ii, K<sub>2</sub>CO<sub>3</sub>, 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<sub>S</sub> and pK<sub>B</sub> values relative to those of the parent  $\alpha$ -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%).<sup>8</sup>

Initial biological screening was carried out with some of the alkylogous 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<sub>5</sub>H<sub>7</sub>NO<sub>2</sub>, *M* = 113.1 g mol<sup>-1</sup>, 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<sup>3</sup>, *T* = 293 K, *D<sub>c</sub>* = 1.20 g cm<sup>-3</sup>, μ(Cu-Kα) = 0.79 mm<sup>-1</sup>, *F*(000) = 240 e, *Z* = 4, orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> [No. 19], Enraf-

Nonius CAD4 diffractometer, λ = 1.54178 Å, measuring method ω-2θ, 2676 measured reflections (±*h*, ±*k*, +*l*), [(sinθ)/λ]<sub>max</sub> 0.63 Å<sup>-1</sup>, 1278 independent reflections, 1247 observed reflections [*I* ≥ 2σ(*I*)] for 76 refined parameters, structure solved by direct methods, non H atoms refined anisotropically, H atom positions riding, Σw(*F<sub>o</sub>*<sup>2</sup> - *F<sub>c</sub>*<sup>2</sup>)<sup>2</sup> minimized, *R* = 0.027, *R<sub>w</sub>* = 0.081 [*w* = 1/[σ<sup>2</sup>(*F<sub>o</sub>*<sup>2</sup>) + 0.002*p*<sup>2</sup> + 0.036*p*] with *p* = (*F<sub>o</sub>*<sup>2</sup> + 2*F<sub>c</sub>*<sup>2</sup>)/3, absolute structure determined [Flack 0.0(3)], final difference Fourier Δ = 0.13 e Å<sup>-3</sup>. 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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