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# A simple synthesis of (*R*)-3-aminooctanoic acid (*D*-BAOA) from (*S*)-1-octyn-3-ol

Marcello Tiecco,* Lorenzo Testaferri, Andrea Temperini,* Raffaella Terlizzi, Luana Bagnoli, Francesca Marini and Claudio Santi

*Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, I-06123 Perugia, Italy*

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**Abstract**—A simple substrate-controlled asymmetric synthesis of (*R*)-3-aminooctanoic acid (*D*-BAOA) is described. The present method involves the conversion of commercially available (*S*)-1-octyn-3-ol into the protected propargylic amine, with complete inversion of configuration, and the successive transformation of the (phenylseleno)acetylene intermediate into the Se-phenyl selenocarboxylate, which is then easily converted into the carboxylic group. The phthalimido group was eventually removed by treatment with hydrazine hydrate.
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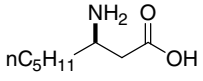
Several bioactive cyclic peptides of lipophilic nature have been isolated from different types of microorganisms[1] such as the antifungal cyclic peptides iturines,[2] bacillomycins and mycosubtilin.[3] An unusual structural motif common to all of these peptides is the occurrence of one β-amino acid[4] with lipophilic and structurally unique side chain. Thus hormothamnin A,[5] a cytotoxic cyclic peptide, was isolated from the tropical marine cyanobacterium *Hormothamnion enteromorphoides* and (*R*)-3-aminooctanoic acid **1** (*D*-BAOA) (Fig. 1) was characterized as the lipid-like β-amino acidic structural component. Because of the importance of this lipophilic β-amino acid its synthesis has attracted increasing interest and this letter reports a simple and enantiospecific route to (*R*)-3-aminooctanoic acid **1** starting from readily available (*S*)-1-octyn-3-ol.

Some reported methods for the synthesis of **1** are mainly based on the stereospecific formation of the C–N bond or the transformation of an α-amino acid. The Michael addition of 'chiral ammonia' equivalent as lithium (*R*)-*N*-benzyl-*N*-α-methylbenzyl amide to achiral α,β-unsaturated ester has been studied by Davies[6] who obtained (*R*)-**1** in good yield and in high ee (>95%) after N-debenzylation and hydrolysis of the β-amino ester intermediate. In a similar way, Enders[7] reported an enantioselective synthesis (ee ⩾95%) of (*S*)-**1** by conjugate addition of lithiated TMS-SAMP to an α,β-unsaturated ester. Moreover, in a different approach, Gmeiner[8] and Jefford[9] transformed the carboxylic group at C-1 of L-asparagine or L-aspartic acid into the desired alkyl substituent to obtain (*R*)-**1** in 99% ee by several steps without altering the integrity of the initial stereogenic center.



(*R*)-**1**
*D*-BAOA

**Figure 1.** Structure of *D*-BAOA.

Following our recent studies[10] on the transformation of terminal alkynes into Se-phenyl selenocarboxylates, we show here an alternative and very convenient method to synthesize (*R*)-**1** starting from commercially available (*S*)-1-octyn-3-ol **2** (99% ee). By reaction with phthalimide under Mitsunobu conditions, compound **2** was easily converted into *N*-phthalimido propargylic amine **3**[11] (Scheme 1) with the expected complete inversion of the configuration at the stereogenic carbon atom. As indicated by HPLC analysis on chiral stationary phase[11] compound **3** presented the same enantiomeric ratio as the starting alkynol **2**. The N-protected propargylic

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* Corresponding authors. Tel.: +39 0755855100; fax: +39 0755855116 (M.T.); e-mail: tiecco@unipg.it

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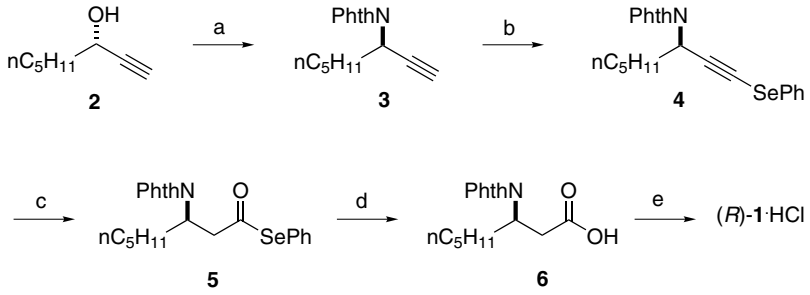


**Scheme 1.** Reagents and conditions: (a) DIAD, PhthNH, $Ph_3P$, THF, 0 °C to rt, 86%; (b) PhSeBr, CuI, DMF, rt, 85%; (c) *p*-TsOH, $CH_2Cl_2$, reflux, 86%; (d) $H_2O_2$, THF, rt, 93%; (e) $H_2N–NH_2$, EtOH, reflux, 97%.

amine **3** was then converted, according to the general procedure reported in the literature,[12] into the corresponding alkynyl phenyl selenide **4**, which, in the presence of an excess of *p*-toluenesulfonic acid monohydrate,[10] gave the Se-phenyl selenocarboxylate **5**[13] in excellent yield. No racemization occurred during this conversion as demonstrated by the enantiomeric ratio of **5** measured by HPLC.[13] The Se-phenyl selenocarboxylate **5** was then treated with a 30% solution of hydrogen peroxide in tetrahydrofuran at room temperature[14] and the corresponding (*R*)-*N*-phthalimido-3-aminooctanoic acid **6**[15] was obtained in good yield. Finally, the phthalimido group was removed by treating **6** with hydrazine hydrate in refluxing ethanol. Compound (*R*)-**1** was isolated as the hydrochloride in 97% yield. Since under these reaction conditions the stereogenic carbon atom is not involved, it is suggested that the enatiomeric ratio of **1** is >99:1. Comparison of the spectroscopic data and of the sign of the specific rotation[16] of the (*R*)-**1** hydrochloride synthesized by this protocol with those reported in the literature[6] allowed the unambiguous assignment of its structure and of its absolute configuration to be made. These results also confirm that all the steps described above proceed without loss of enantiomeric purity.

Following the same procedure the commercially available (*R*)-1-octyn-3-ol *ent*-**2** (99% ee) was easily transformed in four steps into the (*S*)-*N*-phthalimido-3-aminooctanoic acid *ent*-**6** with practically the same global yield (54%). The HPLC analysis on the chiral stationary phase of *ent*-**3** and *ent*-**5** was effected as described above for the (*R*) enantiomers. The measured enantiomeric ratios were >99:1. Compound *ent*-**6** can then be transformed into the (*S*) enantiomeric form of **1**.

In conclusion, starting from a commercially available chiral building block, enantiomerically pure (*R*)-3-aminooctanoic acid **1** (*D*-BAOA) was synthesized through very simple chemical reactions involving the versatile organoselenium intermediates. The reaction is based on our previously described conversion of a terminal alkyne into a carboxylic group.[10] Because of the stereospecific transformation of a C–O bond of the starting alkynol into a C–N bond, this procedure could be easily applied to the synthesis of other optically active β-amino acids. Further applications of our method are presently under investigation.

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## Supplementary data

HPLC data for compounds **3** and **5** are reported in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.115.

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11. Selected data for compound **3**: mp 59 °C; $[\alpha]_D^{18}$ −3.57 (*c* 1.97 in $CHCl_3$); HPLC analysis: Chiralcel OD-H column (250 × 4 mm, Daicel), eluent: *i*-PrOH/hexane (0.5:99.5) flow rate: 0.5 mL/min, UV detection at 220 nm; $t_R$ 29.6 min: er >99:1; $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 0.8$ (t, $^3J_{H,H} = 6.8$ Hz, 3H; $CH_3$) 1.1–1.5 (m, 6H; $CH_2$), 1.86–2.2 (m, 2H; $CH_2$), 2.36 (d, $^4J_{H,H} = 2.1$ Hz, 1H; CH), 4.90–5.08 (m, 1H; CH), 7.63–7.90 (m, 4H; CH); $^{13}$C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 13.8$, 22.4, 25.7, 30.8, 33.1, 41.2, 71.9, 80.2, 123.2 (2C), 131.5 (2C), 134.0 (2C), 166.6 (2C); GC–MS *m*/*z* (%): 226 (13) [$M^+$], 212 (13), 199 (8), 184 (100), 130 (16); FT-IR (diffuse reflectance): 2924, 2118, 1773, 1708, 1387, 1087 cm$^{-1}$. Elemental Anal. Calcd (%) for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 12.53. Found: C, 74.69; H, 6.55; N, 12.39.
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13. Selected data for compound **5**: oil; $[\alpha]_D^{18}$ −90.69 (*c* 2.48 in $CHCl_3$); HPLC analysis: Chiralcel OD-H column (250 × 4 mm, Daicel), eluent: *i*-PrOH/hexane (2:98) flow rate: 0.6 mL/min, UV detection at 220 nm; $t_R$ 25.8 min: er >99:1; $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 0.7$–0.9 (m, 3H; $CH_3$), 1.1–1.4 (m, 6H; $CH_2$), 1.79–1.80 (m, 1H; $CH_2$), 1.95–2.25 (m, 1H; $CH_2$), 3.18 (dd, $^2J_{H,H} = 15.9$ Hz, $^3J_{H,H} = 5.2$ Hz, 1H; $CH_2$), 3.6 (dd, $^2J_{H,H} = 15.9$ Hz, $^3J_{H,H} = 9.3$ Hz, 1H; $CH_2$), 4.71 (ddt, $^3J_{H,H} = 9.3$, 5.2, 4.6 Hz, 1H; CH), 7.25–7.45 (m, 3H; CH), 7.50–7.60 (m, 2H; CH), 7.70–7.80 (m, 2H; CH), 7.80–7.90 (m, 2H; CH); $^{13}$C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 13.8$, 22.3, 25.8, 31.1, 32.2, 47.8, 49.1, 123.2 (2C), 125.9, 128.9, 129.3 (2C), 131.6 (2C), 133.9 (2C), 135.6 (2C), 168.1 (2C), 197.6; FT-IR (diffuse reflectance): 2929, 1772, 1711, 1370, 976 cm$^{-1}$. Elemental Anal. Calcd (%) for $C_{22}H_{23}NO_3Se$ (428.4): C, 61.68; H, 5.41; N, 3.27. Found: C, 61.39; H, 5.77; N, 3.00.
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15. Selected data for compound **6**: mp 80–82 °C; $[\alpha]_D^{19}$ −5.01 (*c* 1.95 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 0.85$ (t, $^3J_{H,H} = 6.5$ Hz, 3H; $CH_3$), 1.10–1.31 (m, 6H; $CH_2$), 1.60–1.81 (m, 1H; $CH_2$), 1.95–2.11 (m, 1H; $CH_2$), 2.82 (dd, $^2J_{H,H} = 16.5$ Hz, $^3J_{H,H} = 5.5$ Hz, 1H; $CH_2$), 3.21 (dd, $^2J_{H,H} = 16.5$ Hz, $^3J_{H,H} = 9.3$ Hz, 1H; $CH_2$), 4.65 (ddt, $^3J_{H,H} = 9.3$, 5.5, 4.9 Hz, 1H; CH), 7.76–7.90 (m, 4H; CH), 8.3 (br s, 1H; OH); $^{13}$C NMR (50 MHz, $CDCl_3$, TMS): $\delta = 13.9$, 22.3, 25.8, 31.1, 32.2, 36.7, 47.7, 129.2 (2C), 131.6 (2C), 133.9 (2C), 168.3 (2C), 176.3; FT-IR: 3002, 2925, 1773.7, 1712.5, 1376.4 cm$^{-1}$. Elemental Anal. Calcd (%) for $C_{16}H_{19}NO_4$ (289.3): C, 62.42; H, 6.62; N, 4.84. Found: C, 62.28; H, 6.81; N, 4.72.
16. Formation of **1** by deprotection of **6**. Hydrazine hydrate (0.22 mL, 4.70 mmol) was added to a stirred solution of **6** (0.17 g, 0.58 mmol) in EtOH (10 mL). After stirring for 2 h at 110 °C, the reaction mixture was allowed to slowly reach room temperature and concentrated. The residue was treated with 10 mL of 4 N hydrochloric acid and then the solid was allowed to settle down. Evaporation of the filtrate gave crude (*R*)-**1** hydrochloride, which was dissolved in distilled water (5 mL). Hydrogen peroxide 30% w/w (0.5 mL) was then added at rt to decompose the residual hydrazine. The mixture was then concentrated in vacuo and the residue dried under reduced pressure to afford (*R*)-**1** hydrochloride. Selected data for compound **1**: mp 110–112 °C (lit,[6] mp 103–104 °C); $[\alpha]_D^{16}$ −11.16 (*c* 1.35 in $H_2O$). The value reported in the literature[6] is $[\alpha]_D^{20}$ −16.6 (*c* 1.10 in $H_2O$). Anal. Calcd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27; N, 7.16. Found: C, 48.84; H, 9.43; N, 6.84.