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Enantioselective synthesis and absolute configurations of the enantiomers of *o*-carboranylalanine

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Abstract

We report two new asymmetric syntheses of *o*-carboranylalanine, [3-(1,2-dicarba-*closo*-dodecaborane(12)-1-yl)-2-aminopropanoic acid] (**1**), using the Fitzi–Seebach imidazolidinone and the Oppolzer–Lienard sultam procedure, respectively. Both methods gave high diastereoselectivity but some racemisation of **1** (EP, 91–96%) was observed after the final hydrolysis step in the imidazolidine procedure. The Oppolzer procedure gave **1** with EP>99%. The absolute configuration of the (−)-**1** (CH_3OH) was established as *S*. The preparation of (*S*)-Boc-**1** is reported. Attention is drawn to a spontaneous self-degradation of the zwitterionic form of **1** in water and methanol solutions.

Keywords: *o*-carboranylalanine; absolute configuration; carborane; boron neutron capture therapy; asymmetric synthesis.

o-Carboranylalanine is a potential candidate for use in Boron Neutron Capture Therapy (BNCT) either per se or incorporated into peptides.

Syntheses of racemic[1] and optically active **1**[2] have been reported by several authors and the use of (*S*)-**1** as an isostere for (*S*)-phenylalanine in peptides has been reviewed.[3] We have recently reported a new intramolecular self-degradation reaction of **1** to the corresponding diastereomeric *nido*-analogues in water and methanol solutions. The reaction is pH-dependent and has a rate maximum at the pH of the isoelectric point (p_i=4.9).[4] Accordingly, some care must be taken when **1** is used in biological experiments.

The enantiomers of the more lipophilic analogues of **1** namely *para*- and *meta*-carboranylalanine have recently been prepared in our laboratories.[5a,b]

In earlier papers we reported results concerning studies of penetration and binding of (*S*)-**1** and (*R*)-**1** in human melanoma spheroids,[6] and their cellular binding to cultured melanoma B16 cells and some effects of boron neutron capture.[7]

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We have successfully prepared (*S*)-**1** according to Fauchère et al.[2b] and determined its EP value to be 97%. As this procedure contains nine steps, including an enzymatic resolution, we have tried other routes.

In early preparations[2c] the imidazolidinone **4a,**† obtained from the corresponding propargyl analogue **4b**, was hydrolysed with acidic ion exchange resin (100°C), according to the procedure described by Fitzi and Seebach,[8] to give (*S*)-**1**. (*R*)-**1** was obtained analogously. Diastereomerically pure **4a** and its enantiomer gave amino acids with EP varying in the range 91–96%. In our present method (*S*)-**1** is obtained (EP=99.6%), using the sultam approach,[9] in two steps from the propargylsultam **2**, obtainable by the procedure of Oppolzer et al.[9a] No *nido*-compounds were formed in the basic conditions used in the hydrolytic step (LiOH) or by the ammonia used for the liberation of (*S*)-**1** from the ion exchange resin.

The absolute configuration was confirmed by NOE-measurements on **4b** in which the configuration at the stereocentre in the 2-position of the imidazolidinone ring is known.[8] (*S*)-**1** is leavorotatory in MeOH (λ=589 nm). The EP was for earlier preparations determined via HPLC of the *N*-α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alanineamide derivatives using the general method of Marfey.[10] In addition a chiral open tubular column SFC on the trifluoroacetamide *n*-propylester of (*S*)-**1** was used for the determination of the EP in the present synthesis.[11]

Synthesis of sultam **3**: Decaborane (1.35 g, 11.0 mmol) was suspended in toluene, diethyl sulphide (5.1 mL) was added and the resulting mixture was refluxed for 2.5 h under nitrogen. Propargylsultam **2**[9a] (4.17g, 10.1 mmol) in toluene (25 mL) was added and the mixture refluxed for 5 h. The reaction was monitored by ^{1}H NMR (C_6D_6). The reaction mixture was filtered through silica gel (30 g) and the silica was washed with benzene (300 mL) and the filtrate concentrated. The residue in 100 mL methanol was refluxed for 1.5 h and the solution concentrated to give 1.99 g of crude product which was flash chromatographed on silica gel (100 g) with chloroform as eluent to give **3** (1.48 g, 28%).‡

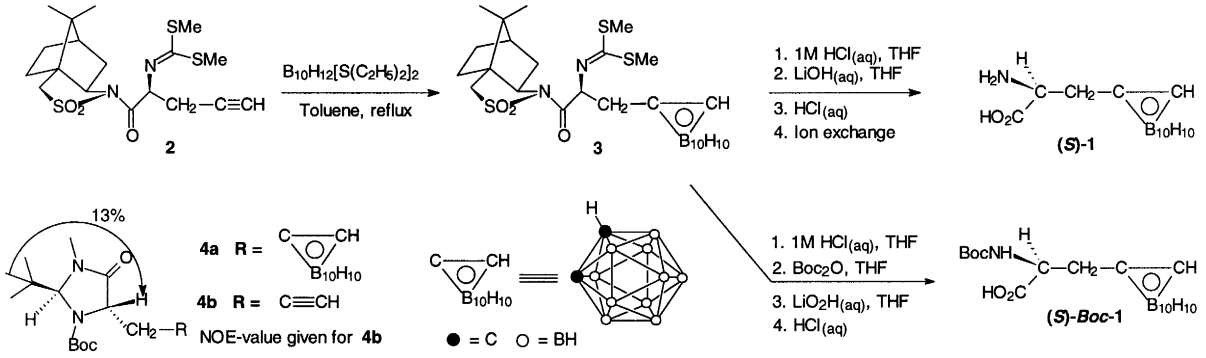
(*S*)-*o*-Carboranylalanine [(*S*)-**1**]: Sultam **3** (0.736 g, 1.38 mmol) in a mixture of THF (45 mL) and 1.5 M hydrochloric acid (19 mL, 29 mmol) was stirred at 35°C until the amino-protecting group was removed (ca. 30 h). The reaction was monitored by ^{1}H NMR in CD_3OD on evaporated samples. The solvent was stripped off at room temperature and the residue treated with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2×20 mL), the organic layer was washed with water (2×10 mL) and dried over Na_2SO_4 to give the free aminosultam (**5**) (0.523 g). This sultam (0.333 g) and LiOH (69.2 mg, 2.89 mmol) in THF:H_2O (18 mL, 2:1) was stirred at room temperature for 22 h and was acidified with 1 M hydrochloric acid (pH=1). Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (five

† ^{1}H NMR ($CDCl_3$): δ 4.89 (s, 1H, C*H*-C(CH_3)$_3$), 4.43 (broad s, 1H, C*H* cage), 4.11 (broad d, 1H, -(C=O)-C*H*), 3.21 (dd, J=15.7, 2.1 Hz, 1H, -CH-C*H*$_2$-), 2.99 (s, 3H, N-C*H*$_3$), 2.82 (broad s, 1H, -CH-C*H*$_2$-), 1.49 (s, 9H, -O-C-(C*H*$_3$)$_3$), 0.98 (s, 9H, CH-C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$): δ 171.0 ((*C*=O)-CH), 152.1 ((*C*=O)-O-), 82.3 (-O-*C*-(CH_3)$_3$), 81.3 (broad, *C*H-C(CH_3)$_3$), 72.8 (*C* cage), 61.4 (*C*H cage), 58.4 (-(C=O)-*C*H), 40.8 (CH-*C*(CH_3)$_3$), 36.7 (-*C*H$_2$-CCH), 32.3 (N-*C*H$_3$), 28.3 (-O-C-(*C*H$_3$)$_3$), 26.6 (CH-C(*C*H$_3$)$_3$). ^{11}B NMR ($CDCl_3$, $BF_3 \cdot E_2O$ as internal standard): δ −2.3, −5.3, −10.2, −13.0.

‡ Anal. calcd for $C_{18}B_{10}H_{36}N_2S_3O_3$: C, 40.58; H, 6.81; N, 5.26. Found: C, 40.1; H, 6.8; N, 5.2. ^{1}H NMR ($CDCl_3$): δ 4.83 (dd, J=7.8, 4.5 Hz, 1H, (C=O)-C*H*), 3.98 (broad s, 1H, cage C), 3.89 (dd, J=7.2, 5.6 Hz, 1H, N-C*H*-CH$_2$-CH-), 3.47 (AB, J=13.8 Hz, δ=12.2, 1H, -SO$_2$-C*H*$_2$), 3.06 (dd, J=14.8, 4.5 Hz, 1H, (C=O)-CH-C*H*$_2$), 2.79 (dd, J=14.8, 7.9, 1H, (C=O)-CH-C*H*$_2$), 2.59 (s, 3H, -S-C*H*$_3$), 2.42 (s, 3H, -S-C*H*$_3$), 2.06 (m, 2H, -CH-C*H*$_2$-CH-), 1.90 (m, 1H, -C*H*$_2$-CH$_2$-CH-), 1.89 (m, 1H, -CH$_2$-C*H*$_2$-CH-), 1.88 (m, 1H, -CH$_2$-CH$_2$-C*H*-), 1.42 (m, 1H, -C*H*$_2$-CH$_2$-CH-), 1.35 (m, 1H, -CH$_2$-C*H*$_2$-CH-), 1.13 (s, 3H, C-C*H*$_3$), 0.97 (s, 3H, C-C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 168.8 (*C*=O), 166.6 (N=*C*(SCH$_3$)$_2$), 72.6 (cage-*C*), 65.5 (N-*C*H-CH$_2$-CH-), 64.1 ((C=O)-*C*H), 59.8 (cage *C*H), 52.9 (-SO$_2$-*C*H$_2$), 48.8 (-CH-*C*-CH$_2$-), 47.9 (*C*-CH$_3$)$_2$), 44.4 (-CH$_2$-CH$_2$-*C*H-), 40.8 ((C=O)-CH-*C*H$_2$), 38.0 (-CH-*C*H$_2$-CH-), 32.7 (-*C*H$_2$-CH$_2$-CH-), 26.4 (-CH$_2$-*C*H$_2$-CH-), 20.5 (C-*C*H$_3$), 19.8 (C-*C*H$_3$), 15.3 (S*C*H$_3$), 14.8 (S*C*H$_3$). ^{11}B NMR ($CDCl_3$): δ −5.2, −5.7, −10.4, −11.9, −13.2.

times with a total of 50 mL). The water phase was filtered, evaporated to dryness to give 0.258 g residue containing (*S*)-**1**·HCl and lithium chloride. This product (0.085 g) was dissolved in water and enough 1 M hydrochloric acid was added to get a clear solution, which was stirred with wet Dowex 50W-X2 100–200 mesh (7 g, activated with 1 M aqueous hydrochloric acid) for 2 h. The solution was removed and the resin washed with water (100 mL), ethanol (20 mL) and with water (30 mL). The amino acid was eluted from the resin at 0°C with 10% ammonia (30 mL) and the eluent evaporated to dryness at 0°C to give (*S*)-**1** (0.040 g, 60%).§ EP=99.6% and 99.8% according to the method using a chiral open tubular column SFC[11] and the method of Marfey,[10] respectively. In three independent experiments the latter method gave EP-values in the range 49.8–51.5% (with regard to (*S*)-**1**) for *rac*-**1**.

The Boc-derivative of (*S*)-*o*-carboranylalanine [(*S*)-Boc-**1**] first reported by Fauchère et al.[2b] was prepared either directly from the free amino acid (*S*)-**1** or via the Boc derivative [(*S*)-Boc-**5**] of the free amino sultam (*S*)-**5** according to the general procedure by Oppolzer[8a] (Scheme 1). ^{1}H and ^{13}C NMR data for (*S*)-Boc-**1** are reported.¶ ^{1}H NMR spectrum in $CH_3OH(d_6)$ and $CDCl_3$ both give broad signals at 25°C. At 50°C signals with fine splittings were observed.



Scheme 1.

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§ $[\alpha]_{589}^{20.0}=-4.2$, $[\alpha]_{578}^{20.0}=-4.3$, $[\alpha]_{546}^{20.0}=-4.6$, $[\alpha]_{436}^{20.0}=-6.1$, $[\alpha]_{365}^{20.0}=-5.8$ (c=1.34 in CH_3OH) measured on a freshly prepared solution. The optical rotation diminishes with time due to the degradation reaction mentioned. ^{1}H NMR (CD_3OD): δ 3.68 (t, 1H, J=5.9 Hz, -C*H*-CH_2-), 3.08 (dd, 1H, J=16, 5.9 Hz, -CH-C*H*$_2$-), 2.64 (dd, 1H, J=16, 5.9 Hz, -CH-C*H*$_2$-). The proton in 2-position on the carbon cage is hidden under the OH-signal from the solvent, (δ_H 4.94). ^{13}C NMR (CD_3OD): δ 171.9 (C=O), 74.4 (C cage), 63.6 (*C*H-CH_2), (cage *C*H), 55.0 (*C*H-CH_2), 40.0 (-CH-*C*H$_2$-), ^{11}B NMR (CD_3OD): δ −2.2, −5.0, −9.3, −11.7. MS (electrospray, 3.1 kV): calcd for $C_5H_{17}{}^{11}B_{10}NO_2$, *m/z* 233, observed: clusters of peaks centred around 232.

¶ ^{1}H NMR ($CDCl_3$) δ ppm: 5.89 (br s, 1H, NH), 4.09 (br s, 1H, cage C*H*), 3.87–3.96 (m, 1H, C*H*α), 2.71–2.83 (m, 1H, CH_2), 2.42–2.48 (m, 1H, CH_2), 1.42 (s, 9H, CH_3-Boc); ^{1}H NMR (CD_3OD, 50°C) δ ppm: 4.59 (br s, 1H, cage C*H*), 3.98 (dd, J=3.7, 8.9, 1H, C*H*α), 2.92 (2.57 dd, J=8.9, 15.4, 1H, CH_2), 1.44 (s, 9H, CH_3-Boc). ^{13}C NMR (CD_3OD) δ ppm: 157.8 (*C*ONH), 80.8 (*C*Me$_3$), 75.3 (cage-*C*), 62.8 (cage-*C*H), 56.2 (*C*HCH$_2$), 40.9 (CH*C*H$_2$), 28.8 ((*C*H$_3$)$_3$C).

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