Asymmetric Synthesis of Carboranyl Amino Acids with Potential Use in BNCT

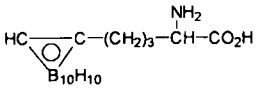
Stefan Sjöberg,* M. Frederick Hawthorne, Serge Wilmouth, and Peter Lindström

Abstract: Two α-amino acids containing the 1,2-dicarba-*closo*-dodecaborane(12) cage, namely, 5-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid (**1**) and 5-(2-methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid (**2**), were prepared by asymmetric synthesis (e.p. > 98%) by using the chiral glycine equivalent, imidazolidinone **3**, introduced by Seebach, and Oppolzer's camphor-derived sultam derivative **4**. The dextrorotatory enantiomers (sodium D line in methanol) of the amino acids **1** and **2** were both shown to have (*S*) configuration.

Keywords
amino acids · asymmetric synthesis · BNCT · carboranes

Introduction

Boron neutron capture therapy (BNCT) is based on the cytotoxic radiation formed when the stable nuclide ^{10}B is irradiated with low energy (thermal) neutrons [$^{10}B(n_{th},\alpha)^7Li$]. The present status of BNCT has recently been reviewed.[1]. Much interest is currently being paid to the synthesis of boron compounds that could be delivered selectively to tumor cells either per se or by use of targeting strategies, including the use of monoclonal antibodies, growth factors, and liposomes. α-Amino acids containing the *closo*-1,2-$C_2B_{10}H_{11}$-carborane cage, their corresponding *nido* analogues, and peptides derived from these amino acids could potentially be used for this purpose. Peptides of the racemic amino acids **1**[2] and **2**[3] have recently been synthesized and conjugated to antibodies. In this paper the asymmetric synthesis of the amino acids **1** and **2** is described.[4]



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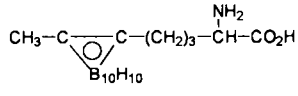

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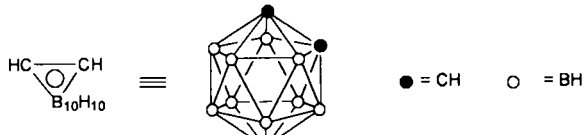

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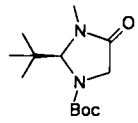
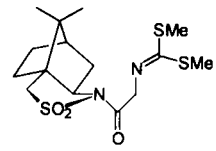
Results and Discussion

Several chiral glycine equivalents have recently been used for the asymmetric synthesis of α-amino acids, in high enantiomeric purity, by alkylation of the corresponding enolate anions. Seebach's imidazolidinone **3**[5] and Oppolzer's camphor-derived sultam derivative **4**[6] are used in this work for the asymmetric synthesis of **1** and **2**.



(*S*)-3



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The amino acid **1** was prepared by three different routes. In two of these (Routes 1 and 3), the chiral glycine equivalents were alkylated with preformed carboranylalkyl iodides (Scheme 1 and 3, respectively), whereas in Route 2 (Scheme 2) the alkylation preceded the carborane-forming step.

Route 1—Synthesis of (*S*)-1·HCl (Scheme 1): Starting with commercially available *ortho*-carborane, the monosilylated carborane **5** was obtained in quantitative yield.[7] Alkylation of **5** with oxetane gave, after acidification, the carboranylpropyl alcohol **6**[2] in 95% yield. This alcohol was converted to the iodide **7** (94%) via the corresponding bromide by using triphenylphosphine and carbon tetrabromide in methylene chloride, followed by sodium iodide in acetone.

Alkylation of imidazolidinone (*S*)-**3** with the protected iodoalkylcarborane **7** gave the silylated imidazolidinone (*S,S*)-**8** (75%). The silyl protecting group was removed efficiently with tetrabutylammonium fluoride in tetrahydrofuran solution, without any accompanying degradation of the carborane cage to the corresponding diastereomeric *nido* analogues. The *tert*-butoxycarbonyl group (Boc) of (*S,S*)-**9** was removed by using

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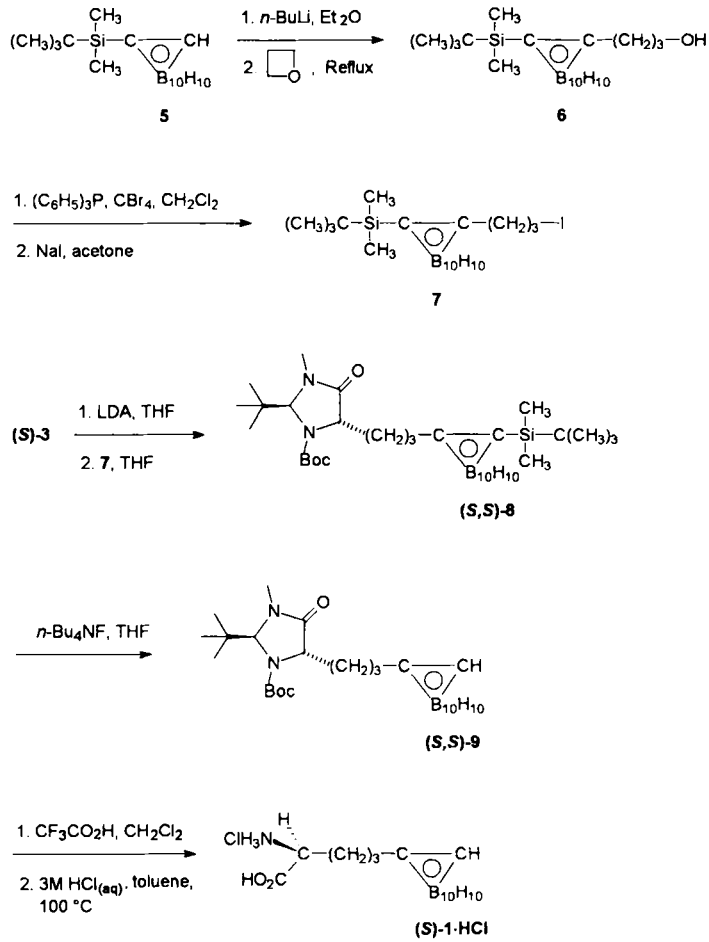
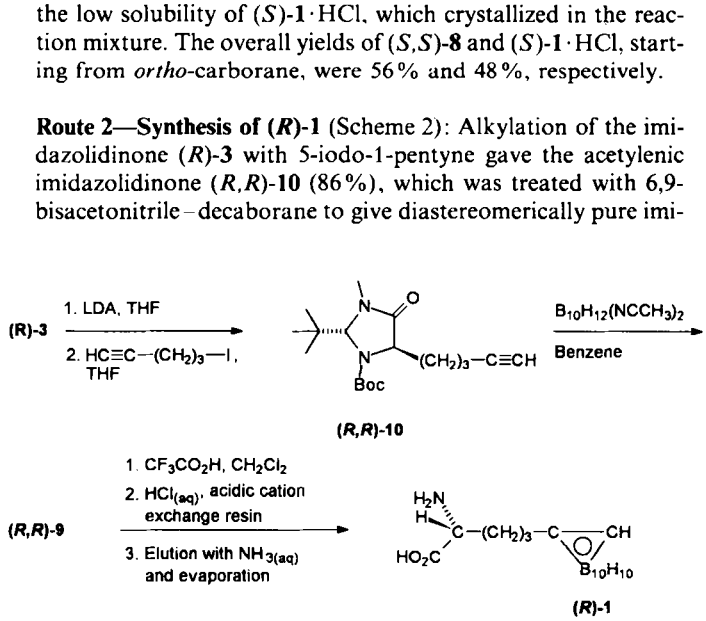


Scheme 1. Asymmetric synthesis of (*S*)-**1**·HCl by Route 1.

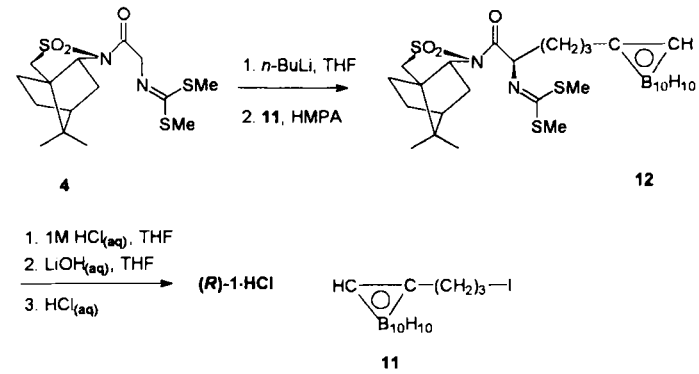
trifluoroacetic acid, and the deprotected imidazolidinone was converted to the pure amino acid derivative (*S*)-**1**·HCl (e.p. = 99.6%, e.p. = enantiomeric purity) by heating in a closed vessel in the presence of 3M hydrochloric acid and toluene. The side products of the reaction, namely methylammonium chloride and pivalaldehyde, could easily be removed by making use of the low solubility of (*S*)-**1**·HCl, which crystallized in the reaction mixture. The overall yields of (*S,S*)-**8** and (*S*)-**1**·HCl, starting from *ortho*-carborane, were 56% and 48%, respectively.

Route 2—Synthesis of (*R*)-1 (Scheme 2): Alkylation of the imidazolidinone (*R*)-**3** with 5-iodo-1-pentyne gave the acetylenic imidazolidinone (*R,R*)-**10** (86%), which was treated with 6,9-bisacetonitrile-decaborane to give diastereomerically pure imidazolidinone (*R,R*)-**9** (53%). Conversion of (*R,R*)-**9** to the free amino acid (*R*)-**1** (e.p. = 98.3%) was achieved in three steps: removal of the Boc group with trifluoroacetic acid, hydrolysis on an acidic ion-exchange resin, and elution with aqueous ammonia. The yield of (*R*)-**1** after evaporation to dryness was 32%, calculated from (*R*)-**10**. The elution and removal of ammonia were carried out at 0 °C to ensure that no degradation of the carborane cage took place.



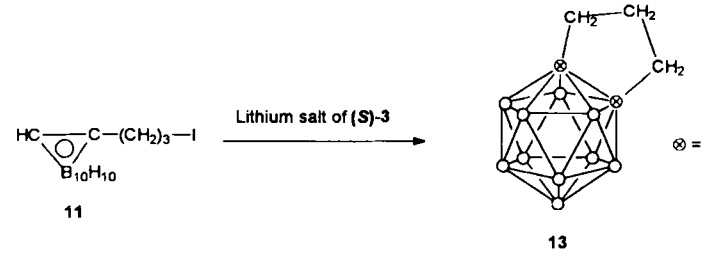
Scheme 2. Asymmetric synthesis of (*R*)-**1** by Route 2.

Route 3—Synthesis of (*R*)-1·HCl (Scheme 3): The third route involved alkylation of the sultam **4** with the unprotected 3-iodopropyl-*ortho*-carborane **11**, which was obtained from 5-chloro-1-pentyne in 59% yield. The carboranylsultam **12** was obtained diastereomerically pure in 71% yield. Removal of the amino protecting group under mild acidic conditions and subsequent hydrolysis of the sultamamide gave, after acidification, (*R*)-**1**·HCl (e.p. = 100%) in approximately 35% overall yield .



Scheme 3. Asymmetric synthesis (*R*)-**1**·HCl by Route 3.

For the alkylation of the imidizaloidinone (*S*)-**3** (Scheme 1), a silyl protecting group was chosen for the carboranylpropyl iodide **7**, because initial attempts to alkylate the lithium salt of (*S*)-**3** with the unprotected iodide **11** resulted in the formation of the ring-closed carborane μ-1,2-trimethylene-1,2-dicarba-*closo*-dodecaborane(12) (**13**) (Scheme 4).[8] This is in contrast to the alkylation of the sultam **4** with **11** (Scheme 3).

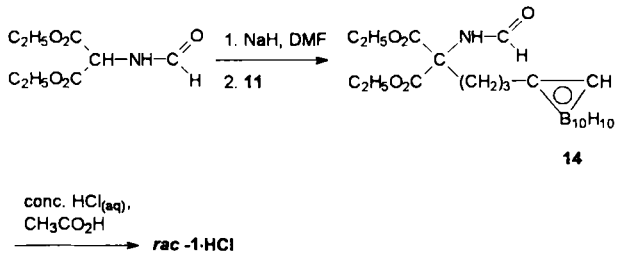


Scheme 4. Cyclization of 1-(3-iodopropyl)-*ortho*-carborane (**11**).

As shown in Scheme 2, **3** can be alkylated with the acetylenic halide 5-iodo-1-pentyne. The carboranylpropyliodide **11**, 5-iodo-1-pentyne, imidiazolidinone **3**, and sultam **4** are all CH acids. The pK_a values of the four compounds have not been determined, but some values for carboranes and substituted acetylenes have been reported: *ortho*-carborane and 1-methyl-*ortho*-carborane have pK_a values of 23.3 and 23.1, respectively,[9] while butylacetylene has a pK_a value of 26.2.[10] It is tempting to assume that the different results of alkylation reactions

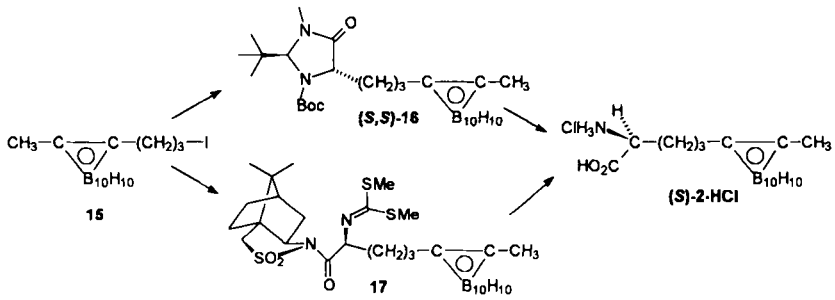
reflect the differences in equilibrium acidities of the compounds involved and that imidazolidinone **3** is a stronger acid than 5-iodo-1-pentyne and a weaker acid than carboranyl iodide **11**. The sultam **4** is the strongest of the four acids.

Synthesis of *rac*-1·HCl (Scheme 5): The racemic amino acids were needed as reference compounds in the determination of the enantiomeric purities of the optical active forms. Racemic **2** was available from previous work by Hawthorne et al.,[3] and *rac*-1·HCl was obtained by hydrolysis of the carboranylformamidomalonester **14** in a mixture of fuming hydrochloric acid and acetic acid (Scheme 5).



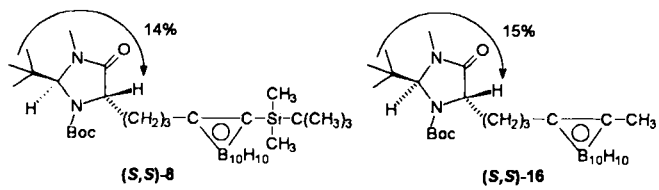
Scheme 5. Synthesis of *rac*-1·HCl.

Synthesis of (S)-2·HCl (Scheme 6): Carborane (*S*)-**2**·HCl was obtained from the iodide **15** (prepared from the corresponding bromide[11]) by halogene exchange) via imidazolidinone (*S,S*)-**16** and via sultam **17** (Scheme 6). Both routes gave (*S*)-**2**·HCl with e.p. > 99%. The yields calculated from **15** were 67 and 57%, respectively.



Scheme 6. Two asymmetric routes to (*S*)-**2**·HCl

Determination of absolute configurations: The absolute configurations of the enantiomers of the amino acids **1** and **2** were established by nuclear Overhauser measurements on the imidazolidinones (*S,S*)-**8** and (*S,S*)-**16**, respectively (Scheme 7), in which the configuration at the stereocenter in the 2-position of the imidazolidinone ring is known.[5] Both (*S*)-**1** and (*S*)-**2** have positive optical rotation at the sodium D line in methanol solution.



Scheme 7. Assignment of absolute configurations of the amino acids **1** and **2** by NOE measurements on the imidzolidinones (*S,S*)-**8** and (*S,S*)-**16**, respectively.

Determination of enantiomeric purities: The enantiomeric purities of the amino acids were determined by chromatographic separation (HPLC) of the diastereomeric derivatives formed with *N*-α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alanineamide.[12] The accuracy of the method was checked by repeating the procedure with the racemic amino acids **1** and **2**.[5]

Experimental Section

General: The ^1H, ^{13}C, and ^{11}B NMR spectra were recorded on a Varian Unity 400 spectrometer operating at 400, 100.6, and 128.3 MHz, respectively. The two-dimensional NMR spectra for some imidazolidinones were recorded at 50–55 °C to reduce the problems with broad signals. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. Optical rotations were measured on a Perkin–Elmer 241 LC polarimeter. For flash chromatography Merck Silica Gel 60, 230–400 mesh, and C-18 gel from Waters was used. Dowex 50W-X2 cation exchange resin, 100–200 mesh from Bio-Rad, was used in the hydrolysis of the imidazolidinone (*R,R*)-**9** and (*S,S*)-**16** to the free amino acids (*R*)-**1** and (*S*)-**2**, respectively. TLC was performed on Merck Silica 60 gel. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. For the determination of the enantiomeric purities of the amino acids an HP 1094 LC equipped with a UV detector (340 nm), a 250 × 4.6 Spherisorb ODS 1 10 μ column was used. Solvents A (potassium dihydrogen phosphate, 0.01 M, pH = 4.6) and B (acetonitrile/water, 50/7, v/v), with the gradient system 25% B to 50–60% B, were used as the eluting system. Elemental analyses were performed by Micro kemi AB, Uppsala (Sweden). The enantiomers of imidazolidinone **3** were purchased from Merck. Mass spectra were performed on a Platform single quadrapole mass spectrometer from VG Biotech with Electrospray ionization (3.1 kV). The samples were introduced through a RP-column in mixtures of the solvent systems C (water 10 mM in HOAc) and D (acetonitrile 10 mM in HOAc): 15–100% C in 6 min. Solvents were dried by standard methods.

1-*tert*-Butyldimethylsilyl-2-(3-hydroxypropyl)-*ortho*-carborane (6): Alcohol **6** was prepared according to a procedure outlined in ref. [3]. The silylated carborane **5** [7] (15.0 g, 0.0580 mol) was dissolved in dry ether (75 mL) and cooled in an ice bath. *n*BuLi (1.6 M, 44.3 mL, 0.071 mol) was added, and the solution stirred for 5 h. Then oxetane (4.7 mL, 0.073 mol) was added, and the mixture refluxed overnight to give a yellow syrup. The reaction mixture was cooled to 0 °C and water (40 mL) was added. The aqueous layer was acidified with 2 M hydrochloric acid. The product was extracted with ether (3 × 20 mL), and the combined ether fractions were washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated to provide the crude product (18.2 g). Recrystallization from hexane (40 mL) and flash chromatography of the evaporated mother liquor with pentane/ether (1:1) as solvent (R_f = 0.29) yielded 17.39 g (95%) of **6**. M.p. 83–85 °C; ^1H NMR ($CDCl_3$): δ = 3.61 (m, 2H; CH_2OH), 2.33 (m, 2H; $CH_2(CH_2)_2$), 1.76 (m, 2H; $CH_2CH_2CH_2$), 1.25 (m, 1H; O*H*), 1.02 (s, 9H; *t*Bu), 0.31 (s, 6H; Me).

1-*tert*-Butyldimethylsilyl-2-(3-bromopropyl)-*ortho*-carborane: A solution of triphenylphosphine (8.38 g, 0.0319 mol) in dichloromethane (15 mL) was added to an ice cold solution of the alcohol **6** (6.738 g, 0.0213 mol) and carbon tetrabromide (8.83 g, 0.026 mol) in dichloromethane (30 mL). The resulting mixture was stirred for 15 min and evaporated. The residue was stirred with dry ether (80 mL) during 40 min. The mixture was filtered and the solvent evaporated. The crude product was purified by flash chromatography on silica with pentane as eluant (R_f = 0.22). Yield: 7.81 g (97%) of the bromide. M.p. 78–80 °C; ^1H NMR ($CDCl_3$): δ = 3.38 (t, 2H; CH_2Br), 2.39 (m, 2H; $CH_2CH_2CH_2$), 2.08 (m, 2H; $CH_2(CH_2)_2Br$), 1.07 (s, 9H; *t*Bu), 0.35 (s, 6H; Me).

1-*tert*-Butyldimethylsilyl-2-(3-iodopropyl)-*ortho*-carborane (7): A solution of 1-*tert*-butyldimethylsilyl-2-(3-bromopropyl)-*ortho*-carborane (7.20 g, 0.0189 mol) and NaI (3 equiv) in acetone (120 mL) was stirred under reflux for 24 h. The solvent was stripped off, and the residue extracted with ether (80 mL). The ether phase was washed with water (3 × 50 mL), brine (1 × 30 mL), and dried over $MgSO_4$. Evaporation gave 7.9 g of crude **7** which was purified by flash chromatography on silica (60 g) with pentane as solvent (R_f = 0.37). Yield: 7.74 g (97%). M.p.: 81–82 °C. The NMR spectral data agreed with those reported earlier [3].

(2*S*,5*S*)-2-*tert*-Butyl-1-*tert*-butoxycarbonyl-5-(3-(2-*tert*-butyldimethylsilyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)propyl)-3-methyl-4-imidazolidinone [(*S,S*)-8]: A solution of imidazolidinone (*S*)-**3** (1.261 g, 4.92 mmol) in THF (4 mL) was added dropwise over a period of 5 min to a stirred solution of LDA (5.37 mmol) in THF (4 mL) and hexane (3.6 mL) at −50 °C. After 45 min the temperature was lowered to −70 °C, and silylated iodide **7** (1.994 g, 4.675 mmol) in THF (4 mL) was added. The mixture was stirred at −70 °C for 2.25 h. The temperature was raised to −30 °C at a rate of 10 °C h^{-1} (the reaction was monitored by TLC), and the reaction

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quenched with saturated aqueous NH_4Cl (1 mL). The THF was evaporated, and the residue dissolved in ether (30 mL) and washed with citric acid (0.7 M, 10 mL), saturated sodium bicarbonate (15 mL), water (15 mL), and brine (10 mL). The ether layer was dried with $MgSO_4$ and concentrated. The residue was purified on silica (40 g) with pentane/ether (2:1) as the eluant to give (*S,S*)-**8**. Yield: 1.94 g (75%). M.p. 121–122 °C; ^1H NMR ($CDCl_3$): $\delta = 4.92$ (brs, 1H; C*H*C(CH_3)), 3.98 (brs, 1H; (C=O)C*H*), 2.99 (s, 3H; NCH_3), 2.40 (brs, 1H; $CHCH_2$), 2.11 (m, 2H; $CHCH_2CH_2CH_2$), 1.72 (m, 1H; $CHCH_2$), 1.46 (s, 9H; $OC(CH_3)_3$), 1.24 (m, 1H; $CHCH_2CH_2$), 1.07 (m, 1H; $CHCH_2CH_2$), 1.02 (s, 9H; $SiC(CH_3)_3$), 0.94 (s, 9H; $CHC(CH_3)_3$), 0.27 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$): $\delta = 171.5$ ((*C*=O)CH), 152.5 ((C=O)O), 81.2 (cage *C*CH_2), 81.0 (*OC*$(CH_3)_3$), 81.0 (*CHC*$(CH_3)_3$), 76.0 (cage *C*Si), 58.9 ((C=O)*C*H), 40.6 (*CHC*$(CH_3)_3$), 37.5 ($CHCH_2CH_2CH_2$), 31.8 (*NCH*$_3$), 28.2 ($OC(CH_3)_3$), 28.20 (br. $CHCH_2$), 27.5 ($SiC(CH_3)_3$), 26.4 ($CHC(CH_3)_3$), 23.8 ($CHCH_2CH_2$), 20.3 ($SiC(CH_3)_3$), −2.4 ($Si(CH_3)_2$), −2.7 ($Si(CH_3)_2$); ^{11}B NMR ($CDCl_3$): $\delta = -5.0$, −6.2, −10.3, −11.0; IR (KBr disk): $\tilde{\nu}$ = 3409 (w), 2975 (m), 2576 (m), 1707 (s), 1475 (m), 1383 (s), 1366 (s), 1257 (m), 1171 (m), 1129 (m) 820 (m), 732 (w) cm^{-1}; $C_{24}B_{10}H_{54}N_2O_3Si$: calcd C 51.95, H 9.81, N, 5.05; found C 51.9, H 10.2, N 5.1.

(2*S*,5*S*)-2-*tert*-Butyl-1-*tert*-butoxycarbonyl-5-(3-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)propyl)-3-methyl-4-imidazolidinone [(*S,S*)-**9**]: Bu_4NF (1 equiv) was added to a solution of (*S,S*)-**8** (1.00 g, 1.80 mmol) in THF (60 mL) at −10 °C, and the reaction temperature was allowed to reach 10 °C for 20 min. The reaction was quenched with water (40 mL), the THF evaporated and the aqueous mixture extracted with ether (3 × 40 mL). The combined ether fractions were washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue flash chromatographed on silica gel (15 g) with pentane/ether (1:2) as the eluant to give (*S,S*)-**9** (0.741 g, 94%) with a m.p. of 155–156 °C. Recrystallization of 0.619 g of this product from hexane gave 0.544 g (82%). M.p. 156–157 °C; $[\alpha]_{589}^{20.0} = +27.6$, $[\alpha]_{436}^{20.0} = +51.8$, $[\alpha]_{365}^{20.0} = +74.7$ (c = 0.992 in CH_3OH); ^1H NMR ($CDCl_3$, 50 °C): $\delta = 4.95$ (brs, 1H; C*H*C$(CH_3)_3$), 4.03 (brs, 1H; (C=O)C*H*), 3.57 (brs, 1H; cage CH), 3.02 (s, 3H; NCH_3), 2.39 (brs, 1H; $CHCH_2$), 2.17 (m, 2H; $CHCH_2CH_2CH_2$), 1.82 (m, 1H; $CHCH_2$), 1.48 (s, 9H; $OC(CH_3)_3$), 1.22 (m, 1H; $CHCH_2CH_2$), 1.09 (m, 1H; $CHCH_2CH_2$), 0.96 (s, 9H; $CHC(CH_3)_3$); ^{13}C NMR ($CDCl_3$): $\delta = 171.5$ ((*C*=O)CH), 152.5 ((*C*=O)O), 81.2 (*OC*$(CH_3)_3$), 81.2 (*CHC*$(CH_3)_3$), 74.9 (cage *C*), 61.0 (cage *C*H), 58.9 ((C=O)*C*H), 40.7 (*CHC*$(CH_3)_3$), 37.7 ($CHCH_2CH_2CH_2$), 31.8 (*NCH*$_3$), 28.3 ($OC(CH_3)_3$), 28.3 (br. $CHCH_2$), 26.4 (s, 9H, $CHC(CH_3)_3$), 22.8 ($CHCH_2CH_2$); ^{11}B NMR ($CDCl_3$): $\delta = -2.9$, −6.4, −9.9, −12.3, −13.4; IR (KBr disk): $\tilde{\nu}$ = 3447 (w), 2968 (m), 2602 (m), 7573 (m), 1708 (s), 1464 (m), 1383 (s), 1366 (s), 1298 (m), 1256 (m), 1169 (m), 1128 (m), 896 (w), 724 (w) cm^{-1}; $C_{18}B_{10}H_{40}N_2O_3$: cacld C 49.07, H 9.15, N, 6.36; found C 48.9, H 8.9, N, 6.5.

(*S*)-5-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid hydrogen chloride [(*S*)-**1**·HCl]: To a solution of the imidazolidinone (*S,S*)-**9** (0.485 g, 1.11 mmol) in methylene chloride (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred under a nitrogen atmosphere at room temperature for 10 h. The solvent and excess trifluoroacetic acid were removed at reduced pressure. Hydrochloric acid (30 mL 3 M) and toluene (5 mL) were added to the residue, and the mixture was stirred at 100 °C in a closed flask for 38 h. The two reaction steps were monitored by ^1H NMR (in CD_3Cl and CD_3OD, respectively) on samples evaporated to dryness. The reaction mixture was allowed to attain room temperature and the precipitate was filtered, washed with toluene (3 × 5 mL), and hydrochloric acid (3 M, 5 mL). Yield of (*S*)-**1**·HCl: 0.277 g (85%). M.p. 255–256.5 °C (decomp.); e.p. = 99.7%; $[\alpha]_{589}^{20.0} = +23.5$, $[\alpha]_{436}^{20.0} = +49.8$, $[\alpha]_{365}^{20.0} = +82.6$ (c = 1.10 in CH_3OH); ^1H NMR (CD_3OD): $\delta = 4.60$ (brs, 1H; cage C*H*), 4.02 (t, J = 6.2 Hz, 1H; C*H*CH_3), 2.39 (t, J = 8.4 Hz, 2H; $CHCH_2CH_2CH_2$), 1.91 (m, 2H; $CHCH_2$), 1.78 (m, 1H; $CHCH_2CH_2$), 1.67 (m, 1H; $CHCH_2CH_2$); ^{13}C NMR (CD_3OD): $\delta = 171.4$ (C=O), 76.5 (cage *C*), 64.0 (cage *C*H), 53.4 (*CH*CH_2), 38.1 ($CHCH_2CH_2CH_2$), 30.8 ($CHCH_2$), 26.1 ($CHCH_2CH_2$); ^{11}B NMR (CD_3OD): $\delta = -2.3$, −5.4, −9.0, −11.2, −12.4; MS (electrospray): calcd for [*M*−Cl]: 260; found: cluster of peaks around m/z = 260. The substance was pure according to HPLC system used to introduce the sample into the mass spectrometer.

Attempted alkylation of (*S*)-3 with 1-(3-iodopropyl)-*ortho*-carborane (11): Iodide **11** was treated with the lithium salt of (*S*)-**3** as described for the preparation of silylated imidazolidinone (*S,S*)-**8**. Workup and flash chromatography afforded unchanged (*S*)-**3** and *meta*-1,2-trimethylene-1,2-dicarba-*closo*-dodecaborane(12) (**13**) [7]. ^{13}C NMR ($CDCl_3$): $\delta = 84.4$ (cage *C*), 35.3 (CCH_2), 32.7 ($CH_2CH_2CH_2$); MS (70 eV, EI): calcd for $C_5H_{16}B_{10}$: 184; found: cluster of peaks centered around m/z 183.

(2*R*)-*N*-(*N'*-Bis(methylthio)methylene-(3-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-propyl)glycyl)bornane-2,10-sultam (12): The sultam **4** [6] (1.484 g, 3.94 mmol) was dissolved with stirring in THF (15 mL) and the solution was cooled to −78 °C. A solution of *n*BuLi in hexane (1.6 M, 2.5 mL, 4.0 mmol) was added dropwise over a period of 20 min. The solution was stirred for 1 h at −78 °C, and a solution of the carboranylpropyl iodide **11** (1.20 g, 3.84 mmol) and HMPA (2.0 mL, purified by distillation over CaH_2) in THF (5 mL) was added dropwise over 15 min. The reaction was then slowly warmed up to −10 °C overnight and quenched with water (25 mL). The progress of the reaction was monitored by TLC. The water layer was extracted with THF (2 × 15 mL) and ether (2 × 15 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography (silica gel, 50 g) with toluene/acetonitrile (92.5:7.5) as the eluant to give 1.94 g (90%) of **12** (R_f = 0.46). Recrystallization of 1.67 g of this product from methanol yielded pure **12** 1.32 g (71%). M.p. 175–176 °C; $[\alpha]_{589}^{20.0} = +66.6$, $[\alpha]_{436}^{20.0} = +134$, $[\alpha]_{365}^{20.0} = +215$ (c = 0.665 in DMSO); the following assignments of the NMR shifts are based on a comparison with the data obtained for sultam **17**: ^1H NMR ($CDCl_3$): $\delta = 4.85$ (dd, J = 8.0, 4.8 Hz, 1H; (C=O)C*H*), 3.92 (dd, J = 7.6, 5.2 Hz, 1H; NC*H*CH_2CH), 3.60 (cage C*H*), 3.47 (AB, J = 12, 16 Hz, 2H; SO_2CH_2), 2.57 (s, 3H; SCH_3), 2.42 (s, 3H; SCH_3), 2.28 (m, 2H; $CH_2CH_2CH_2$), 2.06 (m, 2H; $CHCH_2CH$), 1.90 (m, 5H), 1.55 (m, 2H), 1.38 (m, 2H), 1.15 (s, 3H; CCH_3), 0.98 (s, 3H; CCH_3); ^{13}C NMR ($CDCl_3$): $\delta = 171.0$ (C=O), 163.2 (N=*C*$(SCH_3)_2$), 75.2 (cage *C*), 65.4 (NC*H*CH_2CH), 64.0 ((C=O)*C*H), 60.9 (cage *C*H), 53.1 (SO_2CH_2), 48.5 ($CHCCH_2$), 47.8 (*C*$(CH_3)_2$), 44.5 (CH_2CH_2CH), 38.4 ($CHCH_2CH$), 37.2 ($CH_2CH_2CH_2$), 33.6 ((C=O)CH*C*H_2), 32.8 (*CH*$_2CH_2CH$), 26.4 (CH_2CH_2CH), 25.4 ($CH_2CH_2CH_2$), 20.8 (CCH_3), 19.8 (CCH_3), 15.2 (SCH_3), 14.8 (SCH_3); ^{11}B NMR ($CDCl_3$): $\delta = -2.6$, −5.9, −9.5, −11.6, −12.5, −13.3; $C_{20}B_{10}H_{40}N_2O_3S_3$: calcd C 42.83, H 7.34, N 4.90; found C 42.5, H 6.9, N, 4.8.

Hydrolysis of 12 to (*R*)-1·HCl: Sultam **12** (0.926 g, 1.65 mmol) was dissolved in THF (40 mL) and hydrochloric acid (1 M, 16.6 mL, 1.66 mmol) was added. The solution was stirred at room temperature for 20 h and concentrated under reduced pressure. The crystalline residue was stirred with a mixture of water (20 mL) and ether (20 mL) and filtered (filter stick). The precipitate was dissolved in THF (20 mL) and combined with the separated aqueous phase. Evaporation of the THF gave a gelatinous precipitate, to which THF (10 mL) and hydrochloric acid (3 M, 5 mL) were added. The resulting mixture was stirred until a crystalline precipitate was obtained. After concentration to dryness the residue was dissolved in THF (25 mL) and a solution of LiOH (0.165 g, 5.51 mmol) in water (16 mL) was added. The mixture was stirred at room temperature for 20 h. The reaction was monitored by ^1H NMR on an evaporated sample dissolved in CD_3OD. The THF was evaporated at room temperature. Hydrochloric acid (3 M, 8 mL) and CH_2Cl_2 (25 mL) were added to the resulting emulsion, and the mixture was stirred for 1 h to give an easily filtrable precipitate, which was washed with CH_2Cl_2 (50 mL) and hydrochloric acid (3 M, 5 mL), and dried. Yield of (*R*)-**1**·HCl: 0.40 g (90%); e.p. = 100%. *rac*-**1**·HCl gave an e.p. of 49.7% with respect to (*R*)-**1**. The product contained ca. 1% of the camphor sultam formed in the hydrolysis.

***rac*-5-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid hydrogen chloride** (*rac*-**1**·HCl): Racemic **1**·HCl was prepared from 2-formylamido-2-[3-(1,2-dicarba-*closo*-dodecaboran(12)-1-yl)propyl]malonic acid diethyl ester (**14**). M.p. 98–99 °C; ^1H NMR ($CDCl_3$): $\delta = 8.14$ (d, 1H; CO*H*), 7.01 (s, 1H; N*H*), 4.24 (q, 4H; CH_2OCO), 3.59 (s, 1H; cage C*H*), 2.28 (t, 2H; α-CH_2), 2.19 (t, 2H; β-CH_2), 1.30 (m, 2H; γ-CH_2), 1.24 (t, 6H; CH_3CH_2); ^{13}C NMR ($CDCl_3$): $\delta = 167.1$ (*CO*), 160.0 (*CO*), 74.5 (cage *C*), 65.3 (CH_2CNH), 62.9 (CH_2OCO), 61.3 (cage HC), 37.5 (CH_2CNH), 31.5 ($CH_2CH_2CH_2$), 23.5 (CH_2 cage C), 13.9 (CH_3CH_2).
The formylamidoester **14** (0.101 g, 0.26 mmol) was added to a mixture of acetic acid (2 mL) and fuming hydrochloric acid (13 mL), and refluxed for 15 h. The mixture was evaporated to dryness, and the last trace of water was removed by azeotropic distillation with toluene. Yield 0.080 g (100%). M.p. 251–253 °C. The ^1H NMR spectrum was in accordance with that for (*S*)-**1**·HCl.

(2*R*,5*R*)-2-*tert*-Butyl-1-*tert*-butoxycarbonyl-5-(pent-4-yne)-3-methyl-4-imidazolidinone [(*R,R*)-**10**]: To a stirred solution of LDA (3.63 mmol) in THF (4 mL) and hexane (2.3 mL), imidazolidinone (*R*)-**3** (0.869 g, 3.49 mmol) in THF (4 mL) was added over a period of 5 min at −50 °C. After 30 min, the temperature was lowered to −78 °C and 5-iodo-1-pentyne [13] (0.904 g, 4.59 mmol) was added. The temperature was kept at −78 °C for 2 h and then allowed to reach 20 °C for 1.5 h. The reaction was monitored by TLC (ether:hexane, 9:1), and then quenched with saturated ammonium chloride (1 mL). The THF was evaporated and the residue dissolved in ether (20 mL) and washed with 0.7 M aqueous citric acid, saturated sodium hydrogen carbonate, and brine. The ether layer was dried with $MgSO_4$ and the solvent was evaporated. The residue was purified on silica gel (80 g) with ether/hexane (9:1) as the eluant to give (*R,R*)-**10** (R_f = 0.74) 0.970 g (86%). M.p. 93–96 °C; ^1H NMR ($CDCl_3$): $\delta = 4.96$ (brs, 1H; C*H*C$(CH_3)_3$), 4.05 (brd, J = 3 Hz, 1H; COC*H*), 2.99 (s, 3H; NCH_3), 2.52 (brs, 1H; acetylenic *H*), 2.14 (m, J = 2.6 Hz, 2H; $CHCH_2CH_2CH_2$), 1.94 (m, 1H; $CHCH_2$), 1.92 (t, J = 2.6 Hz, 1H; CH_2CCH), 1.48 (s, 9H; $OC(CH_3)_3$), 1.27 (m, 1H; $CHCH_2CH_2$), 1.15 (m, 1H; $CHCH_2CH_2$), 0.94 (m, 9H; $CHC(CH_3)_3$); ^{13}C NMR ($CDCl_3$): $\delta = 171.8$ ((*C*=O)CH), 153.0 ((*C*=O)O), 83.8 (CH_2CCH), 80.9 (*OC*$(CH_3)_3$), 80.8 (br, *CHC*$(CH_3)_3$), 68.6 (*CCH*), 59.2 ((C=O)*C*H), 40.8 (*CHC*$(CH_3)_3$), 31.7 (*NCH*$_3$), 28.6 (br, *CHCH*$_2$), 28.2 ($OC(CH_3)_3$), 26.3 ($CHC(CH_3)_3$), 22.1 ($CHCH_2CH_2$), 18.4 ($CHCH_2CH_2CH_2$); IR (KBr disk): $\tilde{\nu}$ = 3447 (w), 3244 (s), 2962 (m), 2873 (m), 1699 (s), 1685 (s), 1479 (m), 1458 (m), 1389 (s), 1366 (s), 1301 (m), 1256 (m), 1177 (m), 1125 (m), 896 (w), 708 (w) cm^{-1}; $C_{18}H_{30}N_2O_3$: calcd C 67.0, H 9.37, N 8.69; found C, 67.0, H 9.4, N 8.7.

(*R*)-5-(1,2-Dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid [(*R*)-1] from the pentynimidazolidinone (*R,R*)-10: The acetylenic imidazolidinone (*R,R*)-**10** (0.440 g, 1.37 mmol) dissolved in benzene (8 mL) was added over a period of 5 min

to 6,9-bisacetonitrile decaborane [14] (0.346 g, 1.64 mmol) suspended in boiling benzene (25 mL). The solution was refluxed for 3 h and then allowed to attain room temperature. The reaction mixture was filtered and the filtrate was concentrated. The solid residue was extracted with *n*-heptane at 50 °C and filtered. The residue was flash chromatographed on silica gel (50 g) with ether/hexane (9:1) as the eluant to yield (*R,R*)-**9** (0.321 g, 53%). Trifluoroacetic acid (0.34 mL) was added to a solution of this product (0.104 g, 0.235 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred at room temperature for 18 h. The reaction was monitored by ^{1}H NMR ($CDCl_3$). The solvent and excess of trifluoroacetic acid was removed at reduced pressure and the residue was dissolved in aqueous hydrocloric acid (1 M, 3 mL) and wet Dowex 50W-X2 100–200 mesh (2.5 mL, activated with 1 M aqueous hydrocloric acid) was added. The mixture was stirred for 48 h at 110 °C (the disappearance of the intermediate *N*-methyl amide was followed by ^{1}H NMR on samples liberated from the ion exchange resin with 10% aqueous ammonia; the samples were returned to the reaction vessel). The reaction mixture was transferred to a glass column (chilled with ice), and washed to neutrality with water (40 mL) and ethanol (20 mL). The product was eluted with 10% ammonia (30 mL) in portions of 10 mL. The solvent was evaporated at 0 °C, and the product (50 mg) was flash chromatographed on C-18 silica gel with methanol/water (4:1) as the eluant to give (*R*)-**1** (0.037 g, 33%). M.p. 229.5–233 °C (dec); e.p. = 98.3%; $[\alpha]_{589}^{20.0} = -5.7$, $[\alpha]_{578}^{20.0} = -6.0$, $[\alpha]_{546}^{20.0} = -6.9$, $[\alpha]_{436}^{20.0} = -12.8$, $[\alpha]_{365}^{20.0} = -22.1$ ($c = 1.49$ in CH_3OH); ^{1}H NMR (CD_3OD): $\delta = 4.52$ (brs, 1H; cage C*H*), 3.50 (t, $J = 6.0$ Hz, 1H; C*H*CH_2), 2.31 (t, $J = 8.5$ Hz, 2H; $CHCH_2CH_2CH_2$), 1.75 (m, 2H; $CHCH_2CH_2$), 1.62 (m, 2H; $CHCH_2CH_2$); ^{13}C NMR (CD_3OD): $\delta = 174.8$ (C=O), 76.8 (cage *C*), 63.6 (cage *C*H), 55.7 (*CH*CH_2), 38.4 ($CHCH_2CH_2CH_2$), 31.9 ($CHCH_2$), 26.4 ($CHCH_2CH_2$). ^{11}B NMR (CD_3OD): $\delta = -2.6$, -5.8, -9.4, -11.6, -12.8; IR (KBr disk): $\tilde{\nu} = 3447$ (m), 2927 (m), 2582 (s), 1636 (s), 1508 (m), 1498 (m), 1121 (w), 722 (w), 537 (w) cm^{-1}.

(2*S*)-*N*-(*N*′-Bis(methylthio)methylene-(3-(2-methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)propyl)glycyl)bornane-2,10-sultam (17): The sultam **4** (1.547 g, 4.109 mmol) was dissolved with stirring in THF (15 mL), and the solution was cooled to −75 °C. A 1.5 M solution of *n*BuLi in hexane (2.7 mL, 4.05 mmol) was added over a period of 15 min. The solution was stirred for 1 h at −75 °C, and a solution of (2-methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-propyl iodide (**15**) (1.202 g, 3.684 mmol) and HMPA (2.0 mL) in THF (8 mL) was added during 15 min. The reaction was then slowly warmed up to −5 °C over twelve hours and quenched with water (1 × 50 mL). The progress of the reaction was monitored by TLC. The water layer was extracted with ether (4 × 50 mL). The combined organic layers were washed with water (2 × 30 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated. The crude product (2.26 g) was purified by flash chromatography (silica gel, 95 g) with toluene/acetonitrile (95:5) as the eluant, to give 1.89 g (90%) of **17**. Recrystallization of 1.88 g of this product from methanol gave the pure sultam **17** (1.44 g, 68%). M.p. 163–164 °C; $[\alpha]_{589}^{20.0} = -60.9$, $[\alpha]_{436}^{20.0} = -124$, $[\alpha]_{365}^{20.0} = -201$ ($c = 0.527$ in DMSO): ^{1}H NMR ($CDCl_3$): $\delta = 4.89$ (dd, $J = 7.9$, 4.7 Hz, 1H; (C=O)C*H*), 3.90 (dd, $J = 7.4$, 5.2 Hz, 1H; NC*H*CH_2CH), 3.47 (AB, $J = 13.8$, 17.7 Hz, 2H; SO_2CH_2), 2.55 (s, 3H; SCH_3), 2.41 (s, 3H; SCH_3), 2.20 (m, 2H; $CH_2CH_2CH_2$), 2.04 (m, 2H; $CHCH_2CH$), 1.96 (s, 3H; cage CCH_3), 1.95 (m, 2H; (C=O)CHCH_2), 1.90 (m, 1H; CH_2CH_2CH), 1.88 (m, 1H; CH_2CH_2CH), 1.87 (m, 1H; CH_2CH_2CH), 1.62 (m, 2H; $CH_2CH_2CH_2$), 1.40 (m, 1H; CH_2CH_2CH), 1.34 (m, 1H; CH_2CH_2CH), 1.14 (s, 3H; CCH_3), 0.96 (s, 3H; CCH_3); ^{13}C NMR ($CDCl_3$): $\delta = 171.0$ (C=O), 163.1 (N=*C*$(SCH_3)_2$), 78.0 (cage *C*), 74.7 (cage CCH_3), 65.4 (NC*H*CH_2CH), 64.0 ((C=O)*C*H), 53.1 (SO_2CH_2), 48.5 ($CHCCH_2$), 47.8 (*C*$(CH_3)_2$), 44.5 (CH_2CH_2CH), 38.4 ($CHCH_2CH$), 34.6 ($CH_2CH_2CH_2$), 33.9 ((C=O)CHCH_2), 32.8 (CH_2CH_2CH), 26.4 (CH_2CH_2CH), 25.8 ($CH_2CH_2CH_2$), 23.1 (cage CCH_3), 20.8 (CCH_3), 19.9 (CCH_3), 15.2 (SCH_3), 14.9 (SCH_3); ^{11}B NMR ($CDCl_3$): $\delta = -5.0$, -6.3, -10.3 (sh), -11.1; IR (KBr disk): $\tilde{\nu} = 4319$ (w), 2958 (s), 2927 (s), 2594 (w), 1732 (s), 1694 (w), 1458 (w), 1385 (w), 1326 (w), 1277 (s), 1133 (w), 1074 (m), 743 (w), 534 (w) cm^{-1}; calcd $C_{21}B_{10}H_{42}N_2O_3S_3$: C 43.73, H 7.34, N 4.86; found C 43.4, H 7.4, N 4.9.

(2*S*,5*S*)-2-*tert*-Butyl-1-*tert*-butoxycarbonyl-5-(3-(2-methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)propyl)-3-methyl-4-imidazolidinone [(*S,S*)-16**]**: A solution of imidazolidinone (*S*)-**3** (2.060 g, 8.035 mmol) in THF (15 mL) was added dropwise over a period of 10 min to a stirred solution of LDA (8.78 mmol) in a mixture of THF (10 mL) and hexane (6 mL) at −78 °C. The resulting mixture was brought up to −50 °C. After 1 h the temperature was lowered to −78 °C and iodide **15** (2.387 g, 7.318 mmol) in THF (15 mL) was added over 10 min. The mixture was stirred at −78 °C for 1 h. The temperature was raised to −30 °C at a rate of 10 °C h^{-1} (the reaction was monitored by TLC) and quenched with saturated aqueous NH_4Cl (6 mL), and the THF was evaporated. Workup as described for the preparation of (*S,S*)-**8** gave 3.87 g of crude product. Flash chromatography (silica gel 100 g) with toluene/acetonitrile (4:1) as the eluant gave (2.64 g, 79%) of **16**. Recrystallization of 2.45 g of this product from hexane gave the pure imidazolidinone (2.18 g, 71%). M.p. 143–144 °C; $[\alpha]_{589}^{20.0} = +28.9$, $[\alpha]_{436}^{20.0} = +55.1$, $[\alpha]_{365}^{20.0} = +78.9$ ($c = 0.940$ in CH_3OH); ^{1}H NMR ($CDCl_3$): $\delta = 4.96$ (brs, 1H; C*H*$C(CH_3)_3$), 4.06 (brs, 1H; (C=O)C*H*), 3.03 (s, 3H; NCH_3), 2.49 (brs, 1H; $CHCH_2$), 2.11 (m, 2H; $CHCH_2CH_2CH_2$), 1.96 (s, 3H; cage CCH_3), 1.86 (m, 1H; $CHCH_2$), 1.49 (s, 9H; $OC(CH_3)_3$), 1.29 (brs, 1H; $CHCH_2CH_2$), 1.16 (m, 1H; $CHCH_2CH_2$), 0.97 (s, 9H; $CHC(CH_3)_3$); ^{13}C NMR ($CDCl_3$): $\delta = 171.6$ ((*C*=O)CH), 152.5 ((*C*=O)O), 81.1 (*O**C**H*$(CH_3)_3$), 81.1 (*CH**C**H*$(CH_3)_3$), 77.6 (cage *C*), 74.7 (cage *C*), 59.0 ((C=O)*C*H), 40.7 (CH*C*$(CH_3)_3$), 35.0 ($CHCH_2CH_2CH_2$), 31.8 (NCH_3), 28.3 ($OC(CH_3)_3$), 28.3 (br, $CHCH_2$), 26.4 ($CHC(CH_3)_3$), 23.2 ($CHCH_2CH_2$), 23.1 (cage CCH_3); ^{11}B NMR ($CDCl_3$): $\delta = -5.0$, -6.2, -10.2, -11.1 (sh); IR (KBr disk): $\tilde{\nu} = 3395$ (w), 2972 (m), 2931 (m), 2581 (s), 1706 (s), 1461 (m), 1382 (s), 1366 (s), 1298 (m), 1255 (m), 1167 (m), 1129 (m), 896 (w), 742 (w) cm^{-1}; $C_{19}B_{10}H_{42}N_2O_3$: calcd C 50.19, H 9.31, N 6.16; found C 50.5, H 9.7, N 6.0.

(*S*)-5-(2-Methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid hydrogen chloride [(*S*)-**2**·HCl] was prepared from imidazolidinone (*S,S*)-**16** as described for the preparation of hydrogen chloride of (S)-**1**·HCl. A solution of (*S,S*)-**16** (1.001 g, 2.20 mmol) and trifluoroacetic acid (2 mL) in methylene chloride (10 mL) was stirred at room temperature for 8.5 h and then evaporated. The residue in hydrochloric acid (3 M, 50 mL) and toluene (10 mL) was stirred in a closed 100 mL round-bottomed flask at 100 °C for 38 h. Workup furnished 0.47 g (95%) of (S)-**2**·HCl. M.p. 255–256.5 °C; $[\alpha]_{589}^{20.0} = +21.5$, $[\alpha]_{436}^{20.0} = +45.6$, $[\alpha]_{365}^{20.0} = +75.4$ ($c = 0.885$ in CH_3OH); ^{1}H NMR spectral data agreed with those reported earlier for *rac*-**2**·HCl [3]; ^{13}C NMR (CD_3OD): $\delta = 171.5$ (*C*=O), 79.3 (cage *C*), 76.9 (cage *C*), 53.5 ($CHCH_2$), 35.5 ($CHCH_2CH_2CH_2$), 30.9 ($CHCH_2$), 26.4 ($CHCH_2CH_2$), 23.5 (cage CCH_3); MS (electrospray): calcd for [*M* − Cl]: 274; obsd: cluster of peaks centered around $m/z = 274$. The substance was pure according to HPLC system coupled to the mass spectrometer. e.p. > 99%. In two experiments *rac*-**2** gave e.p. = 50.0 and 50.6% respectively with respect to (S)-**2**.

(*S*)-2·HCl from the sultam 17: Sultam **17** (1.104 g, 1.920 mmol) was dissolved in THF (50 mL) and hydrochloric acid (1 M, 20 mL, 20 mmol) was added, and the slurry stirred at room temperature for 20 h. The solution was concentrated to dryness. The residue (1.16 g) was stirred for 2 h in a mixture of hydrochloric acid (3 M, 5 mL) and ether (30 mL). The ether was removed (filter stick), and the procedure repeated twice with ether (2 × 20 mL). The water-containing slurry was evaporated to dryness, and the residue (1.02 g) was dissolved in a mixture of THF (45 mL), water (16 mL), and lithium hydroxide (0.185 g). The mixture was stirred at room temperature for 10 h. The slightly opalescent solution was clarified by filtration (glass fibre filter) and concentrated (evaporator) to ca. 10 mL at room temperature. Hydrochloric acid (3 M, 8 mL) and methylene chloride (20 mL) were added, and the slurry obtained was stirred for 1 h. The methylene chloride was removed (filter stick) and the residue extracted with methylene chloride (4 × 20 mL). The precipitate was filtered and washed with hydrochloric acid (3 M, 8 mL) and dried to give (*S*)-**2**·HCl (0.50 g, 84%). e.p. = 99.5%. The product contained ca. 1.5% of the camphor sultam formed in the hydrolysis.

(*S*)-5-(2-Methyl-1,2-dicarba-*closo*-dodecaboran(12)-1-yl)-2-aminopentanoic acid [(*S*)-**2**]: A sample of (*S*)-**2** was prepared from (*S,S*)-**16** as described for (*R*)-**1**. M.p. 245–249 °C (decomp.); e.p. = 99%; $[\alpha]_{589}^{20.0} = +5.2$, $[\alpha]_{546}^{20.0} = +5.9$, $[\alpha]_{436}^{20.0} = +11.7$, $[\alpha]_{365}^{20.0} = +21.2$ ($c = 1.50$ in CH_3OH); ^{1}H and ^{11}B NMR spectral data agreed with those reported earlier for *rac*-**2** [2]; ^{13}C NMR (CD_3OD): $\delta = 173.9$ (*C*=O), 79.6 (cage *C*), 76.9 (cage *C*), 55.7 (*CH*CH_2), 35.9 ($CHCH_2CH_2CH_2$), 31.7 ($CHCH_2$), 26.6 ($CHCH_2CH_2$), 23.5 (cage CCH_3).

Determination of enantiomeric purity: To ca. 1 mg of amino acid or its hydrochloride, in a 1 mL glass vial, was added Marfey's Reagent [12] (0.200 mL, 1% solution in acetone) followed by 1.0 M aqueous sodium hydrogencarbonate (0.040 mL). The vials were closed and then heated at 40 °C for ca. 1 h. The reaction was quenched with 2 M hydrochloric acid (0.020 mL), diluted with DMSO (0.50 mL), and analyzed. The enantiomeric purity of samples of commercially available (*S*)- and (*R*)-**3** may vary by a few percent and could be determined by ^{1}H NMR spectroscopy (300 MHz, CCl_4 containing 12% C_6D_{12}) in the presence of tris-*d,d*-dicampholylmethanatoeuropium(III) [15]. The concentration with respect to the imidazolidinone was 1.3 mM, and the molar ratio of imidazolidinone:shift reagent was 6.75.

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