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Boron Complexes of L-Cysteine

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Abstract: The synthesis of diphenyl[(*R*)-thiazolidine-4-carboxylato-*O,N*]boron **4**, 9-borabicyclo[3.3.1]non-9-yl[(*R*)-thiazolidine-4-carboxylato-*O,N*]boron **9**, 9-borabicyclo[3.3.1]non-9-yl[S-methyl-(*R*)-cysteinato-*O,N*]boron **10** , and 9-borabicyclo[3.3.1]non-9-yl[S-trityl-(*R*)-cysteinato-*O,N*]boron **11** with potential application in Boron Neutron Capture Therapy is reported. The preparation of two derivatives of 2-oxo-propanoic acid, diphenyl[2-benzylimino-2-oxopropanoato-*O,N*]boron **6** and dicyclohexyl[2-imino-2-oxopropanoato-*O,N*]boron **8** is described. Compound **6** represents the first example of a monocyclic unsaturated oxazaborolidine-5-one whose crystal structure has been determined.

Introduction

Organoboranes have received a great deal of attention since their discovery.[1] There is much current interest in the synthesis of boron compounds with potential use in Boron Neutron Capture Therapy for the treatment of certain malignant cancers. Glioblastoma multiforme and Melanoma brain tumors constitute the main group for which there is no effective treatment. Boron Neutron Capture Therapy is based on the selective delivery of a substance labelled with ^{10}B to a tumor before the area is irradiated by thermal neutrons.[2] Two boron compounds are currently being used clinically, sodium mercaptoundecahydrododecaborate and 4-dihydroxyborylphenylalanine. In order to enhance the utility of this therapy, the synthesis of boron carriers that deliver adequate concentration of ^{10}B atoms to tumors remains a crucial need.[2]

Chiral 1,3,2-oxazaborolidines **1** have proven to be highly effective for the catalytic enantioselective reduction of prochiral ketones and in various other asymmetric reactions.[3] Several efficient catalysts have been developed, most of them obtained from aminoalcohols derived from L-aminoacids.[4] 1,3,2-Oxazaborolidine-5-ones **2** have been synthesized as a means of upgrading the optical purities of chiral borinates and for the simultaneous protection of the amino and carboxyl groups of aminoacids.[5] The crystal structures of both types of compounds have been described.[6]

Our interest in the preparation of cyclic compounds containing the (*R*)-thiazolidine-4-carboxylic acid structure as a subunit[7] has prompted us to examine various methods for the synthesis of 1,3,2-oxazaborolidine-5-ones.

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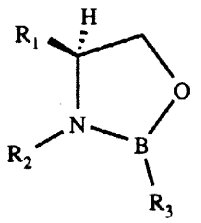

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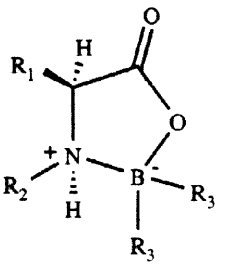
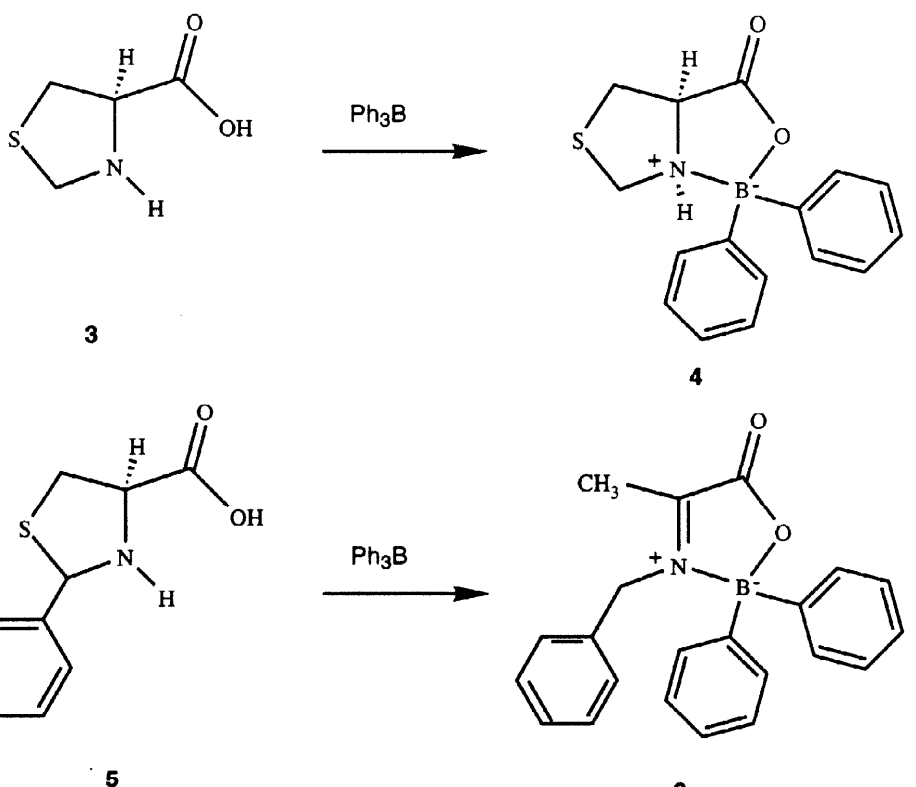


2

Figure 1

Results and Discussion

In particular, we first focused our attention on the use of triphenylboron for the protection of aminoacids.[5a] The reaction of (*R*)-thiazolidine-4-carboxylic acid **3** with triphenylboron was carried out in a closed tube (THF as solvent under an argon atmosphere at 100ºC). Removal of the solvent and silica gel column chromatography allowed the isolation of the expected 1,3,2-oxazaborolidine-5-one **4** in 64% yield. Reaction of (*R*)-2-phenylthiazolidine-4-carboxylic acid **5** with triphenylboron under identical conditions did not produce the expected bicyclic derivative. After column chromatography, compound **6** was obtained in 20% yield. The structure of **6** was tentatively assigned on the basis of its ^{1}H NMR, ^{13}C NMR and IR spectra, and was confirmed by X-ray analysis. This result represents an unusual case where the stereochemistry of the chiral center is unexpectedly lost with concomitant desulfurization, in contrast with the straightforward preparation of **4**. Figure 3 shows a perspective view of compound **6**.



3 4 5 6

Figure 2

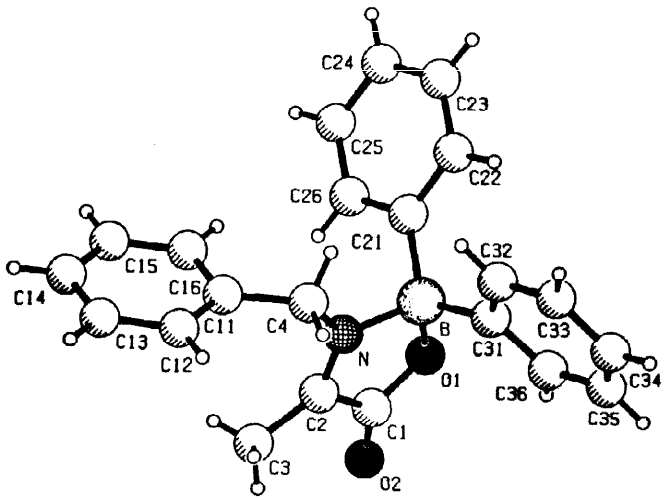
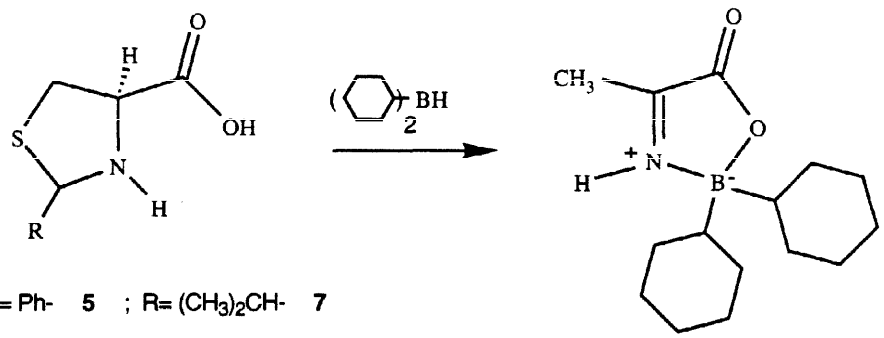


Figure 3

We then examined the reaction of (*R*)-2-phenylthiazolidine-4-carboxylic acid **5** and (*R*)-2-isopropylthiazolidine-4-carboxylic acid **7** with dicyclohexylborane.[8] The reaction was run stoichiometrically (1:1 thiazolidine/borane) by adding a solution of the thiazolidine to the freshly prepared dicyclohexylborane at -20ºC followed by heating in a closed reactor overnight. Removal of solvent followed by silica gel column chromatography allowed the isolation of the boron compiex **8**. The isolation of the same adduct **8** in both cases is remarkable and demonstrates that the cleavage of the ring system is the favored pathway. Although the mechanism for this transformation is not known, the reaction could probably proceed via a thiazolidine ring opening process,[9a] followed by a reductive desulfurization.[9b]

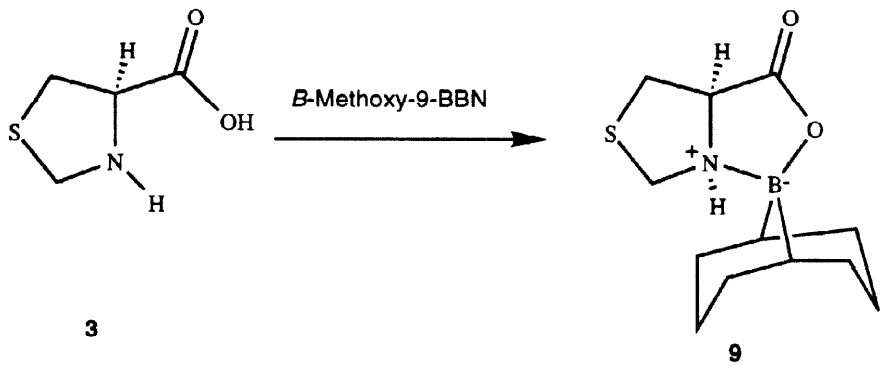


R= Ph- **5** ; R= $(CH_3)_2CH$- **7**

8

Figure 4

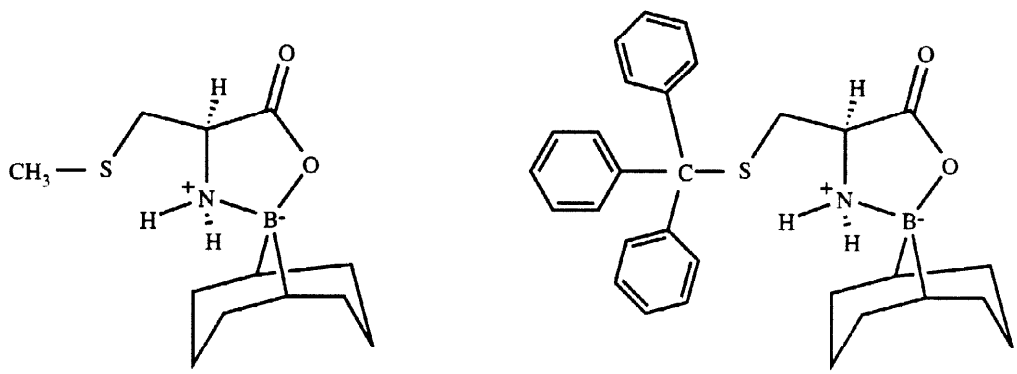
In light of these results, we turned our attention to the use of borinates[5d] in the preparation of 1,3,2-oxazaborolidine-5-ones. (*R*)-thiazolidine-4-carboxylic acid **3** was reacted with 9-methoxy-9-borabicyclo[3.3.1]nonane (*B*-methoxy-9-BBN) to afford the expected bicyclic 1,3,2-oxazaborolidine-5-one **9**.



3 9

Figure 5

Furthermore, 9-borabicyclo[3.3.1]non-9-yl[S-methyl-(*R*)-cysteinato-*O,N*]boron **10** and 9-borabicyclo[3.3.1]non-9-yl[S-trityl-(*R*)-cysteinato-*O,N*]boron **11** were synthesized by treatment of S-methyl-L-cysteine and S-trityl-L-cysteine[10] respectively with 9-methoxy-9-borabicyclo[3.3.1]nonane in dichloromethane at room temperature.



10 11

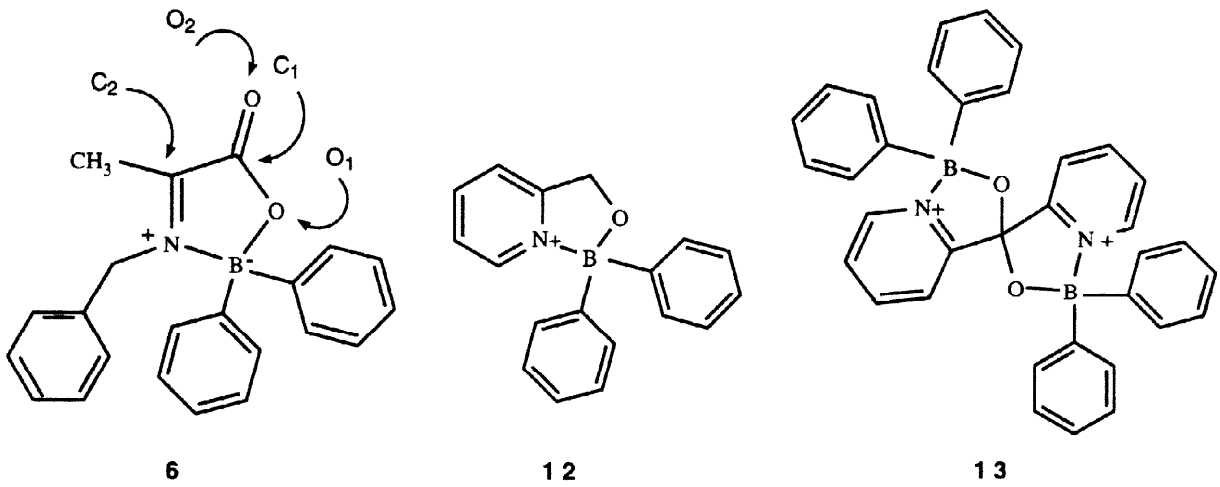
Figure 6

Description and discussion of the crystal structure

To the best of our knowledge, thirty-one crystal structures of 1,3,2-oxazaborolidines have been reported,[11] all of them have single carbon-nitrogen bonds except compounds **12**[6i] and **13**[6j] where the carbon-nitrogen double bond belongs to a pyridine ring (Figure 7). Therefore, compound **6** is the first example of a 1,3,2-oxazaborolidine having a localized carbon-nitrogen double bond, which has been characterized by X-ray analysis.

The carbon-nitrogen bond distance for **6** is remarkably shorter than in compounds **12** and **13** (Table 1). The rest of the reported structures show longer carbon-nitrogen bond distances, ranging from 1.457 to 1.530 Å, in agreement with the presence of a carbon-nitrogen single bond. The other bond distances in the five membered ring of **6** are inside the ranges found for the rest of the reported structures.

There is a clear double bond-single bond alternance in the subunit N-C_2-C_1-O_2 in agreement with the high value of the stretching frequency of the carbonyl function (1747 cm^{-1}) in the infrared spectrum.



6 12 13

Figure 7

The five-membered heterocyclic ring in **6** is nearly planar (torsion angles: B-N-C_2-C_1= -2.4 (2); N-C_2-C_1-O_1= -1.0 (2); C_2-C_1-O_1-B= 4.2 (2); C_1-O_1-B-N= -5.0 (1); O_1-B-N-C_2= 4.4° (1)). The geometry about the nitrogen atom is planar. The boron atom is tetrahedrally coordinated with the bond angles ranging from 97.3 (1) to 117.6° (1).

Table 1. Bond Lengths (Å) for the boron-containing ring.

Bond	6	12	13
C-N	1.274	1.347	1.339
			1.334
C-C	1.507	1.504	1.538
			1.516
C-O	1.313	1.407	1.387
			1.390
O-B	1.514	1.477	1.484
			1.484
B-N	1.623	1.643	1.625
			1.637

In conclusion, we have described the synthesis of six boron complexes with potential application in Boron Neutron CaptureTherapy.

Recent studies have shown that S-trityl-L-cysteine (NSC 83265) can act as a mitotic inhibitor even though it does not seem to interact directly with tubulin.[12] Although the mode of action of S-trityl-L-cysteine is not known, the fact that the aminoacid portion of compound **11** may act as an active carrier for the transport of the trityl radical or used in protein synthesis,[13] coupled with the complexation of a boron moiety makes this compound labelled with ^{10}B particularly attractive for biological studies.

EXPERIMENTAL

General. All solvents were dried by standard methods. All reagents were of commercial quality from freshly opened containers. M.p.s were obtained on a Gallenkamp melting point apparatus and are uncorrected. Unless otherwise noted, ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 instrument at 200 and 50 MHz respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. The assignments of ^{13}C NMR signals were made with the aid of DEPT sequence. Ir spectra were recorded on a Nicolet 205 FT infrared spectrophotometer, and noteworthy absorptions are listed (cm^{-1}). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer; ions are recorded as m/z with percentage abundances given in parentheses.

Diphenyl[(*R*)-thiazolidine-4-carboxylato-*O,N*]boron, 4

A mixture of triphenylboron (158 mg ,0.65 mmol) and (*R*)-thiazolidine-4-carboxylic acid **3** (87 mg ,0.65 mmol) in 20 ml of anhydrous THF under an argon atmosphere was heated at 114ºC for 14 h. After evaporation of solvent, the residue was column chromatographed on silica gel with ether and dichloromethane as eluents. The polar 1,3,2-oxazaborolidine-5-one was eluted with acetone and was isolated as a white solid with mp 233-4ºC in 64% yield (125 mg).

IR (KBr): 3099, 3073, 1725, 1434, 1301, 1274, 1209, 935, 916, 745, 708 cm^{-1}. ^1H NMR (DMSO, 300 MHz): δ 8.74 (broad m, 1H), 7.47 (m, 4H), 7.2 (m, 6H), 4.69 (broad m, 1H), 4.07 (dd, *J* =10.5 and 6.1 Hz, 1H), 3.58 (dd, *J* =10.5 and 7.0 Hz, 1H), 3.33 (dd, *J* =11.4 and 2.8 Hz, 1H), 3.22 (dd, *J* =11.4 and 7.7 Hz, 1H). ^{13}C NMR (DMSO, 75 MHz): δ 172.5 (C=O), 134.3, 131.5, 131.0, 127.5, 127.4, 126.7, 126.6, 65.9 (CH), 53.1 (CH_2), 32.1 (CH_2). MS: 297 (M^+, 1), 220 (31), 162 (7), 105 (13), 88 (100), 61 (37). Elem. Anal.: $C_{16}H_{16}BNO_2S$ (297.18) requires: C,64.67 ; H,5.43 ; N,4.71 ;found: C,64.40 ; H,5.61 ; N,4.83 .

Diphenyl[2-benzylimino-2-oxopropanoato-*O,N*]boron, 6

A mixture of triphenylboron (509 mg ,2.1 mmol) and (*R*)-2-phenylthiazolidine-4-carboxylic acid **5** (440 mg ,2.1 mmol) in 50 ml of anhydrous THF under a nitrogen atmosphere was heated at 110ºC for 14 h. After evaporation of solvent, the residue was column chromatographed on silica gel with ether, dichloromethane and methanol as eluents. The expected bicyclic 1,3,2-oxazaborolidine-5-one was not detected in the fractions. The only identified product was characterized as a crystalline white solid with mp 185-6ºC in 20 % yield (140 mg, eluent ether: CH_2Cl_2 9:1). Crystals suitable for X-ray analysis were obtained by recrystallization from chloroform-hexane.

IR (KBr): 3000, 1747, 1431, 1213, 1197, 1143, 966, 883, 761, 747, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.6- 7.0 (m, 15 H), 4.99 (s, 2H); 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.5 (C=O), 164.3 ($C=N^+$), 132.8, 132.0, 129.0 128.5, 127.8, 127.7, 127.5, 52.6 (CH_2), 14.3 (CH_3). MS: 341 (M^+, 3), 313 (3), 264 (19), 263 (5), 181 (3), 165 (3), 91 (100), 65 (9). Elem. Anal.: $C_{22}H_{20}BNO_2$ (341.22) requires: C,77.44 ; H,5.91 ; N,4.11 ;found: C,77.68 ; H,5.73 ; N,4.02 .

Single crystal X-ray diffraction analysis of 6. All crystallographic measurements were carried out at room temperature on an Enraf Nonius CAD4 automatic diffractometer using graphite monochromated Mo-K_α radiation (λ= 0.71069Å). Unit-cell parameters were obtained from a least-squares fit to automatically centred settings for 25 reflections. Lorentz and polarization corrections were applied but no absorption correction was made. The structure was solved by direct methods using SHELXS-86[14] and refined by full-matrix least-squares (based on F^2) using SHELXL-93[15]. The weighting scheme used was $w= 1/[\sigma^2(F_o^2)+(0.0632P)^2+0.04P]$ where $P= (Max(F_o^2,0)+2F_c^2)/3$.

All non-hydrogen atoms were refined with anisotropic thermal parameters whilst hydrogen atoms were placed in their predicted positions using a Riding model. The residuals wR_2 and R_1 given

below are defined as $wR_2= (\Sigma[w(F_o^2-F_c^2)^2]/\Sigma w[F_o^2]^2)^{1/2}$ and $R_1= \Sigma||F_o|-|F_c||/\Sigma|F_o|$. The final Fourier difference synthesis contained no features of chemical significance with maximum and minimum peak heights of 0.13 and -0.14 $eÅ^{-3}$ respectively.

Crystal data for 6. $C_{22}H_{20}BNO_2$, 0.63x0.56x0.39mm, monoclinic, space group $P2_1/n$, a= 9.516(2), b= 11.557(3), c= 16.972(14)Å, β= 98.47(4)º, V= 1846(2)$Å^3$, Z= 4, D_c= 1.228$Mg.m^{-3}$, μ= 0.077mm^{-1}, F(000)= 720.

Data Collection.- 4<2q<50º. 3242 unique reflections measured. There were 2404 reflections with $F_o>4\sigma(F_o)$.

Structure refinement.- Number of parameters = 236, goodness of fit on F^2= 1.050, wR_2(all data)= 0.1032, R_1(all data)= 0.0533.

Supplementary data, which include atomic coordinates, thermal paramers and complete set of bond lenghts and angles, have been deposited at the Cambridge Crystallographic Data Centre and are avalaible on request.

Dicyclohexyl[2-imino-2-oxopropanoato-*O,N*]boron, 8

A mixture of dicyclohexylborane[8] (12.5 mmol), prepared from 2.5 ml (25 mmol) of cyclohexene and 12.5 ml (12.5 mmol) of borane in THF (1M) , and (*R*)-2-phenylthiazolidine-4-carboxylic acid **5** (2.61 g ,12.5 mmol) in 30 ml of DMF under a nitrogen atmosphere was heated at 100ºC for 17 h. After cooling , the opened reaction vessel had a strong odour characteristic of sulphur derivatives. After evaporation of solvent, the residue was column chromatographed on silica gel with ether, dichloromethane, ethyl acetate and methanol as eluents. The expected bicyclic 1,3,2-oxazaborolidine-5-one was not detected in the fractions. The only identified product was characterized as a white solid with mp 201-2ºC in 23 % yield (0.76 g, eluant ether: CH_2Cl_2 1:1).

IR (KBr): 2914, 2843, 1705, 1445, 1317, 982, 949, 697 cm^{-1}. ^1H NMR (DMSO, 300 MHz): δ 13.7 (bs, 1H), 2.35 (s, 3H), 1.65-0.40 (m, 22H). ^{13}C NMR (DMSO, 75 MHz): δ 170.0 (C=O), 164.8 ($C=N^+$), 28.5, 28.3, 28.0, 27.2, 15.1 (CH_3). MS: 263 (M^+, 1), 181 (100), 180 (36) 138 (5), 99 (76), 98 (36), 55 (43). Elem. Anal.: $C_{15}H_{26}BNO_2$ (263.19) requires: C,68.45 ; H,9.96 ; N,5.32 ;found: C,68.57 ; H,9.82 ; N,5.15 .

Dicyclohexyl[2-imino-2-oxopropanoato-*O,N*]boron, 8

Prepared from dicyclohexylborane (12.5 mmol), and (*R*)-2-isopropylthiazolidine-4-carboxylic acid **7** (2.18 g ,12.5 mmol). After evaporation of solvent, the residue was column chromatographed on silica gel with ether, dichloromethane, ethyl acetate and methanol as eluents. The only identified product was characterized as a white solid with mp 201-2ºC in 21% yield (0.69 g, eluent ether: CH_2Cl_2 1:1) identical in all respects with that previously obtained from (R)-2-phenylthiazolidine-4-carboxylic acid.

9-Borabicyclo[3.3.1]non-9-yl[(R)-thiazolidine-4-carboxylato-*O,N*]boron, 9

A mixture of 9-methoxy-9-borabicyclo[3.3.1]nonane (12.5 ml ,12.5 mmol, 1M in hexanes), and (*R*)-thiazolidine-4-carboxylic acid **3** (1.66 g ,12.5mmol) in 25 ml of DMF under a nitrogen atmosphere was stirred at room temperature for 14 h. After evaporation of solvent, methanol (15 ml) was added, and the product was isolated by filtration, dried in a vacuum dessicator, as a white solid with mp 227-8ºC in 73% yield (2.3g).

IR (KBr): 2881, 2839, 1700, 1375, 1320, 1251, 1210, 1080, 964, 869, 759 cm^{-1}. ^1H NMR (DMSO, 200 MHz): δ 7.84 (broad m, 1H), 4.86 (broad m, 1H), 4.30 (dd, *J* =10.4 and 6.5 Hz, 1H), 4.08 (dd, *J* =10.4 and 7.1 Hz, 1H), 3.36 (dd, *J* =11.4 and 2.6 Hz, 1H), 3.18 (dd, *J* =11.4 and 7.2 Hz, 1H), 2.0-1.2 (m, 12H), 0.7 (broad s,1H), 0.58 (bs, 1H). ^{13}C NMR (DMSO, 50 MHz): δ 171.8 (C=O), 65.6 (CH), 49.9 (CH_2), 31.8 (CH_2), 31.6, 31.1, 30.6, 24.0, 23.9. MS: 254 (M^++1, 100), 253 (M^+, 36), 226 (8), 137 (3), 88 (6), 55 (1). Elem. Anal.: $C_{12}H_{20}BNO_2S$ (253.17) requires: C,56.93 ; H,7.96 ; N,5.53 ;found: C,56.80 ; H,7.75 ; N,5.69 .

9-Borabicyclo[3.3.1]non-9-yl[S-methyl-(*R*)-cysteinato-*O,N*]boron, 10

A mixture of 9-methoxy-9-borabicyclo[3.3.1]nonane (7.4 ml, 7.4 mmol ,1M in hexanes), and S-methyl-(*R*)-cysteine (1 g ,7.4 mmol) in 80 ml of CH_2Cl_2 under a nitrogen atmosphere was stirred at room temperature for 24 h. After evaporation of solvent, the orange solid was purified by recrystallization (ethyl acetate), the product was isolated by filtration, dried in a vacuum desiccator, as a white solid with mp 164-5ºC in 75 % yield (1.41g).
IR (KBr): 3187, 3065, 2921, 2846, 1716, 1322, 1294, 1236, 1212, 962 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 4.92 (broad m, 1H), 4.47 (broad m, 1H), 3.96 (quint, 1H), 3.24 (dd, *J* =14.8 and 6.0 Hz, 1H), 3.03 (dd, *J* =14.8 and 5.4 Hz, 1H), 2.1 (s, 3H), 2.0-1.2 (m, 12H), 0.6 (broad s,2H). ^{13}C NMR (DMSO, 50 MHz): δ 172.6 (C=O), 54.0 (CH), 34.3 (CH_2), 31.5, 30.9, 30.8, 24.5, 24.2, 15.4 (CH_3). MS: 255 (M^+, 8), 227 (3), 166 (10), 117 (5), 90 (18), 61 (100). Elem. Anal.: $C_{12}H_{22}BNO_2S$ (255.18) requires: C,56.48 ; H,8.69 ; N,5.49 ;found: C,56.71 ; H,8.57 ; N,5.60 .

9-Borabicyclo[3.3.1]non-9-yl[S-trityl-(*R*)-cysteinato-*O,N*]boron, 11
A mixture of 9-methoxy-9-borabicyclo[3.3.1]nonane (4 ml ,4 mmol , 1M in hexanes), and S-trityl-(*R*)-cysteine (1.45 g ,4 mmol) in 60 ml of CH_2Cl_2 under a nitrogen atmosphere was stirred at room temperature for 24 h. After evaporation of solvent, the orange solid was purified by recrystallization (ethyl acetate), the product was isolated by filtration, as a nice white needles with mp 196-7ºC in 87 % yield (1.68 g).
IR (KBr): 3219, 2918, 2848, 1710, 1445, 1291, 961, 744, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.5-7.2 (m, 15H), 3.6 (broad s, 1H), 3.4 (broad s, 1H), 3.14 (quint, 1H), 3.00 (d, *J* =6.2 Hz, 2H), 2.0-1.2 (m, 12H), 0.35 (broad s,2H). ^{13}C NMR (DMSO, 50 MHz): δ 172.0 (C=O), 144.3, 129.4, 128.4, 127.2, 66.7 (C), 53.9 (CH), 32.0 (CH_2), 31.9, 31.4, 30.9, 30.7, 24.1, 23.6. MS: 408 (1), 243 (100), 165 (38), 102 (3), 76 (5). Elem. Anal.: $C_{30}H_{34}BNO_2S$ (483.48) requires: C,74.53 ; H,7.09 ; N,2.90 ;found: C,74.45 ; H,7.29 ; N,2.98.

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