Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5111-5114, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01062-3

Hydroboration of Vinylglycine and Allylglycine as a route to Boron-derivatives of α-Amino Acids.

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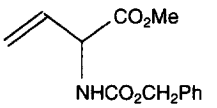
Abstract: The hydroboration of protected vinylglycine and allylglycine with dicyclohexyl- or diisopinocampheylborane occurs chimio- and regioselectively with attachment of boron to the less substituted end of the carbon-carbon double bond. Homoserine or δ-hydroxynorvaline are readily obtained by H_2O_2/CH_3CO_2Na oxidation of dicyclohexylborane derivatives and 2-amino-4-boronobutanoic acid or 2-amino-5-boronopentanoic acid by reaction of diisopinocampheylborane derivatives with excess of ethanal and deprotection.

Organoboron derivatives of polyfunctional molecules are valuable synthetic intermediates [1] and a number of them display interesting biological activities. [2] Boronic analogues of α-amino acids are of particular interest : aspartic acid with boron substituted for the (γ)-carboxylic group [3] proved to be an inhibitor of dihydroorotase [4] and proline boronic acid dipeptides have been used as immunosuppressants. [5] Specific binding of boronic acids with glucids [6] or α-amino acids [7] is also noteworthy.

In the course of a work on hydroboration of unsaturated α-amino acids, [8] we have investigated the reactivity of protected vinylglycinate **1** and allylglycinate **2**.



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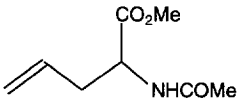
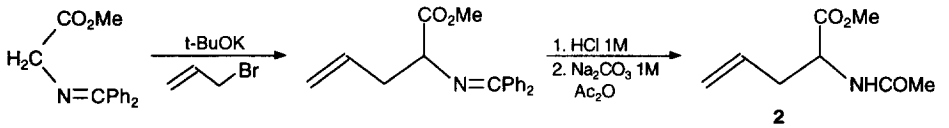


2

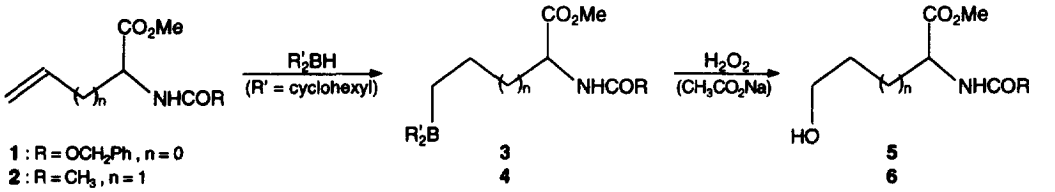
These two compounds are readily available as pure enantiomers or racemic modifications through known procedures. Only the racemic derivatives were used in this preliminary work. **1** [9] was prepared in 37% overall yield from methionine. **2** [10] was obtained by alkylation of methyl N-(diphenylmethylene)glycinate [11] with allyl bromide, [12] mild hydrolysis and protection with acetic anhydride.



2

Hydroboration with dicyclohexylborane

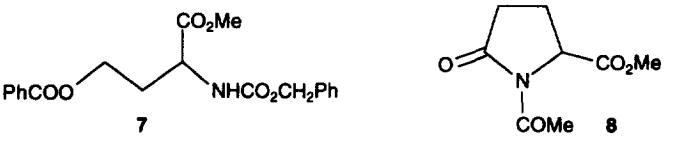
The reagent (1.5 molar equivalents), prepared according to Brown, [13] was allowed to react with amino acids **1** or **2**, in THF, for 12 h at room temperature. Intermediate triorganoboranes **3** and **4** were not isolated but subjected to oxidation by H_2O_2/CH_3CO_2Na [14] affording homoserine or δ-hydroxynorvaline derivatives **5** [15] or **6**, [16] respectively, as the only characterized products (Scheme 1).



Scheme 1

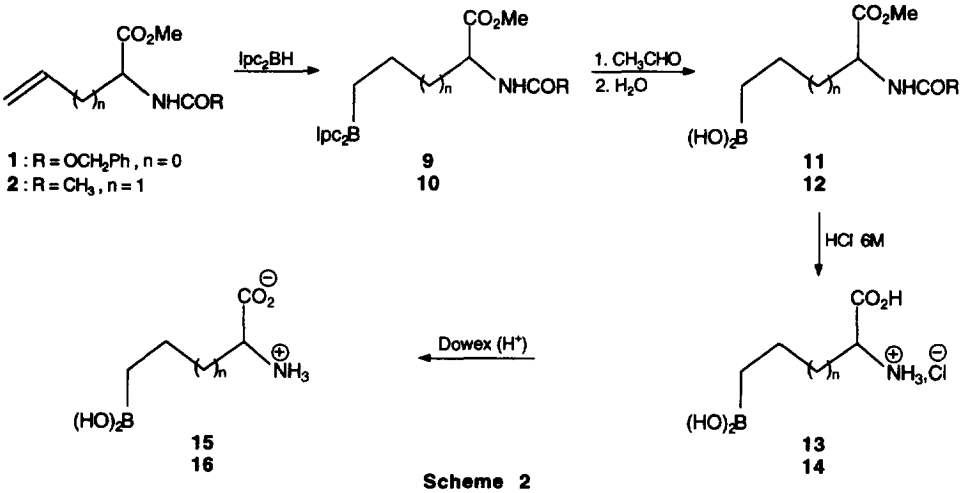
5 was converted to the O-benzoyl derivative **7** [17] with benzoic anhydride.

Other oxidative processes were investigated with triorganoborane **4**. Pyridinium chlorochromate [18] led to unextractable mixtures and chromic acid [19] afforded pyroglutamate **8** [20] in low yield (30%).



Hydroboration with diisopinocampheylborane

These reactions were investigated as a route to ω-boronic-α-amino acids. Diisopinocampheyltriorganoboranes are known to react readily with excess of acetaldehyde, affording α-pinene and the corresponding boronic acids [21] (Scheme 2).



Scheme 2

Diisopinocampheylborane was obtained according to standard procedures [22] and hydroborations were performed with two molar equivalents of the reagent, in THF, for 24 h at room temperature.

Intermediate triorganoboranes **9**, **10** are sensitive to atmospheric oxygen and were reacted *in situ* with an excess of acetaldehyde (10 equivalents) at 45°C for 17 h. [21] The boronic acids proved to be difficult to isolate. They are hygroscopic and give rise to anhydride formation. The best results were obtained after deprotection in boiling 6M HCl (3 h for **11**, 5 h for **12**), trituration of the chlorhydrates **13**, [23] **14**, [24] in dry CH_3CN and

elimination of the residual boric acid as the trimethylborate by repeated additions of methanol and evaporations to dryness (^{11}B NMR determinations).

4-Borono-2-aminobutanoic acid **15** [25] and 5-borono-2-aminopentanoic acid **16**, [26] the boronic analogues of glutamic and 2-aminoadipic acids, respectively, were then readily available through elution on a Dowex (50, H^+) resin with 2M ammonia .

^{11}B NMR spectra are indicative of the structure. Chlorhydrates **13**, **14** exhibit a broad singlet centered near 30 ppm, consistent with a trigonal, non complexed, boron atom. [27] This signal is shifted to about 20 ppm for the free amino acids **15**, **16**, showing that some degree of association has to be taken in account.

Methyl vinylglycinate and allylglycinate are readily hydroborated with diorganoboranes in a chemo- and regioselective way. The synthetic usefulness of the intermediate triorganoboranes is evidenced through the synthesis of homoserine or δ-hydroxynorvaline and of 4-borono-2-aminobutanoic or 4-borono-2-aminopentanoic acids.

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10 All compounds gave satisfactory elemental analysis (An.) and/or mass spectra (MS) and were identified by NMR spectra (300 MHz for ^1H, 75 MHz for ^{13}C, $(CD_3)_2CO$ or $CDCl_3$/TMS int., D_2O/DSS int. ; 96 MHz for ^{11}B, THF-C_6D_6/BF_3-OEt_2 ext.; δ ppm, J Hz).
2 oil, 76% yield from Schiff base of glycinate ; An. $C_8H_{13}NO_3$; MS : m/z = 171 (M^+). ^1H NMR [$(CD_3)_2CO$] δ : 1.91 (s, 3H, $COCH_3$) ; 2.42 (m, 1H, H^3) and 2.52 (m, 1H, $H^{3'}$) ($J_{H^3H^{3'}}$ = 14.5, $J_{H^3H^2}$ = 8, $J_{H^{3'}H^2}$ = 5.5, $J_{H^3H^4}$ = 7.5, $J_{H^{3'}H^4}$ = 6.5, and 1<J<2.5 for long range coupling between H^3, $H^{3'}$ and H^5, $H^{5'}$) ; 3.67 (s, 3H, OCH_3) ; 4.50 (dt, $J_{H^2,NH}$ = 8, 1H, H^2) ; 5.06 (m, 1H, H^5) and 5.12 (m, 1H, $H^{5'}$) ($J_{H^5H^{5'}}$ = 2, $J_{H^5H^4}$ = 10, $J_{H^{5'}H^4}$ = 17) ; 5.78 (m, 1H, H^4) ; 7.38 (br s, 1H, NH). δ and J values were determined after several selective decoupling experiments. ^{13}C NMR ($CDCl_3$) δ : 22.9 ($CO\underline{C}H_3$) ; 36.4 (C^3) ; 51.7 (C^2) ; 52.3 (OCH_3) ; 119.0 (C^5) ; 132.3 (C^4) ; 169.9 (NCO) ; 172.3 (C^1).

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15 **5** oil, 41% yield [column chromatography on silica gel (ether)] ; FAB MS : m/z = 268 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ : 1.54-1.78 (m, 2H, $2H^3$) ; 2.84 (br s, 1H, OH) ; 3.54-3.68 (m, 2H, $2H^4$) ; 3.68 (s, 3H, OCH_3) ; 4.48 (m, 1H, H^2) ; 5.05 (s, 2H, OCH_2Ph) ; 5.65 (d, J = 7, 1H, NH) ; 7.28 (s, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ : 35.7 (C^3) ; 51.2 (C^2) ; 52.6 (OCH_3) ; 58.4 (C^4) ; 67.3 (OCH_2Ph) ; 128.2, 128.3, 128.6, 136.0 (C_6H_5) ; 156.9 (NCO) ; 173.0 (C^1).

16 **6** oil, 79% yield [column chromatography on silica gel (ether/MeOH 90/10 then 50/50)] ; An. $C_8H_{15}NO_4$, 1/4 H_2O ; MS : m/z = 189 (M^+). ^1H NMR ($CDCl_3$) δ : 1.55-1.64 (m, 2H, $2H^3$) ; 1.73-1.96 (m, 2H, $2H^4$) ; 2.03 (s, 3H, $COCH_3$) ; 3.35 (br s, 1H, OH) ; 3.64 (t, J_{H4H5} = 6, 2H, $2H^5$) ; 3.74 (s, 3H, OCH_3) ; 4.56 (dt, J ≈ 5.5 and 7.5, 1H, H^2) ; 6.98 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ : 22.9 ($CO\underline{C}H_3$) ; 28.2 and 28.9 (C^3 and C^4) ; 52.1 (C^2) ; 52.4 (OCH_3) ; 61.6 (C^5) ; 170.7 and 173.1 (NCO and C^1).

17 **7** oil, 45% yield [column chromatography on silica gel (ether)] ; An. $C_{20}H_{21}NO_6$, 1/2 H_2O ; MS : m/z = 371 (M^+). ^1H NMR ($CDCl_3$) δ : 2.21-2.38 (m, 2H, $2H^3$) ; 3.66 (s, 3H, OCH_3) ; 4.39-4.45 (m, 2H, $2H^4$) ; 4.59 (td, J_{H2H3} = 6.5, $J_{H2,NH}$ = 7.5, 1H, H^2) ; 5.10 (s, 2H, OCH_2Ph) ; 5.63 (d, J = 7.5, 1H, NH) ; 7.34 (s, 5H, $CH_2C_6\underline{H}_5$) ; 7.37-7.59 (m, 3H) and 7.98-8.04 (m, 2H) (COC_6H_5). ^{13}C NMR ($CDCl_3$) δ : 31.4 (C^3) ; 51.5 (C^2) ; 52.6 (OCH_3) ; 60.8 (C^4) ; 67.1 (OCH_2Ph) ; 128.1, 128.2, 128.4, 128.5, 129.8, 129.9, 133.1, 136.1 (C_6H_5) ; 155.8 (NCO) ; 166.3 and 172.3 (2CO).

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20 **8** oil, 30% yield [column chromatography on silica gel (ether)] ; An. $C_8H_{11}NO_4$, 1/4 H_2O ; MS : m/z = 185 (M^+). ^1H NMR ($CDCl_3$) δ : 2.08 (m, $J_{H4H4'}$ = 13.5, $J_{H4H3'}$ = 9.5, J_{H4H3} = 3.5, J_{H4H5} = 2.5, 1H, H^4) ; 2.34 (m, $J_{H4'H3'}$ = 10.5, $J_{H4'H3} \approx J_{H4'H5} \approx$ 9.5, 1H, $H^{4'}$) ; 2.53 (s, 3H, $COCH_3$) ; 2.58 (ddd, $J_{H3H3'}$ = 17.5, 1H, H^3) ; 2.73 (ddd, 1H, $H^{3'}$) ; 3.78 (s, 3H, OCH_3) ; 4.77 (dd, 1H, H^5). δ and J values were determined after selective decoupling experiments. ^{13}C NMR ($CDCl_3$) δ : 20.3 (C^4) ; 23.6 ($CO\underline{C}H_3$) ; 30.8 (C^3) ; 51.7 and 56.7 (OCH_3 and C^5) ; 170.0, 170.5 and 173.4 (C^2, NCO and $\underline{C}O_2CH_3$).

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23 **13** hygroscopic solid ; FAB MS : m/z = 418 [M^+ for ester of **13** with NBA (metanitrobenzylic alcohol) matrix]. ^1H NMR (D_2O) δ : 0.82 and 0.87 ($J_{H4H4'}$ = 16, $J_{H4H3} = J_{H4'H3}$ = 8.5, 2H, $2H^4$) ; 2.02 (dt, J_{H3H2} = 6.5, 2H, $2H^3$) ; 3.98 (t, 1H, H^2). δ and J values were determined after selective decoupling experiments. ^{13}C NMR (D_2O) δ : 12.3 (C^4) ; 27.5 (C^3) ; 57.2 (C^2) ; 175.3 (C^1). ^{11}B NMR (D_2O) δ : 30.3.

24 **14** hygroscopic solid ; FAB MS : m/z = 432 (M^+ for ester of **14** with NBA matrix). ^1H NMR (D_2O) δ : 0.84 (t, J_{H4H5} = 8, 2H, $2H^5$) ; 1.43-1.59 (m, 2H, $2H^4$) ; 1.83-2.04 (m, 2H, $2H^3$) ; 4.03 (t, J_{H2H3} = 6.5, 1H, H^2). ^{13}C NMR (D_2O) δ : 16.4 (C^5) ; 21.9 (C^4) ; 35.0 (C^3) ; 55.7 (C^2) ; 175.3 (C^1). ^{11}B NMR (D_2O) δ : 32.6.

25 **15** mp > 260°C (dec), 76% overall yield ; MS (Negative Electrospray ; CH_3CN/H_2O : 1/1) : m/z = 146 $(M - H)^-$. ^1H NMR (D_2O) δ : 0.70 and 0.74 ($J_{H4H4'}$ = 15, $J_{H4H3} \approx J_{H4'H3} \approx$ 8, 2H, $2H^4$) ; 1.90 and 1.94 ($J_{H3H3'}$ = 14, $J_{H3H2} \approx J_{H3'H2} \approx$ 6, 2H, $2H^3$) ; 3.69 (t, 1H, H^2). δ and J values were determined after selective decoupling experiments. ^{13}C NMR (D_2O) δ : 13.4 (C^4) ; 28.5 (C^3) ; 58.9 (C^2) ; 177.9 (C^1). ^{11}B NMR (D_2O) δ : 26.9.

26 **16** mp > 230°C (dec), 77% overall yield ; MS (Negative Electrospray ; CH_3CN/H_2O : 1/1) : m/z = 160 $(M - H)^-$. ^1H NMR (D_2O) δ : 0.30-0.75 (m, 2H, $2H^5$) ; 1.35-1.70 (m, 2H, $2H^4$) ; 1.55-2.00 (m, 2H, $2H^3$) ; 3.45-3.70 (m, 1H, H^2). ^{13}C NMR (D_2O) δ : 17.9 (C^5) ; 23.7 (C^4) ; 34.5 (C^3) ; 58.8 (C^2) ; 179.8 (C^1). ^{11}B NMR (D_2O) δ : 18.1.

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(*Received in France* 9 *May* 1996; *accepted* 30 *May* 1996)