Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 39–44

Synthesis of mono- and bisglucuronylated carboranes

Silvia Ronchi,[a,†] Davide Prosperi,[b] Christian Thimon,[c] Christophe Morin[c] and Luigi Panza[a,*]

[a]*Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale, I-28100 Novara, Italy*
[b]*Istituto di Scienze e tecnologie Molecolari del CNR, via Golgi 19, I-20133 Milano, Italy*
[c]*LEDSS-UMR 5616, Département de Chimie (ICMG- IFR 2607), Université Joseph Fourier, Grenoble-1, F-38402 Saint Martin d'Hères, France*

Received 21 October 2004; accepted 23 November 2004
Available online 25 December 2004

Abstract—A route for the preparation of carborane-containing glucuronic acid derivatives is described, starting from 1,2-*O*-isopropylidene-α-D-glucuronolactone. The obtained compounds are potential BNCT agents ready to be tested for their uptake in selected tumor cell lines.

1. Introduction

Boron neutron capture therapy is a binary therapeutic strategy for cancer treatment, which exploits the capture of thermal neutrons by ^{10}B atoms when irradiated with a neutron flux. The neutron capture results in the formation of an excited ^{11}B nucleus which gives an α particle and a ^{7}Li ion through a fission reaction. Such particles dissipate their energy before traveling one cell diameter with a destructive effect for tumor cells, provided that the boron-containing compound has an elevated concentration in tumor tissue and a ratio of concentration between tumor tissue and blood higher than 3–5.[1]

Among the different boron-containing compounds, carboranes, boron-rich clusters,[2] are of current interest for applications in medicinal chemistry.[3] Multifarious carborane-containing compounds have been synthesized to date. In recent years, there is an increasing interest in carborane-containing carbohydrates,[4] including *C*-glycosides,[4e,i] in order to obtain new compounds suitable for BNCT. The sugar moiety, in fact, is not only able to confer water solubility to the otherwise hydrophobic boron cluster, but could also have a targeting effect on tumor cells. On the other hand, it has been suggested that the saccharidic portion would hamper the product crossing the blood–brain-barrier or the cell membrane. A strategy has, therefore, been suggested in which a antibody–glycosidase conjugate specific for cancer cells should cleave the sugar residues in close proximity to the tumor, thus allowing a selective uptake of the more lipophilic carborane catabolite.[4c] It may also be conceivable that enzymatic hydrolysis could occur in vivo.

A different approach to boron delivery can be envisaged. Namely, it has been observed that small nanoparticles, for example, liposomes, are able to passively diffuse into tumor tissue due the higher permeability of their endothelium. Previously, we observed that carborane–carbohydrate conjugates are efficiently incorporated in liposomes due to their amphiphilic properties.[5] We then decided to synthesize glucuronic acid derivatives exploiting the high reactivity of glucofuranurono-γ-lactone[6] toward amines. We previously exploited such compounds for the preparation of sugar-containing *ortho*-carboranyl amino acids.[4g]

Herein we describe the synthesis of glucuronic acid derivatives bearing an *ortho*-carborane linked trough an amide bond in position 6. As potential BNCT agents, such derivatives could be incorporated in liposomes or

* Corresponding author. Tel.: +39 0321 375845; fax: +39 0321 375821; e-mail: panza@pharm.unipmn.it
† Present address: Dipartimento di Chimica, Biochimica e Biotecnologie per la Medicina, Università di Milano, via Saldini 50, 20133 Milano, Italy.

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.11.059

used as such exploiting the well known glucose transport proteins (GLUTs)[7] which are able to bind glucose derivatives bearing substituents to a region non involved in recognition such as position 6 of the sugar.

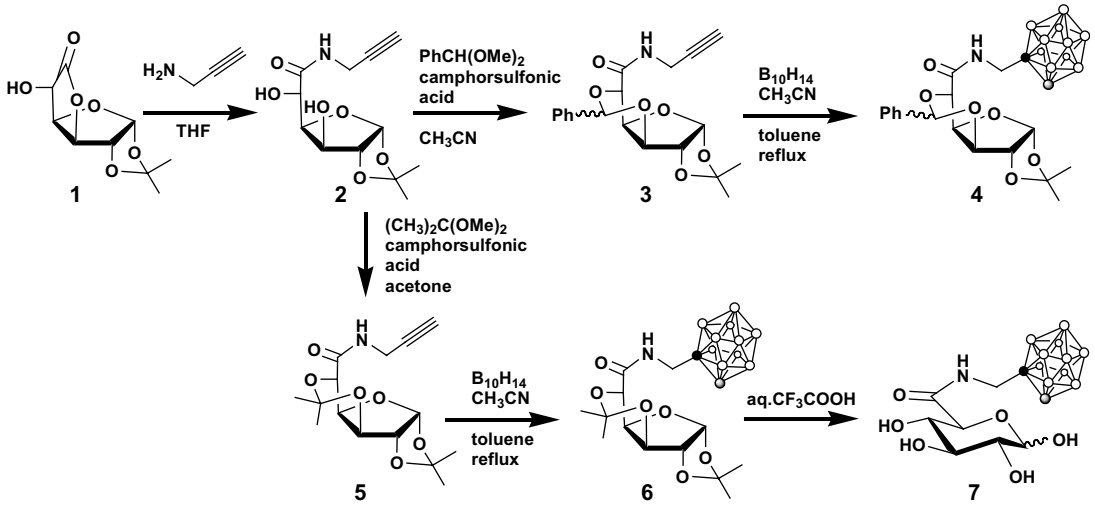
2. Results and discussion

As starting material for the preparation of carborane-containing glucuronic acid derivatives we chose the readily available 1,2-*O*-isopropylidene α-D-glucofuranurono-γ-lactone **1**.[8] When treated with propargylamine, compound **1** gave smoothly the corresponding amide **2**, easily purified by crystallization in high yield. In order to form the carborane cage on the triple bond it is necessary to protect the two hydroxyl groups present on **2**, as the cycloaddition reaction with activated decaborane is sensitive to the presence of nucleophilic species such as alcohols, acids, or amines.[9]

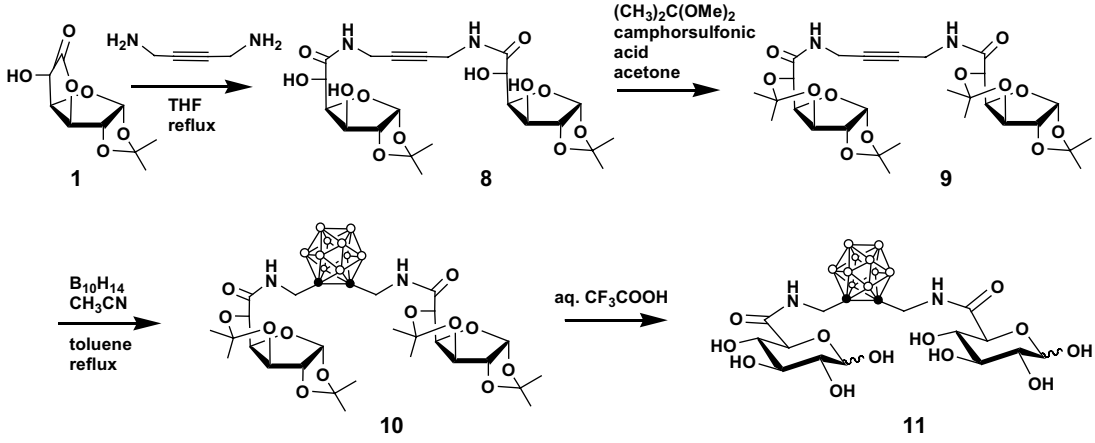
Preliminary attempts have been made to protect the 3,5-diol **2** as silyl ethers or as acetates but, for unclear reasons, the subsequent reaction with decaborane gave a complex mixture in the case of silyl ethers and a quite low yield when attempted on the acetylated derivative.

We then considered the protection of the diol as a benzylidene derivative.[10] The protection reaction with 1,1-dimethoxytoluene gave the corresponding acetal **3** in a satisfactory 90% yield as a non-separable 7:1 mixture of diastereoisomers at the newly formed stereocenter. Such protection proved to be fully compatible with the formation of carborane cage. In fact, treatment of **3** with decaborane in acetonitrile–toluene at reflux afforded compound **4** in good yield, again as a diastereomeric mixture. Unexpectedly, the removal of protecting groups gave many problems. Attempts to remove the benzylidene group by catalytic hydrogenolysis were unsuccessful (Schemes 1 and 2).

On the other hand, attempts to perform acidic hydrolysis gave complex mixtures with some of the products still retaining a benzylidene group. The difficulties encoun-



Scheme 1.



Scheme 2.

tered in the final deprotection step together with the complication arising from the introduction of an unnecessary stereocenter during protection prompted us to change again protecting group.

As acetals proved to be very compatible with carborane formation we finally decided to introduce an isopropylidene group to protect the diol. The reaction was performed using 2,2-dimethoxypropane in acetone, under acidic catalysis by camphorsulfonic acid at rt. The reaction afforded the desired compound **5** in 67% yield. Chromatography of the mother liquor allowed the final yield to be increased to 83%.

Compound **5** was then submitted to the cycloaddition with decaborane–acetonitrile complex in acetonitrile–toluene at reflux for 18 h, affording the carboranyl derivative **6** in 61% yield.

Although widely described in the literature, the final deprotection reaction on our compound gave rise to problems of chemical lability. Treatment with 60% or 80% aqueous trifluoroacetic acid[11,12] at room temperature for 4 h gave a low yield of the desired compound **7** together with some by-products. Other conditions have been attempted, including treatment with acidic resins in water–alcohols mixtures, HCl in THF–water, or methanol–water but none of these reactions gave satisfactory results. Careful examination of the reaction mixtures revealed that, besides the desired hydrolysis of the acetals, a significant hydrolysis of the amide bond had occurred. This surprising behavior can be attributed to the strong electron withdrawing effect of the carborane cage,[13] which makes the amide unusually labile.

We then re-examined the trifluoroacetic acid hydrolysis at different concentrations and reaction times and we found that the use of 90% aqueous trifluoroacetic acid for 10 min, followed by evaporation at low (<30 °C) temperature gave an almost quantitative yield of compound **7**. Encouraged by this result, we decided to extend the procedure to the synthesis of a carborane bearing two glucuronic acid units, starting from **1** and 1,4-diamino-2-butyne.

Since this reactive diamine is air-unstable,[14] we thought of a preparation which would deliver it as a salt, thus improving on previous methods.[15] 1,4-Bismethanesulfonyloxy-but-2-yne,[16] which is readily prepared from commercially available 2-butyne-1,4-diol was reacted with 25% aq. ammonia to form the bismesylate salt; the free base was liberated immediately before use by passing a methanol solution of the salt though a Dowex 1×8 (HO^- form) column. The diamine was reacted with 2 equiv. of lactone **1** in THF at reflux overnight to yield diamide **8** in 65% yield after chromatography. The following steps are essentially the same as previously described for the propargylamine derivative, namely protection as the isopropylidene, carborane formation, and final hydrolysis, eventually affording the doubly acylated diaminocarborane **11**.

3. Conclusion

In conclusion, we developed an efficient synthetic strategy for the preparation of carboranylated glucuronic acid derivatives from glucofuranurono-γ-lactone. The final deprotected compounds will be submitted to in vitro biological testing as such or after inclusion in liposomes to get information on their uptake by selected cancer cell lines.

4. Experimental

Optical rotation were measured in $CHCl_3$ solutions with a 241 Perkin–Elmer polarimeter at 20 °C. ^1H NMR and ^{13}C spectra were recorded with a Jeol Eclipse 300 spectrometer. All reactions were monitored by TLC on Silica Gel 60 F-254 plates (Merck), spots being developed with 5% sulfuric acid in methanol/water (1:1), or with phosphomolybdate based reagent. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Organic solutions were dried over sodium sulfate. Dry solvents and liquid reagents were obtained from analytical solvents with activated molecular sieves.

4.1. 1,2-*O*-Isopropylidene-*N*-(prop-2-ynyl)-α-D-glucofuranuronamide 2

To a solution of compound **1** (9.30 g, 43.0 mmol) in 25 mL of dry THF, 2-propynylamine (3.88 mL, 55.9 mmol) was added under argon. The reaction was stirred overnight at rt. The solvent was removed under reduced pressure and the residue co-evaporated twice with toluene. Crystallization from EtOAc gave 10.2 g of the product. Chromatography of the mother liquor (CH_2Cl_2/MeOH 96:4) gave further 0.95 g of product for a total yield of 95%. Yellowish solid, mp = 135–136 °C (dec). $[\alpha]_D^{20} = -15.7$ (c 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$), δ: 7.53 (br t, 1H, NH), 5.97 (d, 1H, $J_{1\text{-}2} = 3.5$ Hz, H-1), 4.53 (d, 1H, $J_{2,1} = 3.5$ Hz, H-2), 4.39–4.34 (m, 3H, H-3, H-5, OH), 4.26 (dd, 1H, $J_{4,5} = 6.9$ Hz, $J_{3,4} = 2.8$ Hz, H-4), 4.14 (ddd, 1H, $J_{a,b} = 17.3$ Hz, $J_{a,NH} = 5.5$ Hz, $J_{all} = 2.5$ Hz, NCHa), 4.04 (ddd, 1H, $J_{b,a} = 17.3$ Hz, $J_{a,NH} = 5.5$ Hz, $J_{all} = 2.5$ Hz, NCHb), 4.1–4.0 (br s, 1H, OH), 2.25 (t, 1H, $J_{all} = 2.5$ Hz, ≡CH), 1.47 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 170.0 (s, C═O), 110.0 (s, $C_{quat.}$), 102.8 (d, C-1), 82.9 (d), 78.8 (d), 76.8 (s, C≡), 73.4 (d), 69.9 (d), 67.3 (d, ≡CH), 27.2 (t, CH_2N), 24.9 (q, CH_3), 24.2 (q, CH_3). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.28; H, 6.62; N, 5.01.

4.2. 3,5-*O*-Benzylidene-1,2-*O*-isopropylidene-*N*-(prop-2-ynyl)-α-D-glucofuranuronamide 3

To a solution of compound **2** (1.16 g, 4.27 mmol) in 20 mL of dry CH_3CN under nitrogen, α,α-dimethoxytoluene (1.92 mL), and camphorsulfonic acid (50 mg, 0.21 mmol) were added. The solution was stirred at rt overnight, then neutralized by adding 0.5 mL of triethylamine. Evaporation of the solvent under reduced

pressure and flash chromatography (petroleum ether/EtOAc 7:3) of the residue gave 1.38 g of compound **3** (90% yield) as a 7:1 diastereomeric mixture at the benzylidene acetalic carbon. Oil. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ: 7.6–7.2 (m, 6H, ArH and NH), 6.51 (br t, 1H, NH), 6.05 (d, 1H, $J_{1\text{-}2}$ = 3.6 Hz, H-1), 5.48 (s, 1H, benzylidene CH), 4.84 (d, 1H, $J_{3,4}$ = 1.6 Hz, H-4), 4.80 (br s, 1H, H-5), 4.63 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.43 (d, 1H, $J_{3,4}$ = 1.6 Hz, H-3), 4.18 (ddd, 1H, $J_{a,b}$ = 17.6 Hz, $J_{a,NH}$ = 4.9 Hz, J_{all} = 2.7 Hz, NCHa), 4.04 (ddd, 1H, $J_{b,a}$ = 17.5 Hz, $J_{a,NH}$ = 5.0 Hz, J_{all} = 2.6 Hz, NCHb), 2.30 (t, 1H, J_{all} = 2.6 Hz, ≡CH), 1.47 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 168.1 (s, C=O), 136.7 (s, ArC), 129.7 (d, ArCH), 128.5 (d, ArCH), 126.1 (d, ArCH), 112.2 (s, C isopropylidene), 104.9 (d, C-1), 96.5 (s, benzylidene CH), 84.2 (d), 78.9 (s, ≡C), 77.9 (d), 74.7 (d), 72.0 (d, ≡CH), 71.3 (d), 29.9 (t, CH_2N), 26.9 (q, CH_3), 26.3 (q, CH_3). Anal Calcd for $C_{19}H_{21}NO_6$C, 63.50; H, 5.89; N, 3.90. Found: C, 63.73; H, 6.02; N, 3.71.

4.3. 3,5-*O*-Benzylidene-*N*-[1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethy]-1,2-*O*-isopropylidene-D-glucofuranuronamide 4

A solution of decaborane (57 mg, 0.47 mmol) in 2 mL of dry toluene and 0.5 mL of dry acetonitrile under nitrogen was heated at reflux for 1 h. Compound **3** (120 mg, 0.33 mmol) was then added and the mixture was heated at reflux for 18 h. For work-up, methanol (1 mL) was added and the solution was heated for 30 min at reflux, and then cooled to room temperature. Solvents were evaporated at reduced pressure. Flash chromatography of the residue (toluene/acetone 9:1) gave 113 mg (71% yield) of the carborane derivative **4**. Oil. ^{1}H NMR (300 MHz, $CDCl_3$), major isomer, δ: 7.6–7.2 (m, 6H, ArH), 6.78 (br t, NH), 6.04 (d, 1H, $J_{1\text{-}2}$ = 3.7 Hz, H-1), 5.50 (s, 1H, benzylidene CH), 4.80 (br s, 1H, H-5), 4.78 (d, 1H, $J_{3,4}$ = 1.6 Hz, H-4), 4.64 (d, 1H, $J_{2,1}$ = 3.7 Hz, H-2), 4.40 (d, 1H, $J_{3,4}$ = 1.7 Hz, H-3), 4.18 (ddd, 1H, $J_{a,b}$ = 17.6 Hz, $J_{a,NH}$ = 4.9 Hz, J_{all} = 2.7 Hz, NCHa), 4.04 (ddd, 1H, $J_{b,a}$ = 17.5 Hz, $J_{a,NH}$ = 5.0 Hz, J_{all} = 2.6 Hz, NCHb), 3.90 (br s, 1H, CHcarb), 1.47 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 169.4 (s, C=O), 136.3 (s, CPh), 129.9 (d, ArCH), 128.2 (d, ArCH), 125.0 (d, ArCH), 112.3 (s, C isopropylidene), 104.9 (d, C-1), 96.9 (s, benzylidene CH), 85.3 (d), 79.9 (d), 78.2 (d), 74.6 (s, Ccarb), 71.9 (d), 44.4 (t, CH_2N), 26.2 (q, CH_3), 26.4 (q, CH_3). Anal. Calcd for $C_{19}H_{31}B_{10}NO_6$: C, 47.79; H, 6.54; N, 2.93. Found: C, 47.51; H, 6.32; N, 2.98.

4.4. 1,2:3,5-Di-*O*-isopropylidene-*N*-(prop-2-ynyl)-α-D-glucofuranuronamide 5

To a solution of compound **2** (9.80 g, 36.1 mmol) in 100 mL of dry acetone, camphorsulfonic acid (0.42 g, 1.81 mmol), and 2,2-dimethoxypropane (31.1 mL, 252.7 mmol) were added. The reaction mixture was stirred at rt overnight, then 1 g of $NaHCO_3$ was added. The mixture was filtered and the solvent was removed under reduced pressure. Crystallization of the residue from 2-propanol gave 7.55 g of compound **5**. Flash chromatography of the mother liquor (petroleum ether/EtOAc 1:1) gave further 2.1 g of product for a total yield of 85%. Yellowish solid. Mp 129–130 °C. $[\alpha]_D^{20} = +26.2$ (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.53 (br t, 1H, NH), 6.01 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.55–4.51 (m, 2H, H-2, H-4), 4.20 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-3), 4.22–4.08 (m, 2H, NCHa, H-5), 4.12 (ddd, 1H, $J_{b,a}$ = 17.1 Hz $J_{b,NH}$ = 5.3 Hz J_{all} = 2.5 Hz, NCHb), 2.24 (t, 1H, J_{all} = 2.5 Hz, ≡CH), 1.45 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 170.2 (s, C=O), 113.0 (s), 107.0 (d, C-1), 101.8 (s), 84.2 (d), 79.8 (s, C≡), 79.6 (d), 75.4 (d), 72.6 (d, ≡CH), 72.5 (d), 29.4 (t, NCH_2), 27.8 (q, CH_3), 27.3 (q, CH_3), 25.4 (q, CH_3), 24.4 (q, CH_3). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.99; H, 6.52; N, 4.38.

4.5. *N*-[1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethy]-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranuronamide 6

A solution of decaborane (358 mg, 2.93 mmol) in 20 mL of dry toluene and 6.4 mL of dry acetonitrile under nitrogen was heated at reflux for 1 h. Compound **5** (760 mg, 2.44 mmol) was then added and the mixture was heated at reflux for 18 h. For work-up, methanol (2 mL) was added and the solution was heated for 30 min at reflux, and then cooled to room temperature. Solvents were evaporated at reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc 7:3) gave 630 mg (61% yield) of the title compound. White solid. Mp 164–165 °C. $[\alpha]_D^{20} = +8.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 6.81 (br t, 1H, NH), 6.11 (d, 1H, $J_{1\text{-}2}$ = 3.5 Hz, H-1), 4.69 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-2), 4.47 (dd, 1H, $J_{4,5}$ = 6.8 Hz, $J_{3,4}$ = 3.1 Hz, H-4), 4.36–4.31 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 4.19 (d, 1H, $J_{4,5}$ = 6.8 Hz, H-5), 4.09–3.81 (m, 3H, NCH_2, $CH_{carb.}$), 3.16–1.83 (br m, 10H, BH), 1.57 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 172.2 (s, C=O), 113.3 (s), 107.0 (d, C-1), 103.0 (s), 83.8 (d), 80.9 (d,), 80.3 (d), 75.5 (d), 75.1 (s, $C_{carb.}$), 72.0 (d), 44.2 (t, NCH_2), 27.5 (q, CH_3), 26.9 (q, CH_3), 24.5 (q, CH_3), 24.1 (q, CH_3). Anal. Calcd for $C_{15}H_{31}B_{10}NO_6$: C, 41.94; H, 7.27; N, 3.26; Found C, 41.71; H, 7.49; N, 2.98.

4.6. *N*-[1,2-Dicarba-*closo*-dodecaboran(12)-1-ylmethyl]-D-glucopyranuronamide 7

Compound **6** (150 mg, 0.35 mmol) was dissolved in 15 mL of 90% aqueous trifluoroacetic acid. After 10 min the solvent was removed under reduced pressure and the residue was taken up with toluene and the solvent removed under reduced pressure keeping the water bath of the rotatory evaporator under 30 °C. The residue contains the title compound almost pure in nearly quantitative yield. An analytical sample was purified by flash chromatography (CH_2Cl_3/MeOH 7:1). Glassy solid. $[\alpha]_D^{20} = +15.9$ (*c* 1.00, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD), δ: 5.19 (d, 0.7H, $J_{1\text{-}2}$ = 3.6 Hz,

H-1α), 4.55 (d, 0.3H, $J_{1\text{-}2}$ = 8.0 Hz, H-1β), 4.44 (br s, 1H, $CH_{carb.}$), 4.21 (d, 0.7H, $J_{5,4}$ = 9.9 Hz, H-5α), 4.03–3.85 (m, 2H, NCH_2), 3.80–3.66 (d, 0.3H, $J_{5,4}$ = 9.3 Hz, H-5β), (d, 0.7H, $J_{2,3} = J_{3,4}$ = 9.9 Hz, H-3α), 3.55–3.37 (m, 2H, H-3β, H-4, H-2α), 3.20 (t, 0.3H, J = 8.0 Hz, H-2β), 3.10–1.01 (br m, 10H, BH). ^{13}C NMR (75.4 MHz, CD_3OD), δ: 172.1 (s, β C=O), 171.0 (s, α C=O), 97.1 (d, C-1β), 92.9 (d, C-1α), 76.2 (d), 75.1 (d), 75.1 (s, Ccarb), 74.9 (d), 74.3 (d), 73.1 (d), 72.5 (d), 72.1 (d), 71.8 (d), 70.6 (d), 43.4 (t, N–CH_2). ^{11}B NMR (CD_3OD) δ: 3.71 (2 B), 10.68 (4 B), 12.21 (4 B). Anal. Calcd for $C_9H_{23}B_{10}NO_6$: C, 30.94; H, 6.64; N, 4.01. Found: C, 30.71; H, 6.88; N, 3.87.

4.7. *N*-1,4-Bis-(1,2-*O*-isopropylidene-α-D-glucofuranuronamido)-2-butyne 8

Preparation of 1,4-diamino-2-butyne dimesylate: to 1,4-bismethanesulfonyloxy-2-butyne (9.39 g, 38.8 mmol) a 25% aqueous ammonia solution (200 mL) was added. The reaction was stirred for 18 h, then the solvent was evaporated, initially warming the solution under a hood at atmospheric pressure to eliminate the ammonia, then under vacuum. The residue was dissolved in water, treated with decolorizing carbon, filtered, and the water evaporated. The precipitate is washed with 2-propanol, to eliminate traces of the monosubstituted derivative and warm filtered to give almost pure 1,4-diamino-2-butyne dimesylate in 64% yield. White solid. Mp 160 °C (dec). ^{1}H NMR (300 MHz, D_2O), δ: 3.68 (s, 4H, CH_2), 2.58 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, D_2O), δ: 79.14 (s, C-2, C-3), 39.19 (q, CH_3), 29.77 (t, C-1, C-4). A solution of 1,4-diamino-2-butyne dimesylate (640 mg, 2.32 mmol) in methanol was passed through a Dowex 1 × 8 (OH^- form) ion exchange column. The eluate was evaporated under reduced pressure. The residue was dissolved into 12 mL of dry THF and lactone **1** (1.00 g, 4.64 mmol) was added. The solution was warmed to reflux overnight. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 93:7) to give 1.51 g of compound **8** (63% yield). White solid. Mp 108–110 °C. $[\alpha]_D^{20} = -16.8$ (*c* 1.25, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD), δ: 5.90 (d, 2H, $J_{1\text{-}2}$ = 3.6 Hz, H-1), 4.47 (d, 2H, $J_{2\text{-}1}$ = 3.6 Hz, H-2), 4.34 (d, 2H, $J_{4,5}$ = 6.0 Hz, H-5), 4.24–4.18 (m, 4H, H-3, H-4), 4.02 (s, 4H, CH_2), 1.44 (s, 6H, CH_3), 1.29 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, CD_3OD), δ: 171.1 (s, C=O), 109.1 (s), 102.6 (d, C-1), 82.7 (d), 78.2 (d), 75.6 (s, ≡C), 72.1 (d), 67.2 (d), 25.8 (t, N–CH_2), 23.3 (q, CH_3), 22.6 (q, CH_3). Anal. Calcd for $C_{22}H_{32}N_2O_{12}$: C, 51.16; H, 6.24; N, 5.42. Found: C, 50.91; H, 6.52; N, 5.18.

4.8. *N*-1,4-Bis-(1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranuronamido)-2-butyne 9

To a solution of compound **8** (500 mg, 80.97 mmol) in 15 mL of dry acetone, 2,2-dimethoxypropane (6 mL, 48.5 mmol) and camphorsulfonic acid (56 mg) were added. The solution was stirred for 5 h at rt. The reaction was quenched with 500 mg of $NaHCO_3$ and the mixture was filtered through Celite. Evaporation of the solvent under reduced pressure and flash chromatography (petroleum ether/EtOAc 3:7) of the residue gave 476 mg of compound **9** (82% yield). White solid. Mp 89.5–90.5 °C. $[\alpha]_D^{20} = +25.8$ (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.52 (br t, 2H, NH), 6.04 (d, 2H, $J_{1\text{-}2}$ = 3.7 Hz, H-1), 4.59–4.51 (m, 4H, H-2, H-4), 4.22 (d, 2H, $J_{3,4}$ = 3.4 Hz, H-3), 4.14–4.08 (m, 6H, H-5, NCH_2), 1.48 (s, 6H, CH_3), 1.42 (s, 6H, CH_3), 1.39 (s; 6H, CH_3), 1.32 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 168.1 (s, C=O), 112.0 (s), 105.4 (d, C-1), 100.9 (s), 82.5 (d) 78.1 (d), 77.9 (s, C), 73.8 (d), 70.8 (d), 27.1 (t, NCH_2), 26.1 (q, CH_3), 25.5 (q, CH_3), 23.5 (q, CH_3), 22.8 (q, CH_3). Anal. Calcd for $C_{28}H_{40}N_2O_{12}$: C, 56.37; H, 6.76; N, 4.70. Found: C, 56.61; H, 6.42; N, 4.55.

4.9. *N*-1,4-Bis-[(1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranuronamido)methyl]-dicarba-*closo*-dodecaborane(12) 10

The reaction was performed as described for the preparation of compound **6**. Flash chromatography of the residue (petroleum ether/EtOAc 1:1) gave 160 mg of compound **10** (35% yield). White solid. Mp 132–134 °C. $[\alpha]_D^{20} = -20.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.29 (br t, 2H, NH), 6.04 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1), 4.57 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-2), 4.53 (dd, 2H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 6.7 Hz, H-4), 4.47 (m, 2H, $J_{a,b}$ = 16.0 Hz, $J_{b,NH}$ = 7.8 Hz, NCHa), 4.25 (d, 2H, $J_{3,4}$ = 3.4 Hz, H-3), 4.13 (d, 2H, $J_{4,5}$ = 6.7 Hz, H-5), 4.01 (dd, 2H, $J_{a,b}$ = 16.0 Hz $J_{b,NH}$ = 6.0 Hz, NCHb), 3.45–1.70 (br m, 10H, $BH_{carb.}$), 1.47 (s, 6H, CH_3), 1.44 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 1.32 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 169.0 (s, C=O), 112.1 (s), 105.5 (d, C-1), 101.2 (s), 82.5 (d), 78.8 (d, $C_{carb.}$), 78.6 (d), 73.5 (d), 70.7 (d), 41.7 (t, NCH_2), 26.1 (q, CH_3), 25.6 (q, CH_3), 23.1 (q, CH_3); 22.7 (q, CH_3). Anal. Calcd for $C_{28}H_{50}B_{10}N_2O_{12}$: C, 47.05; H, 7.05; N, 3.92. Found: C, 47.41; H, 6.82; N, 3.68.

4.10. *N*-1,2-Bis-[(D-glucopyranuronamido)methyl]-1,2-dicarba-*closo*-dodecaborane(12) 11

The reaction was performed on 144 mg (0.2 mmol) as described for the preparation of compound **7** except that the reaction time was 20 min. An analytical sample was purified by flash chromatography (EtOAc/MeOH/H_2O 6:3:1). Glassy solid. $[\alpha]_D^{20} = +17.2$ (*c* 1.00, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD), δ: 5.22 (d, 1.4H, $J_{1\text{-}2}$ = 3.6 Hz, H-1α), 4.57 (d, 0.6H, $J_{1\text{-}2}$ = 8.0 Hz, H-1β), 4.41–4.17 (m, 5.4H), 3.85–3.67 (m, 2H, H-5β, H-3α), 3.56–3.40 (m, 4H, H-3β, H-2α, H-4), 3.22 (t, 0.8H, $J_{1,2}$ = 8.0 Hz, H-2β), 1.40–2.89 (br m, 10H, BH). ^{13}C NMR (300 MHz, CD_3OD), δ: 171.9 (s, C=O), 171.8 (s, C=O), 170.8 (s, C=O), 170.7 (s, C=Oα), 97.1 (d, C-1β), 92.9 (d, C-1α), 80.9 (s, Ccarb), 80.7 (s, Ccarb), 76.2 (d), 74.9 (d), 74.3 (d), 73.1 (d), 72.6 (d), 72.1 (d), 71.8 (d), 70.5 (d), 41.0 (t, CH_2N). ^{11}B NMR (CD_3OD) δ: 4.21 (2 B), 10.79 (8 B). Anal. Calcd for $C_{16}H_{34}B_{10}N_2O_{12}$: C, 34.65; H, 6.18; N, 5.05. Found: C, 34.41; H, 6.34; N, 4.84.

Acknowledgements

We thank MIUR (COFIN 2001), and Università del Piemonte Orientale (ex 60%) for financial support.

References

1. Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515–1562.
2. Bregadze, V. I. *Chem. Rev.* **1992**, *92*, 209–223.
3. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbei, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173–230.
4. (a) Tietze, L. F.; Bothe, U. *Chem. Eur. J.* **1998**, *4*, 1179–1183; (b) Giovenzana, G. B.; Lay, L.; Monti, D.; Palmisano, G.; Panza, L. *Tetrahedron* **1999**, *55*, 14123–14136; (c) Tietze, L. F.; Bothe, U.; Schuberth, I. *Chem. Eur. J.* **2000**, *6*, 836–842; (d) Tietze, L. F.; Bothe, U.; Griesbach, U.; Nakaichi, M.; Hasegawa, T.; Nakamura, H.; Yamamoto, Y. *ChemBioChem* **2001**, *2*, 326–334; (e) Tietze, L. F.; Bothe, U.; Griesbach, U.; Nakaichi, M.; Hasegawa, T.; Nakamura, H.; Yamamoto, Y. *Bioorg. Med. Chem.* **2001**, *9*, 1747–1752; (f) Donati, A.; Ristori, S.; Bonechi, C.; Panza, L.; Martini, G.; Rossi, C. *J. Am. Chem. Soc.* **2002**, *124*, 8778–8779; (g) Thimon, C.; Panza, L.; Morin, C. *Synlett* **2003**, 1399–1402; (h) Tietze, L. F.; Griesbach, U.; Schuberth, I.; Bothe, U.; Marra, A.; Dondoni, A. *Chem. Eur. J.* **2003**, *9*, 1296–1302; (i) Ronchi, S.; Prosperi, D.; Compostella, F.; Panza, L. *Synlett* **2004**, 1007–1010.
5. Morandi, S.; Ristori, S.; Berti, D.; Panza, L.; Becciolini, A.; Martini, G. *Biochim. Biophys. Acta* **2004**, *1664*, 53–63.
6. (a) Owen, L. N.; Peat, S.; Jones, W. J. G. *J. Chem. Soc.* **1941**, 339–344; (b) Fieser, M.; Fieser, L. F.; Toromanoff, E.; Hirata, Y.; Heymann, H.; Tefft, M.; Bhattacharya, S. *J. Am. Chem. Soc.* **1956**, *78*, 2825–2829; (c) Abbadi, M.; Holman, G. D.; Morin, C.; Rees, W. D.; Yang, J. *Tetrahedron Lett.* **1999**, *40*, 5861–5864.
7. (a) Holman, G. D.; Rees, W. D. *Biochim. Biophys. Acta* **1982**, *685*, 78; (b) Joost, H.-G.; Thorens, B. *Mol. Membr. Biol.* **2001**, *18*, 247–256; (c) Dwyer, D. S.; Vannucci, S. J.; Simpson, I. A. *Int. Rev. Neurobiol.* **2002**, *51*, 159–188; (d) Medina, R. A.; Owen, G. I. *Biol. Res.* **2002**, *35*, 9–26.
8. Kitahara, T.; Ogawa, T.; Naganuma, T.; Masui, M. *Agric. Biol. Chem.* **1974**, *38*, 2189–2190.
9. Grimes, R. N. *Carboranes*; Academic: New York, 1970; p 459.
10. For similar compounds see Baggett, N.; Smithson, A. *Carbohydr. Res.* **1982**, *108*, 59–70.
11. Regelling, H.; Chittenden, G. J. F. *Carbohydr. Res.* **1990**, *205*, 261–268.
12. Blériot, Y.; Masaguet, C. F.; Charlwood, J.; Winchester, B. G.; Lane, A. L.; Crook, S.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron* **1997**, *53*, 15135–15146.
13. See for example: Oliva, J. M.; Viñas, C. *J. Mol. Struct.* **2000**, *556*, 33–42, and references cited therein.
14. Johnson, A. W. *J. Chem. Soc.* **1946**, 1009–1014.
15. (a) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190–192; (b) Saljoughian, M.; Morimoto, H.; Williams, P. G.; Rapoport, H. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 313–328; (c) Klepacz, A.; Zwierzak, A. *Synth. Commun.* **2001**, *31*, 1683–1689; (d) Jeon, H.-B.; Lee, Y.; Qiao, C.; Huang, H.; Sayre, L. W. *Bioorg. Med. Chem.* **2003**, *11*, 4631–4641.
16. (a) Haslinger, F.; Soloway, A. H. *J. Med. Chem.* **1966**, *9*, 792; (b) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925–1928.