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Synthesis of conjugates of polyhedral boron compounds with carbohydrates †

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Abstract. The published data on the methods for the synthesis of conjugates of polyhedral boron compounds with carbohydrates, potential third-generation agents for neutron capture therapy, are systematised and generalised. The bibliography includes 47 references.

I. Introduction

Neutron capture therapy using the ^{10}B isotope (boron neutron capture therapy, BNCT) is a radiation-based method for treatment of a series of oncological diseases. Introduction of a stable ^{10}B isotope into a tumour and its subsequent irradiation with a beam of slow (thermal) neutrons underlie the method. A nuclear reaction is initiated, which results in formation of high-energy fission products having quite short mean free path, comparable to a cell size. This, in principle, allows selective tumour cell destruction while leaving the surrounding healthy tissue intact.[1]

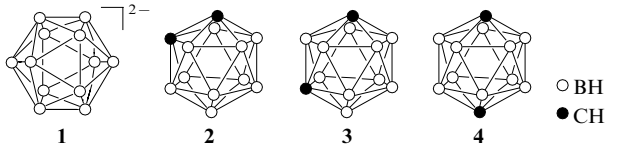
The main limitation of BNCT is currently low selectivity of delivery of boron-containing compounds to the tumour cells. In the last few years, a rapid progress is observed in the field of methods for the synthesis of potential third-generation agents for BNCT. Their molecules comprise boron polyhedral clusters and a transport moiety (usually, a biomolecule fragment) that ensures a targeted delivery of the drug to the malignant cell.[1] On the surface of tumour cells over expression of lectins, carbohydrate-specific receptor proteins, is often observed,[2,3] therefore the use of carbohydrates for targeted delivery of polyhedral boron compounds to the tumour cells seems promising.

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Several comprehensive reviews[1,4–9] are devoted to the third-generation BNCT agents. However, they deal very briefly with carborane – carbohydrate conjugates, and no references are given to syntheses of conjugates with dodecaborates. The present review describes the conjugates of carbohydrates with different polyhedral boron derivatives.

Among polyhedral boron derivatives, several compounds attract the most interest as possible boron-containing fragments of BNCT agents. These are the *closo*-dodecaborate anion (**1**) and carboranes, namely 1,2-dicarba-*closo*-dodecaborane (*ortho*-carborane, **2**), 1,7-dicarba-*closo*-dodecaborane (*meta*-carborane, **3**) and 1,12-dicarba-*closo*-dodecaborane (*para*-carborane, **4**).



1 **2** **3** **4**

High chemical stability and low toxicity are characteristic of these compounds. The presence of 10 or 12 boron atoms in the molecule favours achievement of the necessary therapeutic concentration of ^{10}B isotope in the tumour tissue.[1]

closo-Dodecaborate (**1**) is the most accessible member of the polyhedral boron family. However, the synthesis of its functionalised derivatives, which are necessary for attachment of a transport fragment, is not a trivial task, which prevents its wider application as a component of potential BNCT agents.[10] *ortho*-Carborane (**2**) is a less readily accessible compound than dodecaborate. However, the former is widely used in the synthesis of potential third-generation BNCT agents due to possible application of conventional methods of organic chemistry for the preparation of *ortho*-carborane derivatives.[7] It is the variation in methods of synthesis of functionalised polyhedral boron derivatives

† The review is written in connection with the 75th anniversary of N D Zelinsky Institute of Organic Chemistry of the RAS

that accounts for the fact that, for a long time, no common approach existed to the synthesis of both the carborane–carbohydrate and carborane–carbohydrate conjugates.

The first publication [11] on the synthesis of carborane–carbohydrate conjugates dates back to 1988. Carbohydrates were first considered as only the hydrophilic parts of carborane–carbohydrate conjugates.[11–14] As recently as in 1998 systematic studies on carborane–carbohydrate conjugates started [15,16] where the carbohydrates governed the delivery of polyhedral boron compounds to the tumour cells. Significant number of conjugates of carboranes with different carbohydrates were obtained.

Three research groups reported several examples of carbohydrate conjugates with dodecaborate anions.[17–22] Synthesis of such conjugates is addressed in a separate section of this paper.

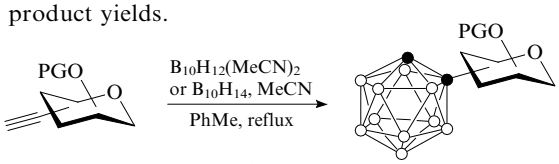
II. Carborane–carbohydrate conjugates

Two basically different approaches to the synthesis of conjugates of carboranes with carbohydrates exist: *de novo* synthesis in which the carborane framework is formed together with the conjugate formation, and synthesis of a conjugate from intermediate functionalised carboranes and carbohydrate derivatives.

1. *De novo* synthesis

In *de novo* synthesis, the carborane framework is formed directly in the conjugate upon addition of decaborane or its acetonitrile complex to the triple bond C≡C. The reaction route generally comprises three main steps: introduction of a triple bond into the carbohydrate precursor, carborane framework formation and deprotection of the carbohydrate fragment.

The second step implies either the use of the preformed decaborane–acetonitrile complex,[13,15,16] or direct addition of equivalent amount of acetonitrile to the reaction mixture.[12,23,24] These two techniques differ insignificantly in the product yields.



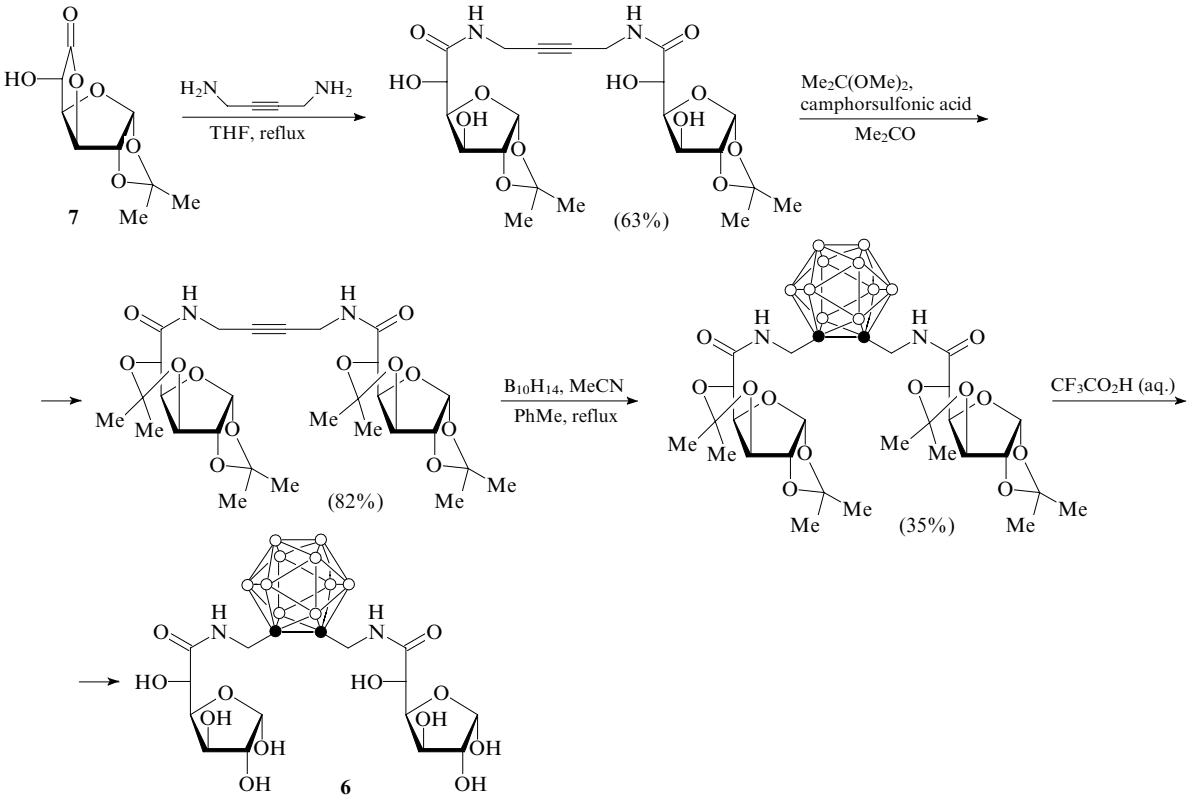
PG is a rotecting group,  is a carbohydrate residue.

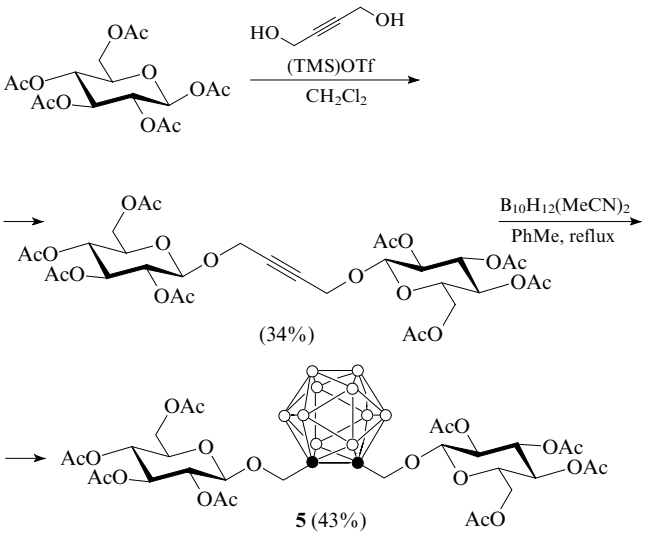
This method afforded conjugates of *ortho*-carboranes with the following carbohydrates: glucose,[12,13,15,16,24] glucuronic acid,[23] galactose,[13,24] mannose,[15,24] gulose, fucose, lactose [15,16] and maltose.[15]

If a bifunctional alkyne (diol, diamine) is used to introduce the triple bond into the sugar moiety, then the formation of a conjugate can be implemented following two different schemes.

According to the first scheme, glycosylation of both functional groups of the alkyne occurs simultaneously, and hence, only symmetrical compounds are obtained. Conjugates of glucose (**5**) and lactose were synthesised [16] following this scheme from the corresponding peracetylated precursors.

Scheme 1





The same method was later used [23] to convert glucuronolactone (**7**) into carboranyl derivative of glucuronic acid (**6**) (Scheme 1).

The second scheme includes protection of one of the functional groups of the alkyne and subsequent glycosylation by only one carbohydrate residue. Reaction with decaborane is followed by deprotection and glycosylation of the second functional group by the other carbohydrate residue. Conjugates with two different carbohydrate units can be obtained in that way. Conjugate **8** incorporating glucose and galactose fragments was synthesised according to this scheme.[24] The carbohydrates were introduced using the corresponding trichloroacetimidates (Scheme 2).

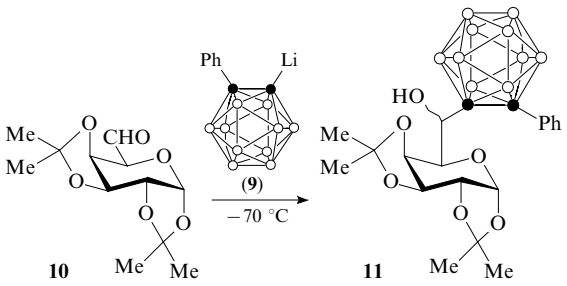
The *de novo* synthesis implies the formation of the carborane cage in the last steps. This minimises the number of steps with involvement of the derivatives enriched in isotope ^{10}B . However, only *ortho*-carborane derivatives are available through this approach. Besides, the yields of the target products strongly depend on the nature of the substrate, varying from 13% to 92%.

2. Synthesis based on preformed carborane derivatives

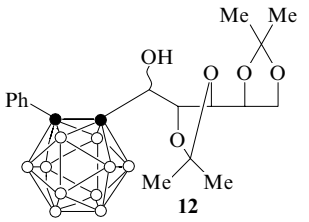
Syntheses based on various carborane derivatives containing metal ions, hydroxy, carboxy or amino groups or halogen atoms, are reported. It is to be noted that, unlike the *de novo* approach, this method affords derivatives of not only *ortho*-, but also *meta*- and *para*-carboranes.

a. Metallated carboranes

Coupling of lithiated carborane **9** obtained *in situ* with galactose derivative **10** affords conjugate **11**.[25] Metallation of phenyl-*ortho*-carborane in THF solution was achieved by the action of Bu^nLi in hexane and then aldehyde **10** was added.

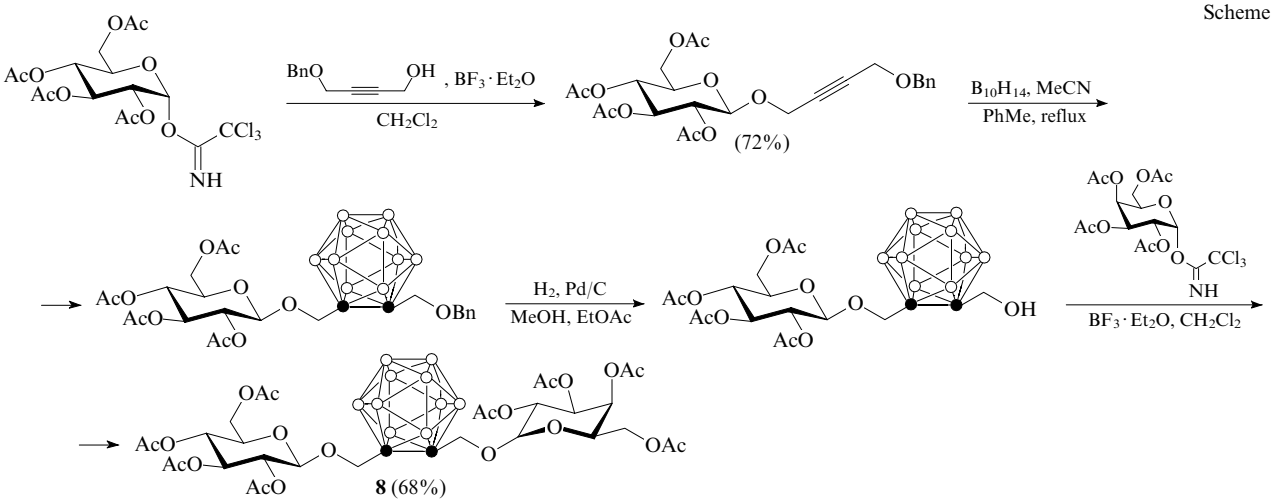


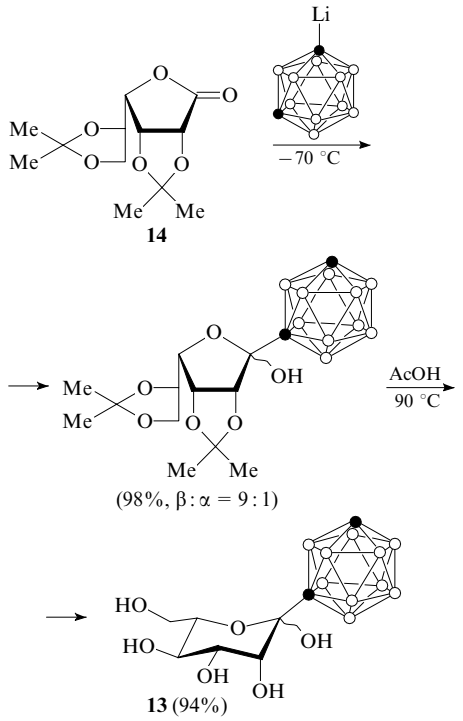
Product **11** was obtained as a mixture of diastereomers (*erythro* to *threo* ratio being 4 : 1) in a total yield of 68% based on the starting 2-phenyl-*ortho*-carborane. In addition to galactose, arabinose in an open-chain form with protected hydroxy groups was used as the sugar component. In this case, product **12** was obtained as a mixture of diastereomers as well (total yield 69%, *erythro* to *threo* ratio being 4 : 1).



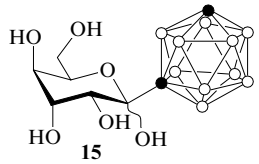
Later, conjugate **13** was obtained similarly [14] from L-mannonolactone **14**. Metallation of *meta*-carborane in tetrahydrofuran solution was carried out with Bu^nLi/hexane at −10 °C for 1.5 h. Reaction mixture was then cooled to −70 °C and a solution of the starting lactone **14** in tetrahydrofuran was added.

Scheme 2





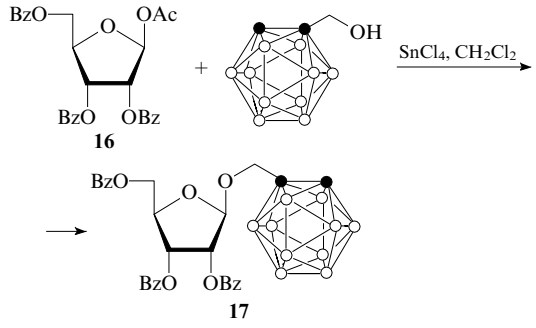
Similar coupling with D-gulonolactone afforded a mixture of anomers (β : α = 7 : 3), total yield being 62%. However, an equimolar mixture of anomers of compound **15** was obtained upon removal of the isopropylidene protecting group with acetic acid at 90 °C.



The formation of isomer mixtures is the main drawback of the above described methods of synthesis of carborane–carbohydrate conjugates. The techniques for the separation of the isomers depend on both the nature of the starting compounds and the type of the bond between the carborane part and the carbohydrate fragment; isolation of isomers is often quite a complicated task.

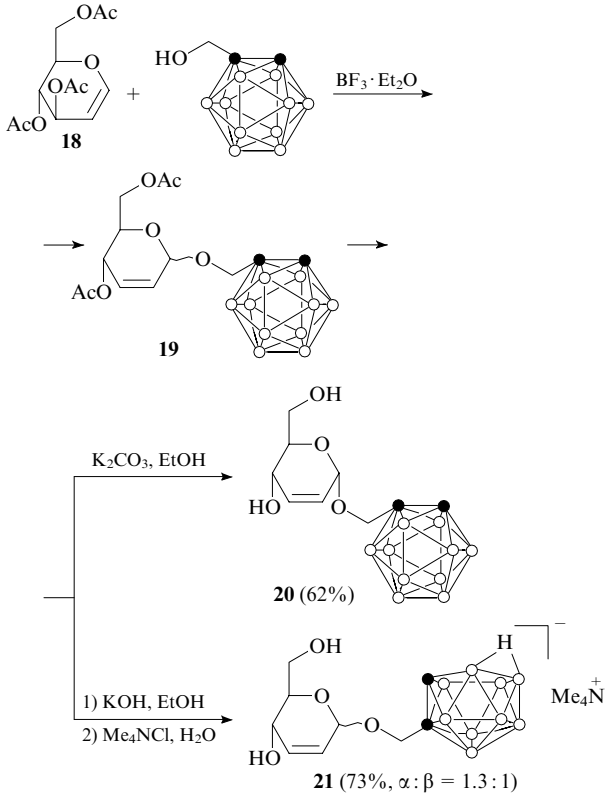
b. Hydroxyl-containing carborane derivatives

The first reported [11] synthesis of a carborane–carbohydrate conjugate included glycosylation of hydroxymethyl-*ortho*-carborane with ribose derivative **16** in the presence of $SnCl_4$.



According to ^1H NMR data, product **17** was mainly the β-anomer (the α-anomer content was as low as 7%). The product was purified by column chromatography to give the target conjugate in 81% yield.

The same study [11] reported the reaction of carboranylalcohols with glycals, namely, acetylated glucal (**18**) and xylal, in the presence of another Lewis acid, $BF_3 \cdot Et_2O$.

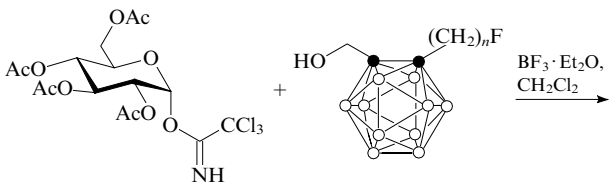


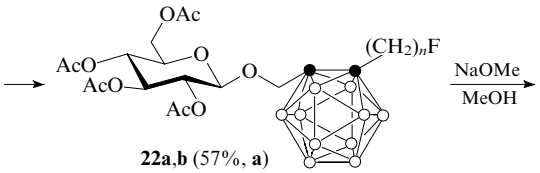
This reaction resulted in mixtures of anomers. With glucal **18**, the α to β anomer ratio varied from 9 : 1 (with hydroxymethylcarborane) to 7.7 : 2.3 [with 1-(3-hydroxypropyl)-2-methylcarborane] (the total yield being in the range from 70% to 90%).[11]

Pure α-isomer of conjugate **19** was deprotected under relatively mild conditions (deacetylation by 12-h stirring in ethanol with K_2CO_3 followed by recrystallisation) to give *closo*-carborane conjugate **20** with exclusively α-configuration of the carbohydrate fragment. More drastic conditions (refluxing in ethanolic KOH) resulted in a mixture of anomers of conjugate **21** with *nido*-carborane, which contained one boron atom less than the starting protected conjugate.

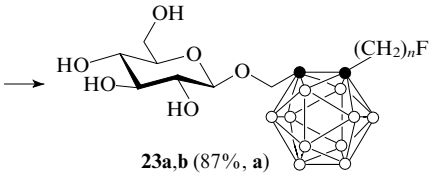
A disadvantage of this synthetic scheme is the formation of anomeric mixtures.

Synthesis of fluorine-containing *ortho*-carborane conjugates with glucose starting from the corresponding hydroxymethyl derivative of *ortho*-carborane was reported.[26]





22a,**b** (57%, **a**)

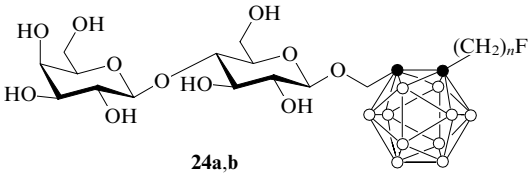


23a,**b** (87%, **a**)

n = 1 (**a**), 6 (**b**).

Glycosylation of the *ortho*-carborane derivative (n = 6) with glucose trichloroacetimidate gave a mixture of the target product with the corresponding orthoester. Upon removal of acetyl protecting groups, the mixture of product **23b** with orthoester was separated by column chromatography, yields being 67% and 9%, respectively

Similar reactions with lactose gave conjugates **24a**,**b**.



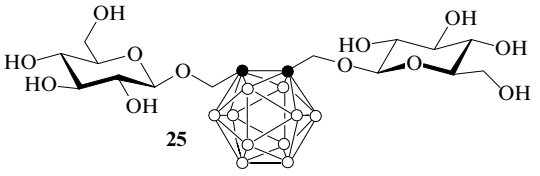
24a,**b**

n = 1 (**a**), 6 (**b**).

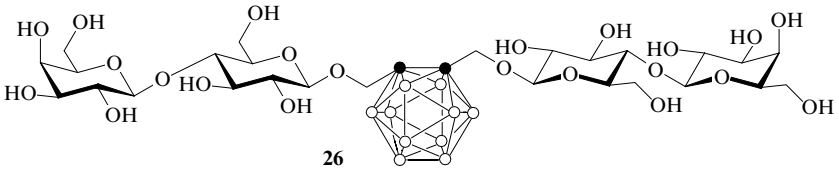
The yields of glycosylation and deprotection reactions were 58% and 72%, respectively, (n = 1) and 53% and 89% (n = 6).

Later, the same research group carried out syntheses [24] of bis-glucoside (**25**) and -lactoside (**26**) conjugates following similar technique. In these cases, two carbohydrate residues were introduced into the diol simultaneously. Glycosylation yields were 83% (glucose) and 68% (lactose), while deprotection yields were 65% (glucose) and 74% (lactose).

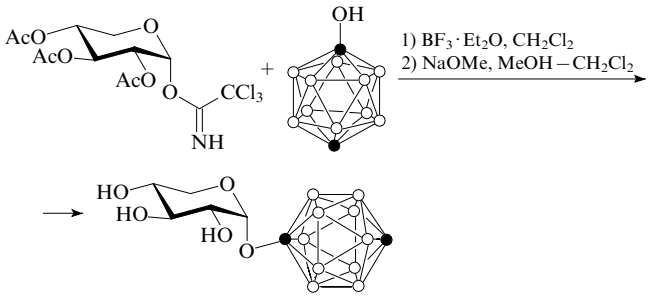
Similar synthesis involving hydroxy-*para*-carborane and xylose trichloroacetimidate was reported recently.[27]



25



26

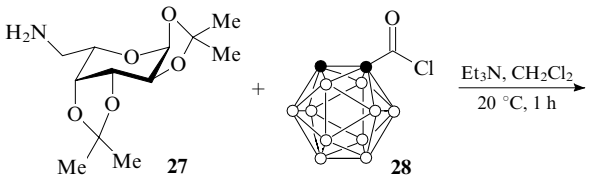


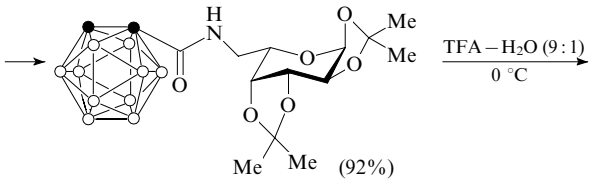
Glycosylation reaction resulted in the conjugate in 90% yield. Deprotection yield was 91%.

Unfortunately, this method cannot be considered versatile as glycosylation reaction is often very sensitive to the change in the substrate.

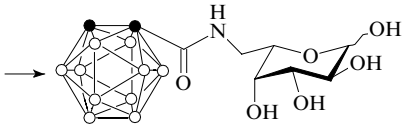
c. Carborane-based carboxylic acids and their derivatives

Carborane carboxylic derivatives were first used in the synthesis of carborane conjugates with fucose.[28] Amino derivative of L-fucose (**27**) was acylated with *ortho*-carboranecarbonyl chloride (**28**), the reaction at room temperature is quite fast, and the yield is high.





(92%)

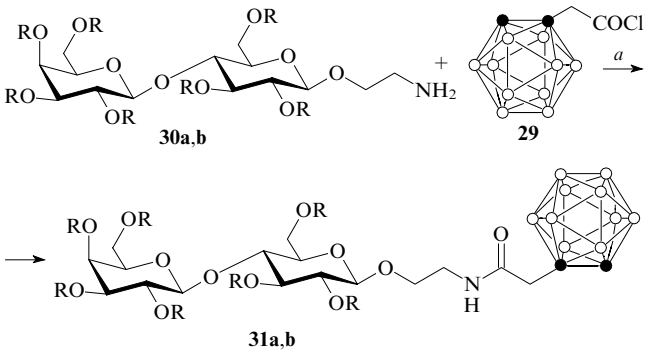


(93%, α : β = 1 : 1.5)

TFA is trifluoroacetic acid.

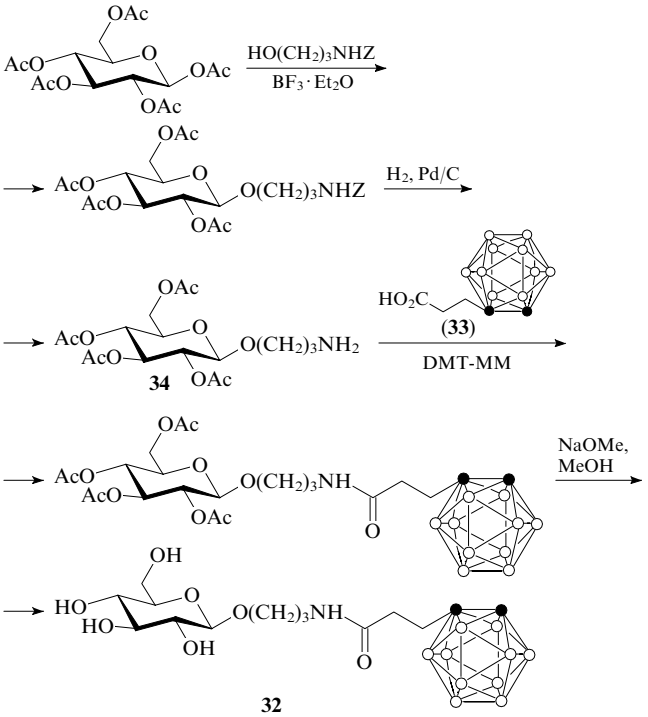
This approach is attractive due to high product yields and simple procedure.

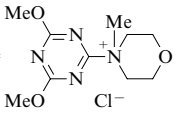
The use of carboranylacetyl chloride (**29**) has been reported.[29] However, a complex mixture of carborane-containing products was obtained under similar conditions. The reason is likely the formation of the corresponding ketene from carboranylacetyl chloride in the presence of Et_3N. Then, a modification of the reaction conditions was implemented to suppress the undesirable ketene formation. Amines **30a**,**b** derived from lactose were acylated in a two-phase system, dichloromethane-saturated sodium hydrogencarbonate solution to give conjugates **31a**,**b**.



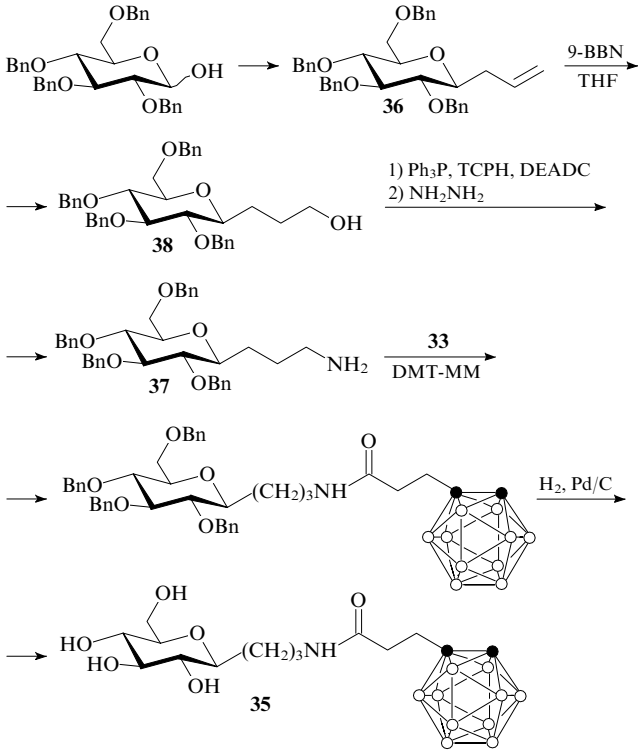
R = Ac (**a**, 47%), Bn (**b**, 53%); (*a*) $NaHCO_3$, $H_2O-CH_2Cl_2$, 1–2 h.

In the synthesis of carborane–carbohydrate conjugate **32**, 3-carboranylpropionic acid (**33**) and amine **34** were used.[30] The latter was prepared starting from peracetylated glucose derivative. The conjugate formation was achieved in the presence of dimethoxytriazinyl(methyl)morpholinium chloride (DMT-MM).



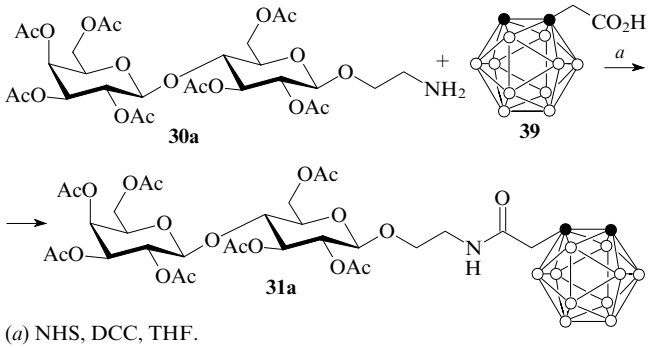
Z is benzyloxycarbonyl, DMT-MM = 

The synthesis of the conjugate of *C*-glucoside **35** started from the preparation of *C*-allylglucoside **36**. Compound **36** was then converted into 3-aminopropyl-*C*-glucoside **37** *via* the corresponding hydroxy derivative **38**.[30] The reaction of amine **37** with carboranylpropionic acid (**33**) in the presence of DMT-MM followed by deprotection of the glucose moiety (debenzylation by hydrogenolysis) represent final steps of the synthesis.



9-BBN is 9-borabicyclo[3.3.1]nonane, TCPH is tetrachlorophthalimide, DEADC is diethyl azodicarboxylate.

Preparation of lactose conjugate **31a** by another method was described,[22,31] namely, by the action of *o*-carboranylacetic acid (**39**) in the presence of *N*-hydroxysuccinimide (NHS) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in THF. The target product **31a** was isolated in 19% yield after purification by HPLC on silica gel.

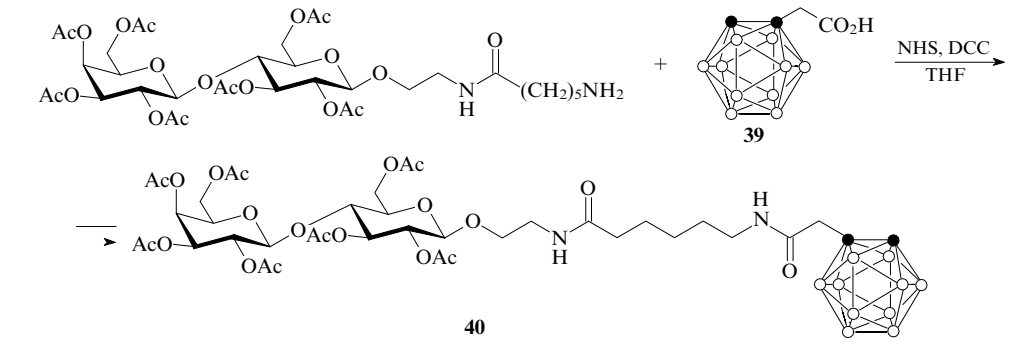


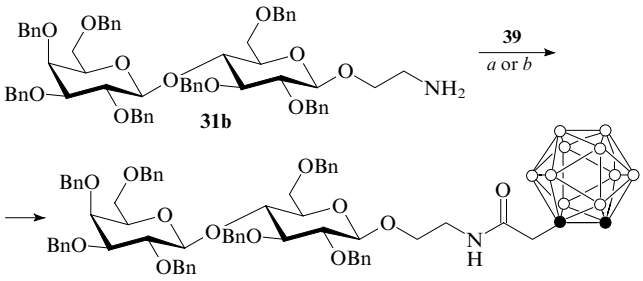
(*a*) NHS, DCC, THF.

Similar approach afforded lactose conjugate **40** containing longer spacer between the carborane and carbohydrate fragments in 32% yield (Scheme 3).

Later, lactose conjugate **31b** was also prepared[29] starting from carboranylacetic acid using NHS–DCC system or DMT-MM as the condensing agents; however, the yields of the product were moderate.

Scheme 3





(*a*) NHS, DCC, THF (15%); (*b*) DMT-MM, MeOH (7%).

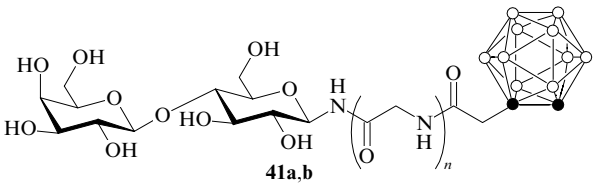
Recently,[32] five carborane–carbohydrate conjugates **41**–**44** comprising spacers of different nature have been synthesised starting from lactose derivatives and carboranylacetic acid (**39**). The NHS–DCC system was used as the condensing agent.

d. Miscellaneous carborane derivatives

Starting from (2-azidoethyl)-*ortho*-carborane (**45**) and glucose pentaacetate, conjugate **46** was synthesised containing both a carbohydrate and an amino acid residue (Scheme 4).[33]

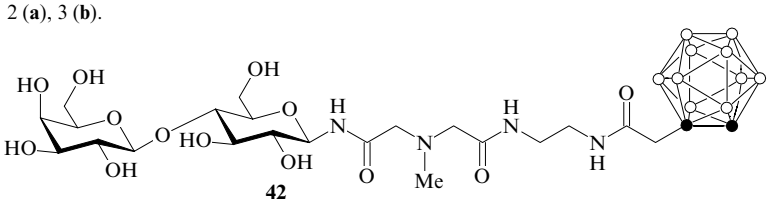
One-pot reaction of amino derivative of *ortho*-carborane **47** prepared from azide **45** with cyanuric chloride in the presence of diisopropylethylamine (DIEA) afforded triazine compound **48** in a total yield of 85%. Compound **48** was further treated with β-D-glucopyranoside **49** in the presence of DIEA in THF. Disubstituted triazine **50** was coupled with protected cysteine giving the target product in high yield.

Lactose was also used as a sugar component in this synthesis. In this case, yields in all steps were somewhat lower, *viz*., 41%, in glycosylation, 60% in the step of conjugate formation with mono-substituted triazine and 70% in the coupling with cysteine.

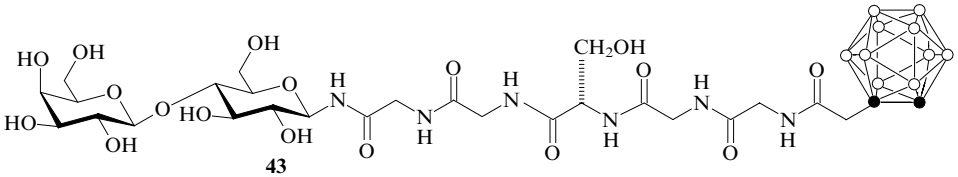


41a,**b**

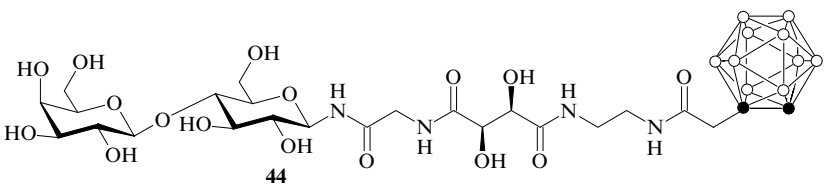
n = 2 (**a**), 3 (**b**).



42

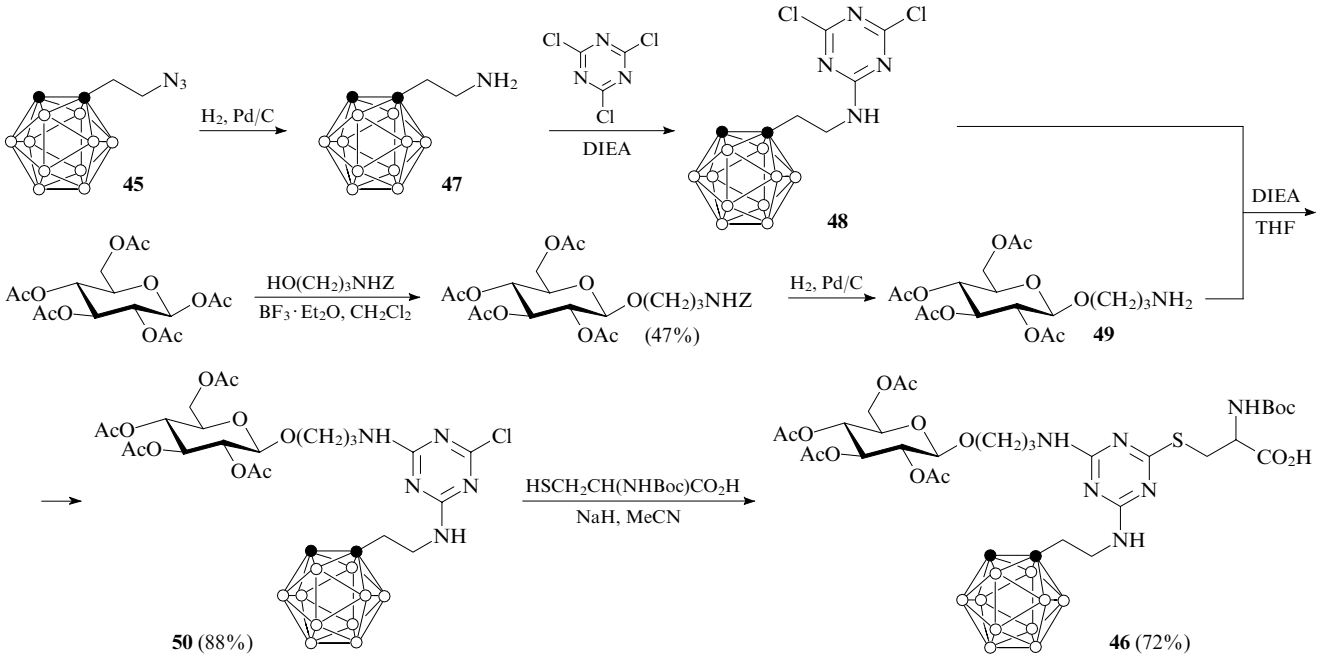


43

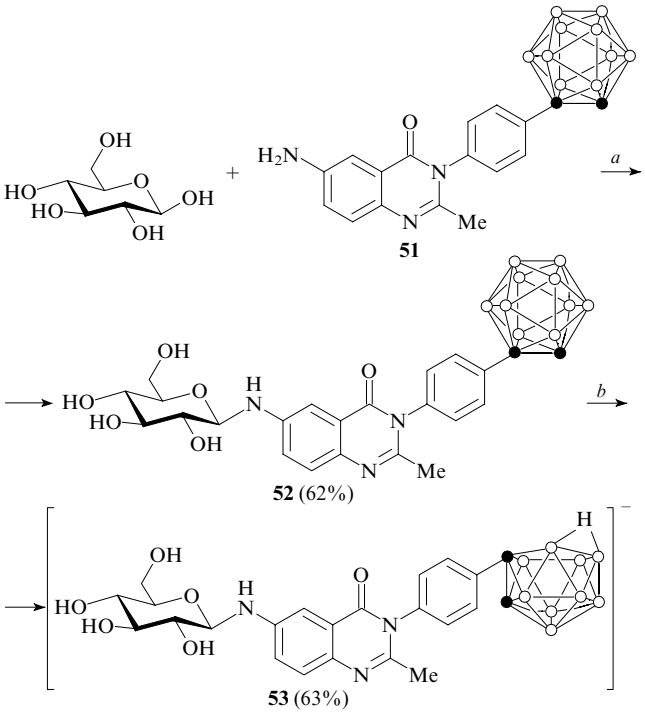


44

Scheme 4



Carborane derivative **51** having free amino group was used to prepare carborane conjugates with glucose.[34]

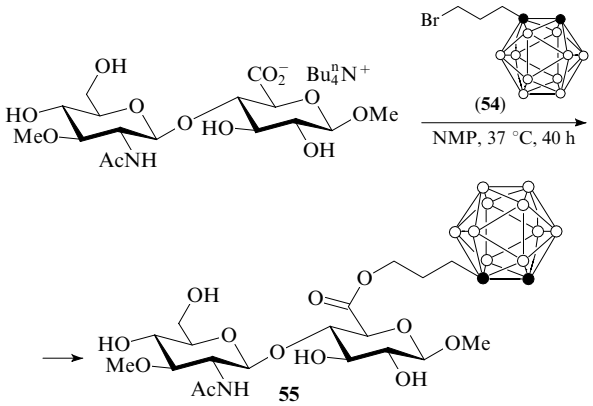


(*a*) AcOH (cat.), MeOH, reflux, 2 h;
(*b*) 1) pyrrolidine, 25 °C, 20 min; 2) Dowex 50 × 8-100 (Na^+), H_2O, 25 °C.

To increase its solubility in water, conjugate **52** was converted into *nido*-carborane conjugate **53**.

Similar reaction sequence was carried out with ribose. The yields in the glycosylation and deboronation steps were 69% and 72%, respectively.

3-Bromopropyl-*o*-carborane (**54**) was used as the starting compound in the synthesis[35] of conjugate **55** (unfortunately, the yield of the target conjugate was not reported).

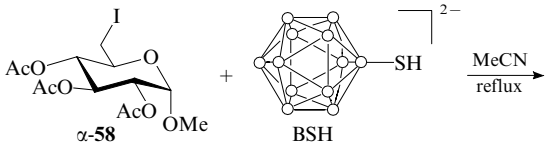


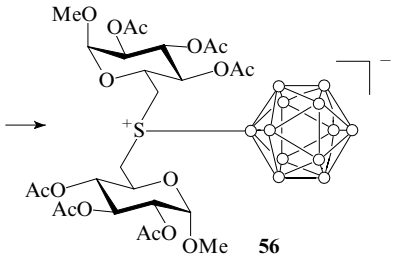
NMP is *N*-methylpyrrolidone .

III. Dodecaborate – carbohydrate conjugates

To date, only a few papers report syntheses of carbohydrate conjugates with the dodecaborate anion. Most synthetic schemes include alkylation of sodium mercapto-*closo*-dodecaborate (BSH) with different carbohydrate halogen derivatives.

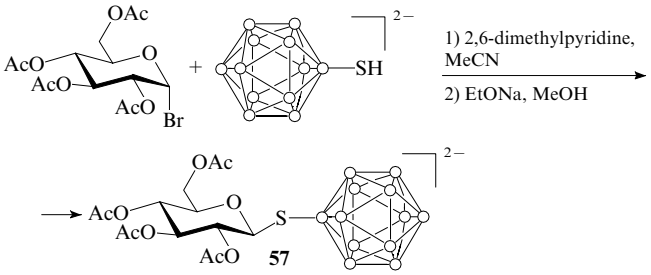
The first paper[17] dealing with the synthesis of dodecaborate – carbohydrate conjugates presented synthetic schemes for obtaining compounds **56** and **57**. However, data on the yields and the reaction conditions were absent. Conjugate **56** was prepared starting from iodo derivative of methyl α-glucoside α-**58**.





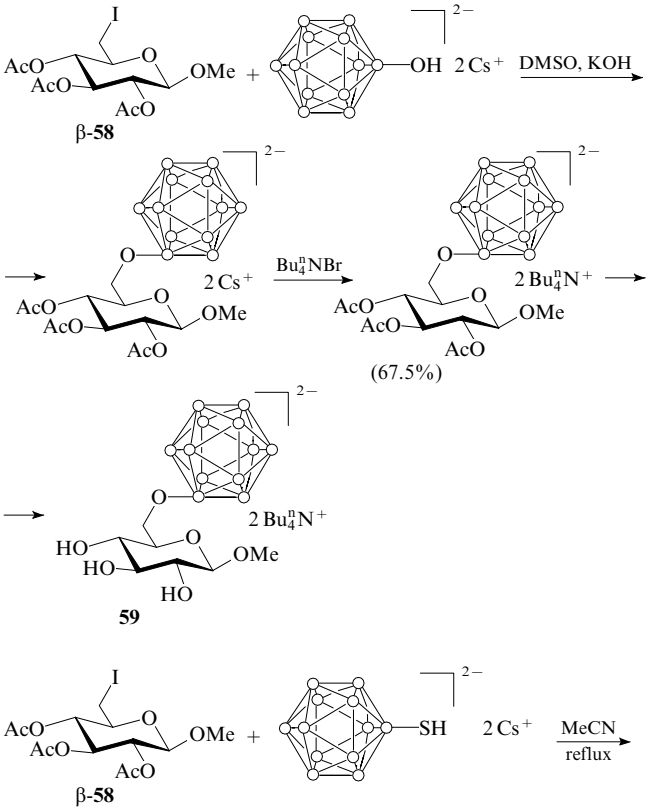
56

Later, the same research group described the synthesis of three dodecaborate conjugates with glucose, galactose and mannose in more detail.[18] The reaction for glucose is schematically represented below. The authors note that purification of the product is not a trivial task. The best results were achieved with the use of ion-pair chromatography, however, the yields were not indicated.



57

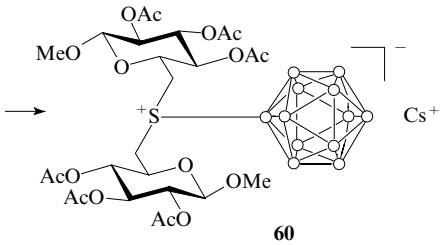
Preparation of two more dodecaborate-containing methyl glucosides (**59** and **60**) starting from β-isomer **58** was reported.[19] The synthetic sequence includes three steps: conjugate formation itself, counter-ion exchange and deacetylation (the yield in the latter step was not given).



β-**58**

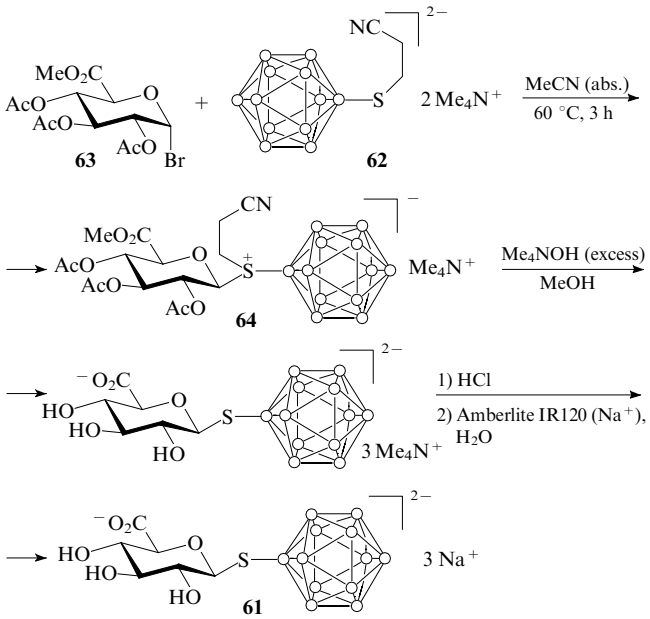
59

β-**58**



60

Dodecaborate–carbohydrate conjugate **61** comprising glucuronic acid as the carbohydrate fragment was synthesised[20] in 2005. The authors used 2-cyanoethyl protection of the sulfur atom of BSH to avoid its additional glycosylation. The first step was glycosylation of protected BSH **62** with methyl (glucopyranosyl bromide)uronate (**63**); β-anomer of conjugate **64** was exclusively formed. Following S- and O-deprotection, the toxic cations Me_4N^+ were replaced by cations Na^+ (the product was intended for biological studies). Unfortunately, the yields of neither intermediate, nor the target products were indicated.

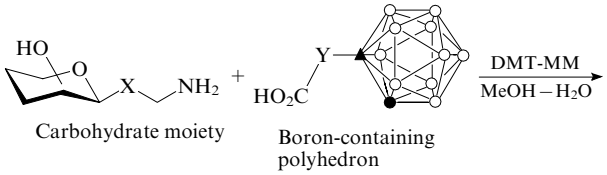


63 **62** **64** **61**

General concerns in preparing dodecaborate–carbohydrate conjugates are non-trivial deprotection and difficulties in purification of the target conjugates.

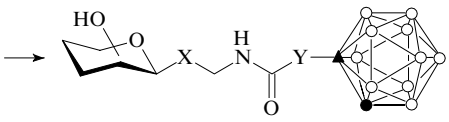
IV. A unified approach to the synthesis of conjugates of polyhedral boron compounds with carbohydrates

In 2006, a unified approach to the synthesis of carbohydrate conjugates with both carboranes and dodecaborate anion was suggested.[22] This approach can be illustrated by the general scheme below.



Carbohydrate moiety

Boron-containing polyhedron

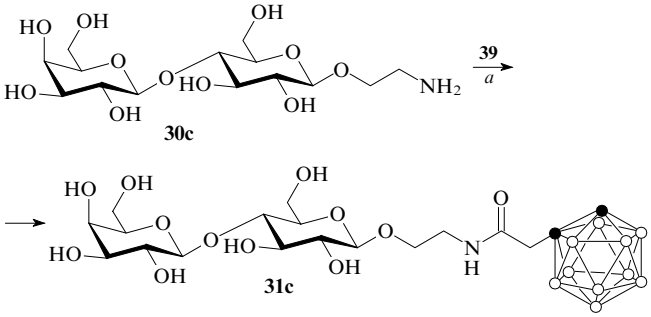


X, Y are spacers; ○ is BH, ● is BH or CH, ▲ is B or C.

Unprotected oligosaccharide derivatives which contain an amino group in the aglycon can be coupled with polyhedral boron carboxylic derivatives using DMT-MM as the condensation agent.

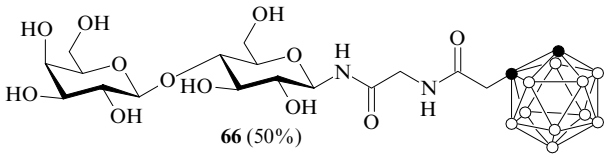
This approach was approved with *O*- and *N*-lactosides, which points to its feasibility not only for synthetic glycosides, but also for oligosaccharides isolated from natural sources, since the latter can easily be converted into glycosylamines and further, to *N*-glycosides containing an amino group in the aglycon.[36, 37]

Formation of a conjugate of carboranylacetic acid (**39**) with unprotected 2-aminoethyl lactoside **30c** was described somewhat earlier.[29] Product **31c** was isolated in 75% yield using reversed-phase chromatography.



(*a*) DMT-MM, MeOH – H_2O, 20 h.

Starting from *N*-glycyl-β-lactosylamine (**65**) as the carbohydrate component, conjugate **66** was obtained under similar conditions.[38]



The same method afforded the dodecaborate conjugate **67** in 57% yield (Scheme 5).[21]

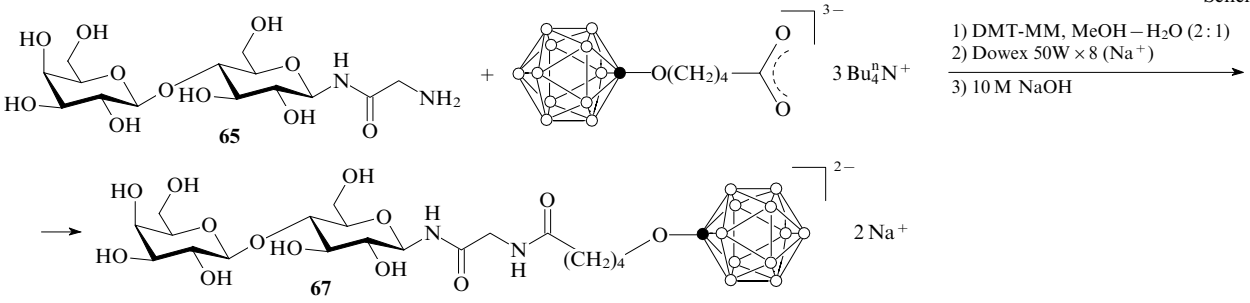
It is to be emphasised that the approach proposed does not require the protection of hydroxy groups of lactose. It is particularly advantageous in the case of dodecaborate conjugates where deprotection often constitutes a rather complicated task (*cf.* Ref. 20).

V. Conjugates of carbohydrates with miscellaneous polyhedral boron compounds

As early as in 1976, the synthesis of three conjugates of glucose with substituted decaborate anion was described[39] (Scheme 6).

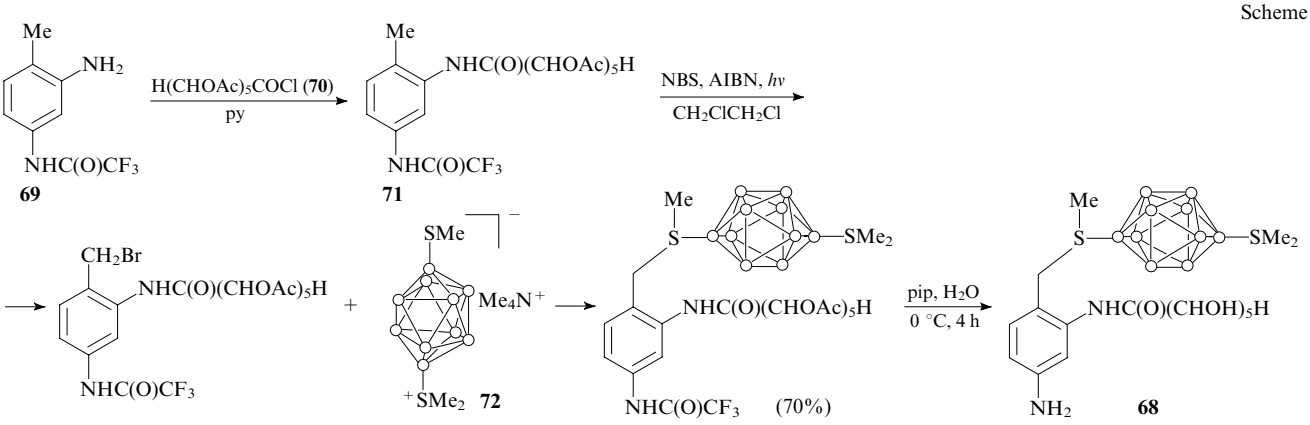
The synthesis of compound **68** started with the reaction of *o*-toluidine derivative **69** with 2,3,4,5,6-penta-*O*-acetyl-(*R*)-gluconyl chloride (**70**) in pyridine. Product **71** was brominated, and the bromo-derivative reacted with the substituted decaborate salt **72**. Hydrolytic removal of acetyl and trifluoroacetyl groups gave the target product **68**. According to the same scheme, conjugates containing isothiocyanate or carboxy group instead of the amino group were obtained.

Scheme 5



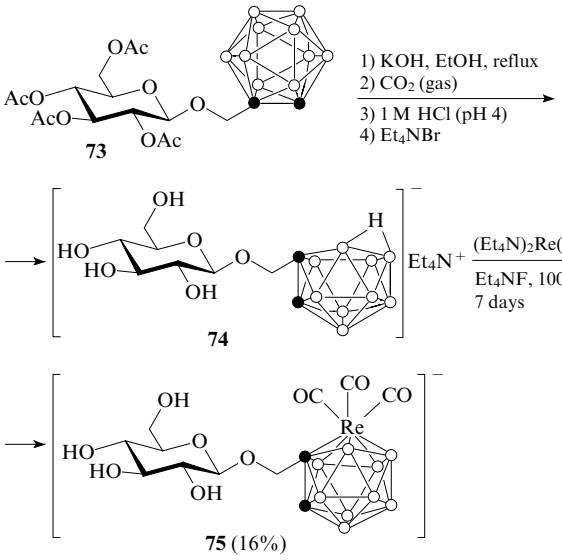
○ is BH, ●is B.

Scheme 6



py is pyridine, NBS is *N*-bromosuccinimide, AIBN is 2,2′-azobis(isobutyronitrile) (initiator), pip is piperidine.

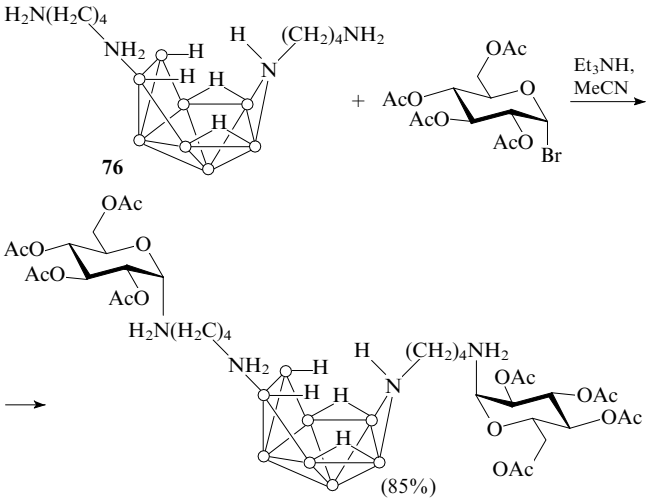
Synthesis of glucose a conjugate with *ortho*-Re(I)-metallacarborane was reported.[40] In the first step, the conjugate of acetylated glucose with *ortho*-carborane **73** was converted into the corresponding conjugate with *nido*-carborane **74**. Reaction of the latter with Re(I) complex gave rise to the target **75** in a low yield.



73 **74** **75** (16%)

Later, conjugate **75** was prepared under the action of microwave radiation.[41] This increased the yield almost twice (up to 31%).

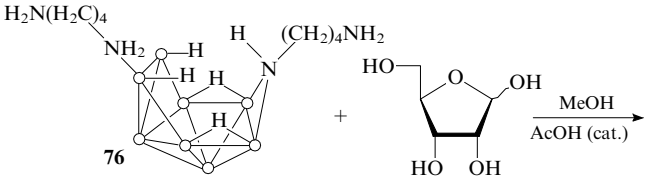
Three conjugates of azanonaborane with glucose, galactose and ribose have been described.[42] In the cases of galactose and glucose, the conjugates were prepared by the reaction of diamino derivative of azanonaborane **76** with glycosyl bromides:



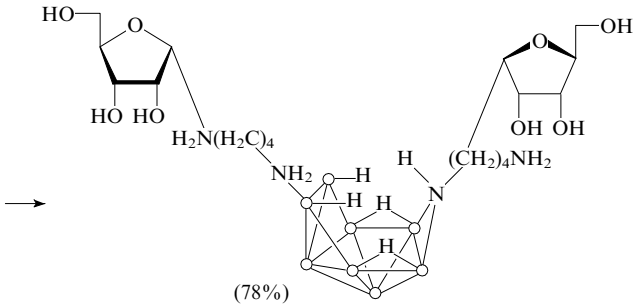
76 (85%)

The yield of conjugate with galactose was 87%.

In the case of ribose, diamino derivative of azanonaborane **76** reacted with unprotected carbohydrate in the presence of acetic acid as a catalyst.

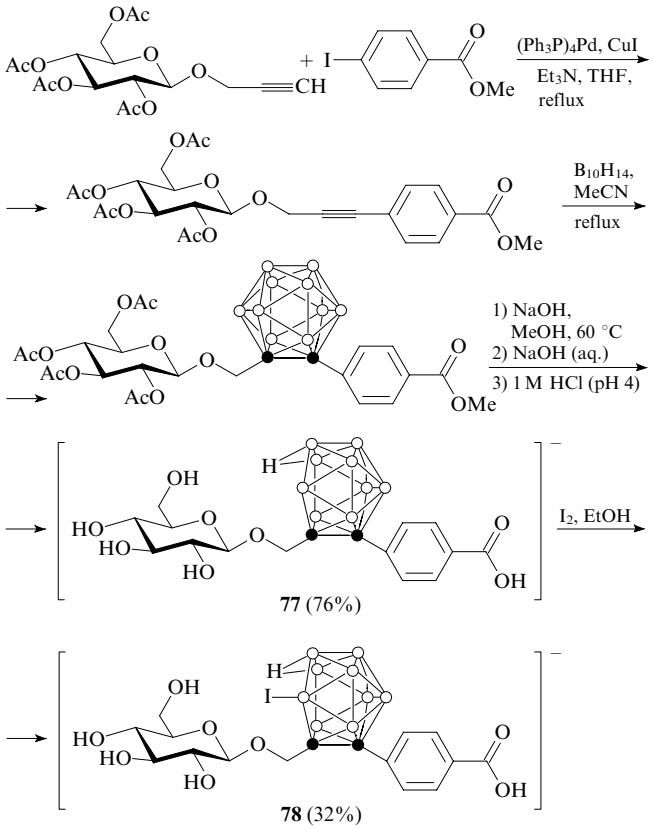


76



(78%)

Conjugates of glucose with *nido*-carborane (**77**) and iodo-*nido*-carborane (**78**) have been obtained.[43] Compound **77** was prepared from the *closo*-derivative **79** in an alkaline medium; acetyl protecting groups were removed simultaneously. Radioactive label ^{125}I was further introduced upon the action of iodine in ethanol.



77 (76%)

78 (32%)

VI. Biochemical properties of conjugates of polyhedral boron compounds with carbohydrates

Compounds with low cytotoxic effect that can be accumulated in tumour cells attract the largest interest as promising BNCT agents. Several studies report the results of biological *in vitro* tests of the obtained carborane–carbohydrate conjugates.[15, 24, 26, 34, 44] Many compounds studied possesseded quite low cytotoxicity together with good solubility in water (Table 1).

A potential BNCT agent must have several specific properties in addition to low cytotoxicity. First of all, these compounds should not penetrate cell membranes and accumulate in normal cells. At the same time, its accumulation on the surfase of malignant cells and further penetration inside. The ability of a series of carboranyl-

Table 1. Data on *in vitro* cytotoxicity of carborane–carbohydrate conjugates.

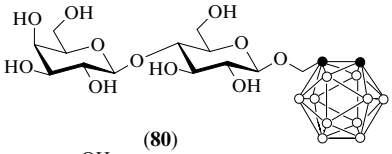
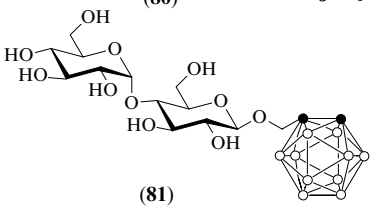
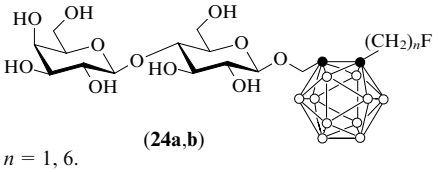
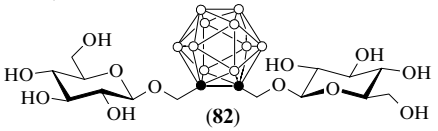
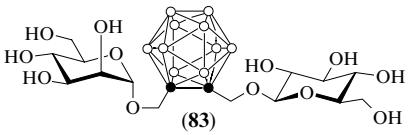
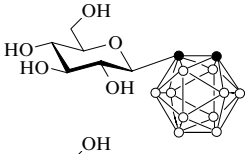
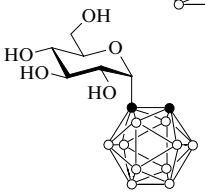
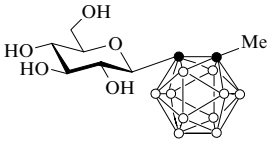
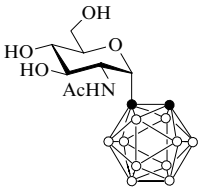
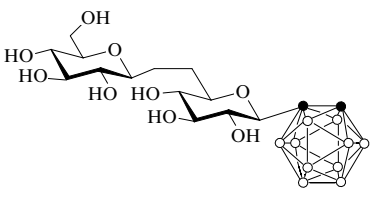
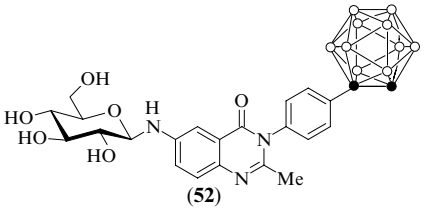
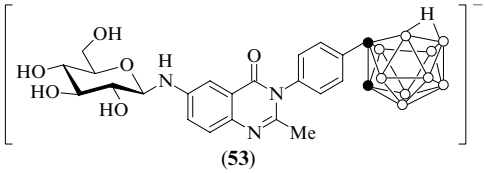
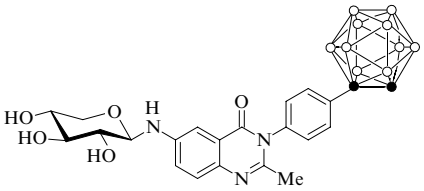
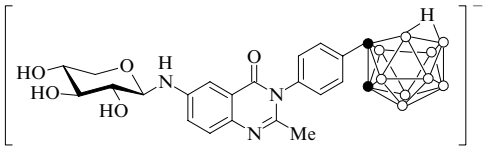
Conjugate	Malignant cell type	Cytotoxicity [a]	Ref.
 (**80**)	A549	0.40	15
 (**81**)	A549	0.40	15
 (**24a**,**b**) n = 1, 6.	A549	300	26
 (**82**)	A549	500	24
 (**83**)	A549	500	24
	A549, B-16, PancTu 1, LoVo	ED_{50} = 355–472	44
	A549, PancTu 1, LoVo	ED_{50} = 227–482	44
	A549, B-16, PancTu 1, LoVo	ED_{50} = 178–203	44
	A549, B-16, PancTu 1, LoVo	ED_{50} = 227–482	44
	A549, B-16, PancTu 1, LoVo	1100	44

Table 1 (continued).

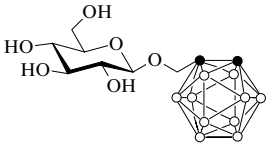
Conjugate	Malignant cell type	Cytotoxicity [a]	Ref.
 (**52**)	B-16	LD_{50} > 200 [b]	34
 (**53**)	B-16	300 [b]	34
	B-16	LD_{50} > 200 [b]	34
	B-16	300 [b]	34

Note. The following designations are used: A549 is the human bronchial carcinoma cell line, B-16 is the rat melanoma cell line, PancTu 1 is the human pancreatic carcinoma cell line, LoVo is the human colon adenocarcinoma cell line. [a] Either threshold concentration (in μmol litre^{-1}) of the compound below which it displays virtually no cytotoxic effect, or ED_{50} or LD_{50} values, are given; [b] in these cases, boron concentration is expressed in mg of boron per ml.

containing glycosides to accumulate in tumour cells B-16 was studied [24, 25] (Table 2). Boron concentration was determined using inductively coupled plasma atomic emission spectroscopy (ICP-AES). It is to be noted that conjugate **81** manifested better results than 4-dihydroxyborylphenylalanine currently used in medical practice.

It was found [46] that carborane–carbohydrate conjugates, due to their amphiphilic nature, in aqueous solution are embedded into double layer of liposomes consisting of lipids, DOTAP, *N*-[1-(2,3-dioleoyloxypropyl)-*N*,*N*,*N*-trimethylammonium]methyl sulfate and DOPE, 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine. Further studies [47] on the structure and properties of the resulting aggregates by small-angle X-ray and neutron scattering revealed the possibility of their use as BNCT agents in treatment of oncologic diseases.

Table 2. Data on *in vitro* uptake of carborane–carbohydrate conjugates in the B-16 rat melanoma cells.[24, 45]

Conjugate	Boron concentration, 6×10^6 g per 10^7 cells		
	3 h	12 h	24 h
	11.2	8.5	9.0
80	11.7	13.2	13.5
81	6.1	10.5	20.0
82	see [a]	0.72	see [a]
83	0.48	0.69	see [a]

[a] Boron concentration appeared to be below the detection limit of ICP-AES method.

* * *

The data surveyed present clear evidence of importance of conjugates of polyhedral boron compounds with carbohydrates as potential BNCT agents. Quite simple and robust synthetic approaches have been developed. They allow production of wide arrays of conjugates by varying the sugar moieties and spacers. The aim of further research is selection of conjugates most suitable for the use in medicine.

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