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Synthesis of conjugates of polyhedral boron hydrides with nucleosides †

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Methods of synthesis of the conjugates of polyhedral boron hydrides with natural and non-natural nucleosides are overviewed. These conjugates are of interest for their potential pharmaceutical use. Main synthetic approaches toward nucleosides based on 12-vertex *closo*-carboranes ($C_2B_{10}H_{12}$), 11-vertex *nido*-carboranes ($[C_2B_9H_{11}]^-$), metallacarboranes [cobalt and iron bis(1,2-dicarbollides)] or *closo*-dodecaborates ($[B_{12}H_{12}]^{2-}$) are described including modifications of nucleoside at nucleobase and sugar units.
The bibliography includes 98 references.

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I. Introduction

In recent years, an appreciable rise of interest in boron-containing nucleosides has taken place in the context of practical aspects of their applications. Nucleosides are the major low-molecular-weight building blocks of ribonucleic acids (RNAs) and deoxyribonucleic acids (DNAs) and perform an important role in biological processes. Thus they and their derivatives are widely used as therapeutic agents.[1] Eight canonical nucleosides are currently known (Fig. 1). Diverse derivatives of nucleosides are of interest as potential therapeutic agents. They can also appear useful for studying the structure and functions of nucleic acids and internucleotide and protein – nucleic acid interactions. A search for efficient antiviral and antitumour agents suggests modifying nucleoside structures. Boron-containing nucleosides are a very promising modification of these natural compounds. The derivatives that contain both boron polyhedra and nucleosides are of great interest and can potentially find wide use in biology and medicine.[2,3] Initially, boron-containing nucleosides were regarded as potential agents for boron neutron capture therapy (BNCT) of cancer,[4–6] where nucleosides served as the transport component capable of selectively piling-up in tumour cells and then transforming into the DNA and RNA nucleotides of proliferating cells. Boron-containing precursors of nucleic acids (nucleosides) provide for the selective delivery and accumulation of ^{10}B directly in the nucleus of a cancer cell to considerably enhance the damaging effect of fission products and decrease the required therapeutic dose of the agent.[7–11]

At the same time, modifying of biomolecules by a boron unit can appreciably affect the biological properties of

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† Dedicated to Academician O.M.Nefedov on the occasion of his 85th birthday.

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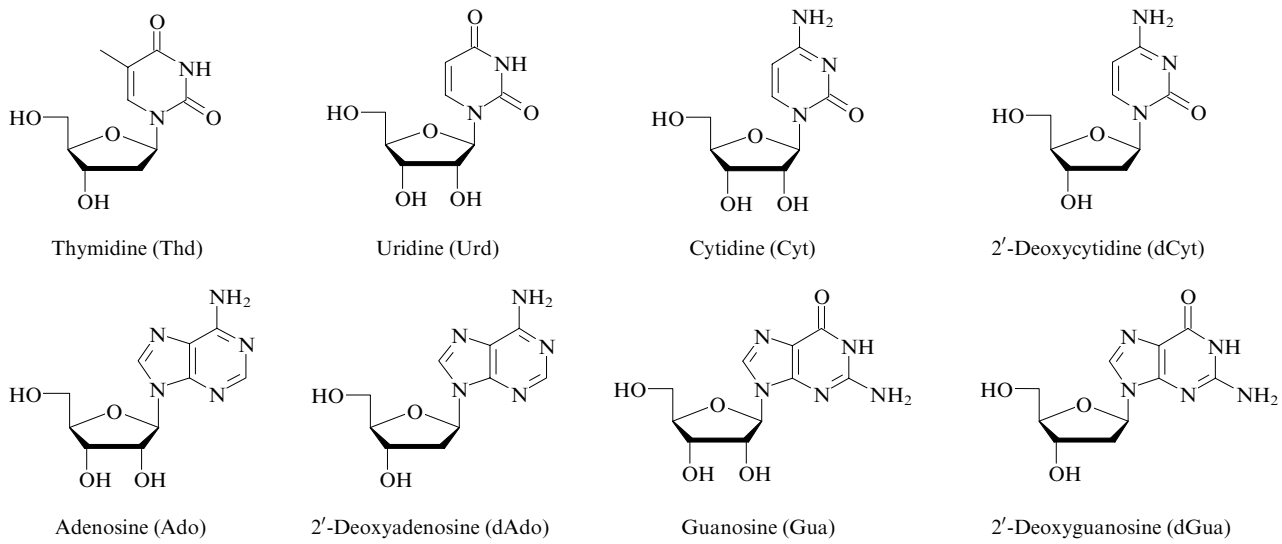


Figure 1. 'Canonical' nucleoside structures.

biomolecules. There are various types of boron clusters useful for preparing BNCT agents. The boron polyhedra considered in this review are shown in Fig. 2.

Recently, however, boron-containing nucleosides have found some other applications, like antiviral agents, antisense RNA agents, diagnostic probes for genetic diseases, lipophilic pharmacophores, and electrochemical and IR labels. All these applications have been described thoroughly and in detail in a number of reviews.[12–16]

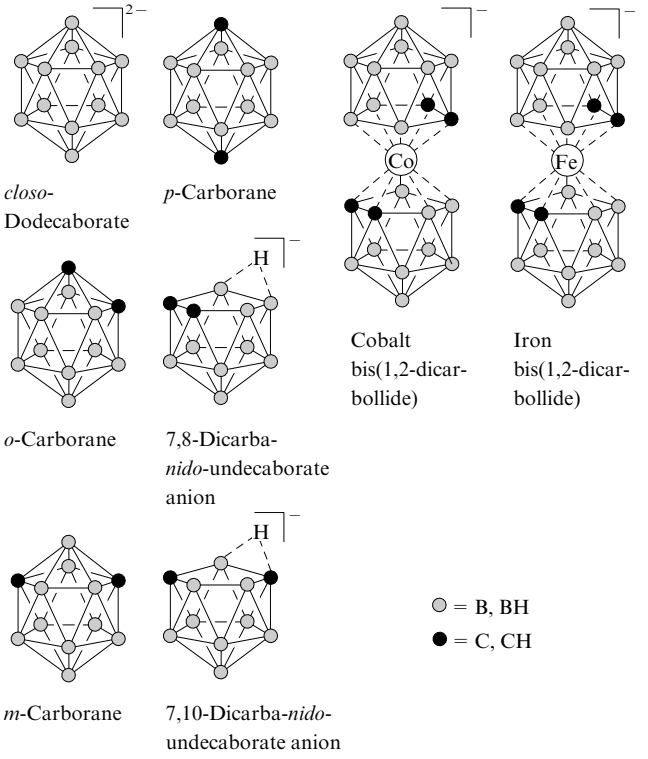


Figure 2. Polyhedral boron hydrides to be a part of conjugates with nucleosides.

There are reviews on the preparation of boron-containing nucleosides,[2,3] focusing either on the conjugates that contain one boron atom in the structure, or on the preparation and application of boron-containing thymidine derivatives and their N(3)-modified analogues.[9,11]

Studies into the preparation of new compounds are initiated by the need for modifying some parameters of materials.[17] In the case of boron-containing nucleosides, modification can be achieved *via* varying either constituents of a biologically active molecule, or the structure and electronic properties of the boron cluster. Many studies are now underway in this field, as their results can soon be implemented in the design of various products, which can appear to be useful pharmaceuticals or reagents for biochemistry, molecular biology or medical diagnosis. Their results are published in tens of scientific journals, so there is an avalanche rise in the number of review articles that systematize the results of studies into the chemistry of boron-containing nucleosides. However, despite the diversity of reviews on the topic, they yet do not systematize approaches to the preparation of boron-containing nucleosides, but rather focus on the use of these compounds.

Over the past decades, enough facts have been accumulated in favour of the fundamental and applied importance of boron-containing nucleosides. In this context, the systematics, studies of synthetic methods to prepare these compounds and critical comparison of their results are of particular importance. This review summarizes the publications concerning the synthetic methods for preparing conjugates of polyhedral boron hydrides with nucleosides. The review covers relevant papers published over the period from 2000 to the beginning of 2016, but some earlier works will also be cited. We describe approaches towords the preparation of boron-containing nucleosides and their derivatives modified both at the heterocyclic base and at the carbohydrate component.

The simplest boron unit in a nucleoside molecule is a single boron atom, which can be present in the compound as a dihydroxyboryl group $B(OH)_2$ (a structural analogue of a carboxy group),[18,19] a BOH group (an analogue of a carbonyl group) or borane complex NBH_2CN. These units

can be pending substituents on the periphery of a biomolecule[20–23] or enter nitrogen-containing heterocyclic moieties,[24,25] which determine the activity of the molecule.[26] Our review is concerned with the nucleosides modified with carboranes (*o*-, *m*- or *p*-carboranes), metallacarboranes [cobalt and iron bis(1,2-dicarbollides)] or *closo*-dodecaborate anions.

II. Conjugates with carboranes

The main types of boron-containing nucleosides are represented by carborane derivatives. A routine method of preparation of *o*-carboranes includes reaction of appropriate acetylenes with decaborane. This process requires the presence of a Lewis base (LB) to remove H_2 from $B_{10}H_{14}$ to yield $B_{10}H_{12}(LB)_2$. The dissociation of one LB unit from a $B_{10}H_{12}(LB)_2$ molecule yields intermediate $B_{10}H_{12}(LB)$, which then reacts with acetylene (A) to yield the complex $B_{10}H_{12}A(LB)$. The subsequent elimination of LB and H_2 generates carborane $C_2B_{10}H_{12}$ (Scheme 1).[27]

Scheme 1

$$B_{10}H_{14} + 2\,LB \longrightarrow B_{10}H_{12}(LB)_2 + H_2$$

$$B_{10}H_{12}(LB)_2 \longrightarrow B_{10}H_{12}(LB) + LB$$

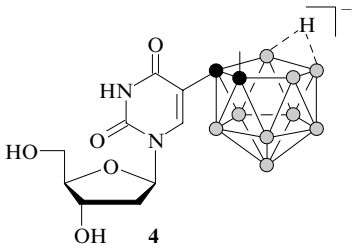
$$B_{10}H_{12}(LB) + A \longrightarrow B_{10}H_{12}A(LB)$$

$$B_{10}H_{12}A(LB) \longrightarrow \text{carborane} + LB + H_2$$

The first example of carborane–nucleoside conjugate, 5-(1-*o*-carboranyl)-2′-deoxyuridine (CDU, **1a**), was prepared by Yamamoto *et al.*[28] using the above-described method. The reaction of 3′,5′-bis(*O*-benzoyl)-5-ethynyl-2′-deoxyuridine (**2a**) with decaborane ($B_{10}H_{14}$) in the presence of Lewis acid (LA), followed by removal of benzoyl groups in intermediate **3a**, affords product **1a** (Scheme 2).

The same method was employed to prepare the *nido* form of 5-(1-*o*-carboranyl)-2′-deoxyuridine (**4**) and uridine derivatives with *o*-carborane: 5-carboranyluridine (**1b**) and 5-hydroxymethylcarboranyluridine (**1c**) (see Scheme 2).[28]

Structure 4

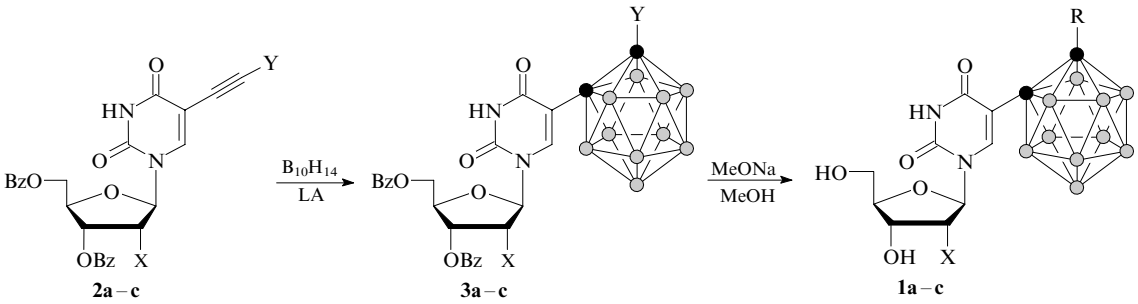


4

Although this reaction between acetylenes and decaborane is well studied, the Yamamoto's team studied the role of Lewis bases in reactions of compound (**2b**) with acetylenes.[29] The researchers found that the reaction times were considerably shorter when the Lewis base was Et_2S or PPh_3, but observed no gain in the yield of the desired compound. When propionitrile was added to acetylene **2b** and decaborane under an argon atmosphere, however, the product yield increased appreciably. Refluxing of the mixture for 18 h yields 2′,3′,5′-tris(*O*-benzoyl)-5-carboranyluridine (**3b**). After the benzoyl group is removed, derivative **1b** is generated in 83% yield. For compound **2c**, the use of Et_2S provides the best yield of product **3c** (40%).[29] The subsequent removal of protecting group yields derivative **1c**. Thus, the product yield depends on the choice of Lewis base at the boration stage. The best yields are observed for terminal acetylenes. However, phenylacetylene derivative **2** (X = OBz, Y = Ph) does not react with decaborane in the presence of EtCN or Et_2S.

The same ppaper[29] describes attempts to prepare an adenosine derivative of *o*-carborane (see Scheme 2). When compound **5** reacts with $B_{10}H_{14}$ in the presence of EtCN, protected product **6** is formed. The removal of acetyl groups from product **6** is accompanied by the dissociation of the C–N bond between the purine ring and the ribofuranosyl moiety, and this was the reason behind the failure of the preparation of an unprotected adenosine derivative with *o*-carborane.

Scheme 2



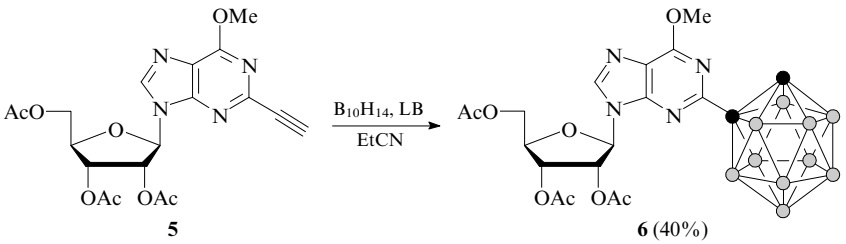
2a–c X = H, Y = H (**a**); X = OBz: Y = H (**b**), CH_2OAc (**c**)

$B_{10}H_{14}$, LA

3a–c X = H, Y = H (**a**, 74%); X = OBz: Y = H (**b**, 67%), CH_2OAc (**c**, 40%)

MeONa, MeOH

1a–c X = H, R = H (**a**, 91%); X = OH: R = H (**b**, 83%), CH_2OH (**c**, 89%)



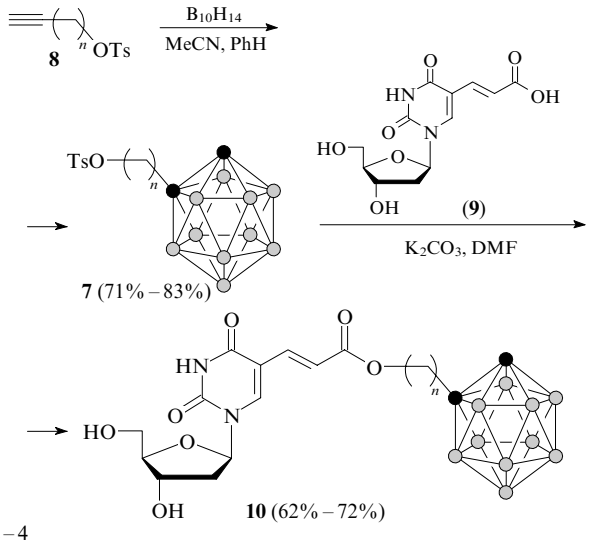
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$B_{10}H_{14}$, LB, EtCN

6 (40%)

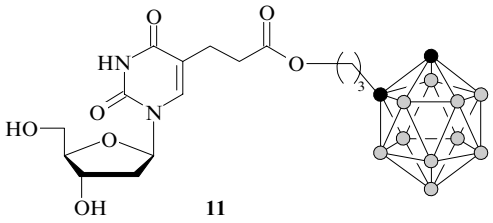
The very high intrinsic hydrophobicity of carboranes frequently leads to the water insolubility of biomolecules based on them, so various hydrophilic substituents should be introduced into the carborane cage. For example, a series of *o*-carborane derivatives with 5-substituted 2′-deoxyuridines linked through an ester linker were prepared to increase the water solubility of CDU analogues. The precursors were carboranylalkyl tosylates **7**, which can be prepared by boration of terminal acetylene tosylates **8** (Scheme 3, Ts = 4-$MeC_6H_4SO_2$). Strong bases are known to destroy the *o*-carborane cluster, thereby transforming the *closo* structure to the anionic *nido* structure.[30 – 32] Therefore, carborane tosylates **7** were reacted with nucleoside **9**[33] converted to an anionic form using K_2CO_3 to yield conjugates **10**. Further, Rong *et al.*[34] hydrogenated compound **9** over a palladium catalyst in methanol. The thus-prepared methyl ester was hydrolyzed to the acid, which was then used to prepare conjugate **11** (in 76% yield) as described in the earlier publication.[33]

Scheme 3



5-Substituted long-chain boron-containing nucleosides where the linker contains an amide group have also been prepared.[34] The preparation of these carboranes is complicated by the ability of amines to destroy the carborane cluster to transform it to the *nido* form. In view of this, two routes were proposed to prepare such compounds. One route comprises generating an amide by the cross-coupling of a nucleoside containing a carboxy group with an amino-substituted carborane. The other route comprises the preparation of a nucleoside containing an alkynylamide moiety, followed by its boration (Scheme 4).

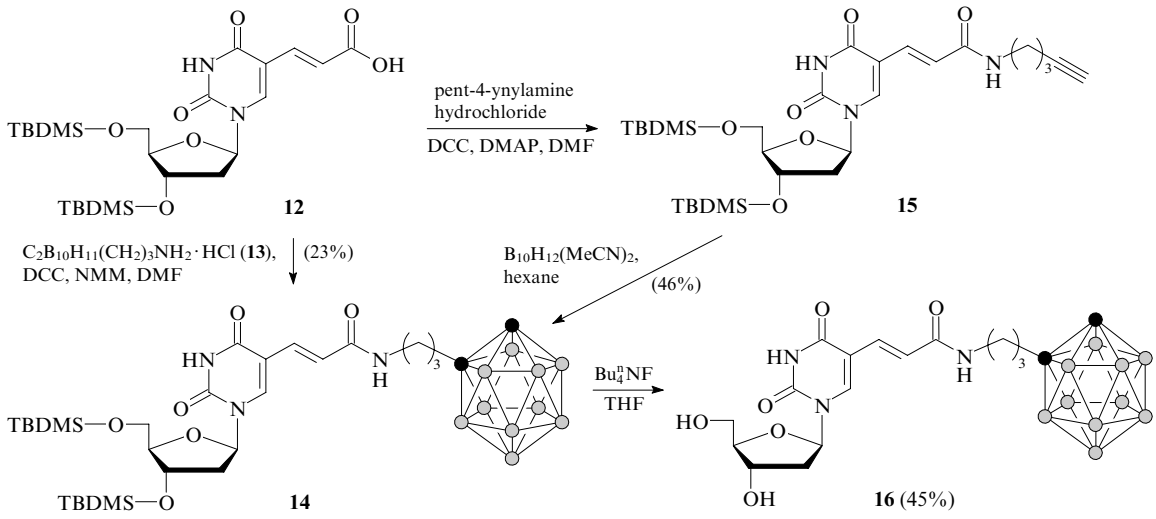
Structure 11



The first method yields compound **14** by the cross-coupling reaction of protected nucleoside **12** with 1-(3-aminopropyl)-*o*-carborane hydrochloride (**13**) in the presence of 1,4-dicyclohexylcarbodiimide (DCC) and 4-methylmorpholine (NMM).[34] However, this process yields the *nido* form as a minor product. In order to avoid the destruction of the carborane by the amino derivative and increase the yield of the desired product, the second method was employed to prepare compound **14** from nucleoside **15**, which contains an alkynylamide moiety. Nucleoside **15** was prepared by the cross-coupling of derivative **12** with pent-4-ynylamine hydrochloride in the presence of DCC and 4-dimethylaminopyridine (DMAP). The subsequent reaction of nucleoside **15** with a bisacetonitrile decaborane complex in hexane followed by desilylation yields product **16**. The second route is preferable, despite some degradation of the *o*-carborane species.

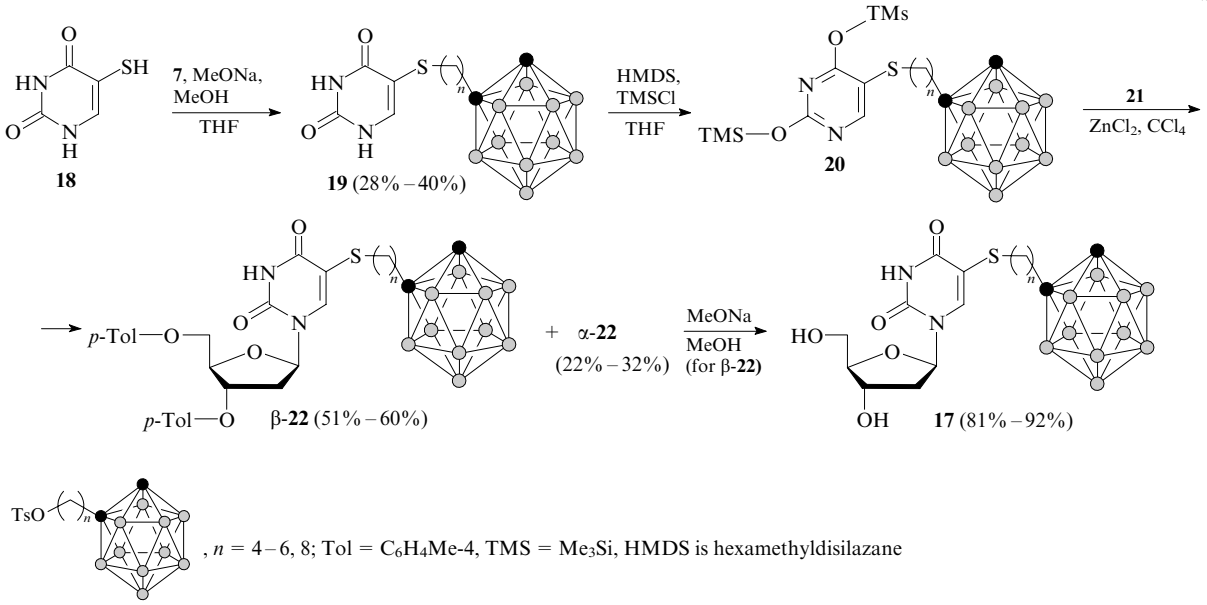
Examples of carboranylalkyl sulfanylpyrimidine nucleosides **17**, where the *o*-carborane is attached to uridine through a sulfur-containing linker, are also described in the literature (Scheme 5).[35] Tosylates **7** are prepared from alkynyl tosylates[36] and then react with 5-sulfanyluracil (**18**) in an argon atmosphere. To keep the carborane from

Scheme 4



TBDMS = Bu^tMe_2Si

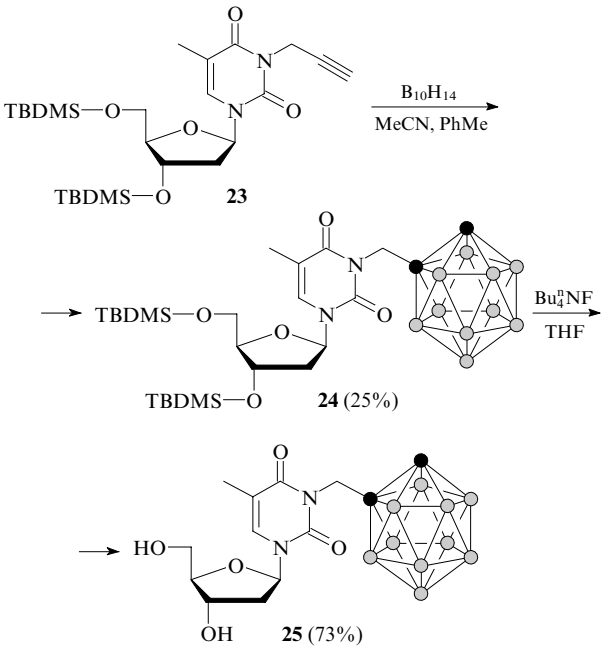
Scheme 5



oxidation during this reaction, 1 equiv. MeONa is used. The silylation of 5-S-alkylated sulfanyluracils **19** yields 2,4-disilylated pyrimidine intermediates **20**, which then react *in situ* with α-D-2-deoxy-3,5-di-*O*-*p*-tolylribofuranosyl chloride (**21**) in CCl_4 in the presence of $ZnCl_2$ to yield nucleosides **22**. The authors of that publication mention that the nucleophilic substitution of the chlorine atom in protected 2-deoxyribofuranosyl chloride **21** in the presence of a catalyst preferably yields nucleosides in the β-configuration (the ratio between the β- and α-anomers is 3 : 1 in the catalyzed reaction and 1 : 1 in the reaction without catalyst). The anomers are separated chromatographically; removal of protecting groups from the β-anomer yields product **17** (see Scheme 5).

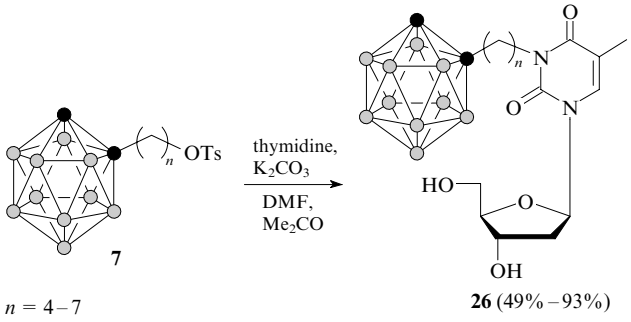
Strategies were developed to prepare various derivatives substituted at the thymidine N(3) atom. The reaction of protected thymidine **23** with a decaborane – acetonitrile complex in toluene yields product **24**. A relatively low yield of this compound (25%) is due to the steric hindrances arising in the course of the reaction involving the terminal triple bond and the bulky decaborane. The elimination of the *tert*-butyldimethylsilyl group in compound **24** affords 3-[(1-*o*-carboranyl)methyl]thymidine (**25**), where the linker consists of one methylene group (Scheme 6).[37]

Scheme 6



3-(*o*-Carboranylalkyl)thymidines **26** with four to seven methylene groups in the linker between the carborane and thymidine are prepared in one step from thymidine and proper tosylates **7** in the presence of K_2CO_3 (Scheme 7).[35] The decomposition of the *o*-carborane cluster is not observed under these conditions, and alkylation proceeds selectively at the N(3) atom.

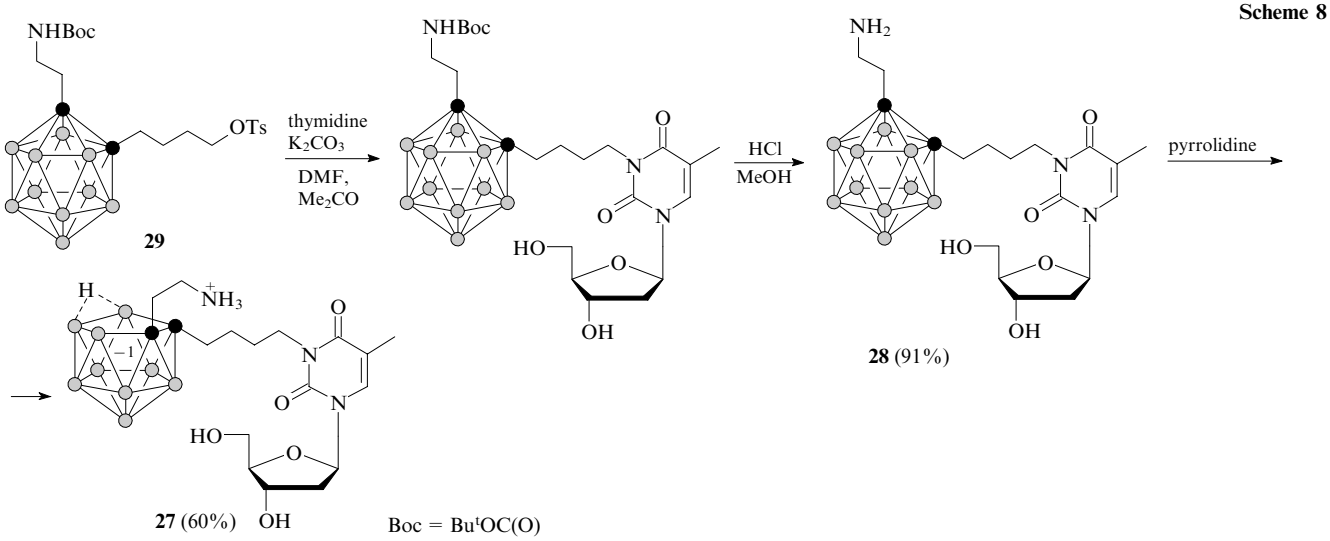
Scheme 7



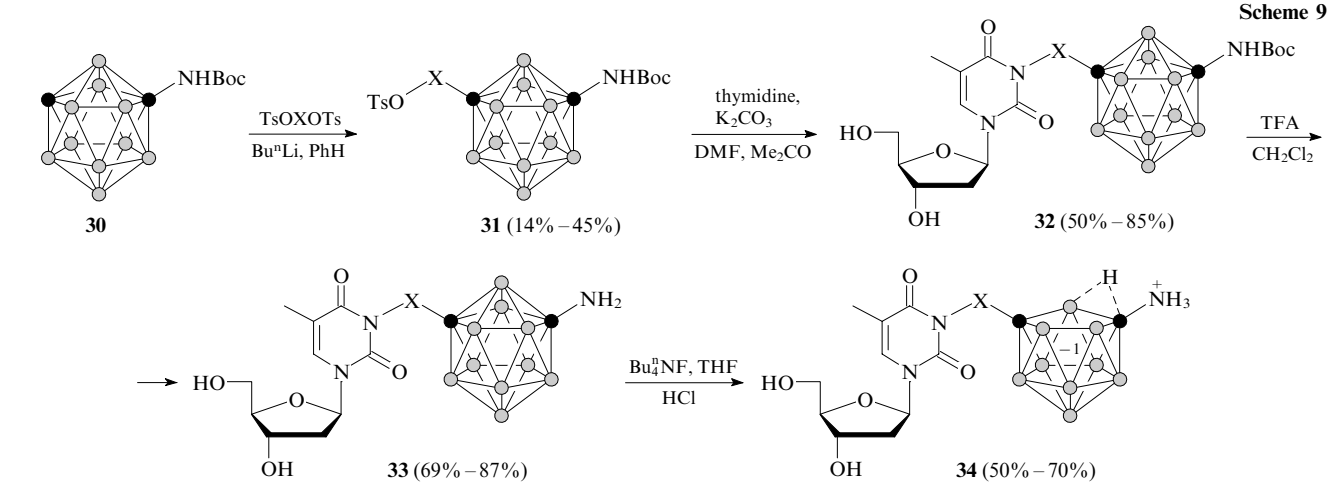
The zwitterion form of *nido*-*o*-carborane derivative **27** and its *closo* analogue **28** were also prepared (Scheme 8). The condensation of *o*-carborane **29** with thymidine in the presence of K_2CO_3 followed by removal of the Boc group in acid medium yields *closo* compound **28**, which is then converted to *nido* derivative **27** on treatment with pyrrolidine.[38]

The preparation of the zwitterion ammonium form of *nido*-*m*-carborane-containing thymidines is described (Scheme 9).[37] The alkylation of compound **30** by alkane-1,ω-diyl ditosylate or 3-oxapentane-1,5-diyl ditosylate in the presence of Bu^nLi in benzene yields *m*-carboranyl deriva-

Scheme 8



Scheme 9



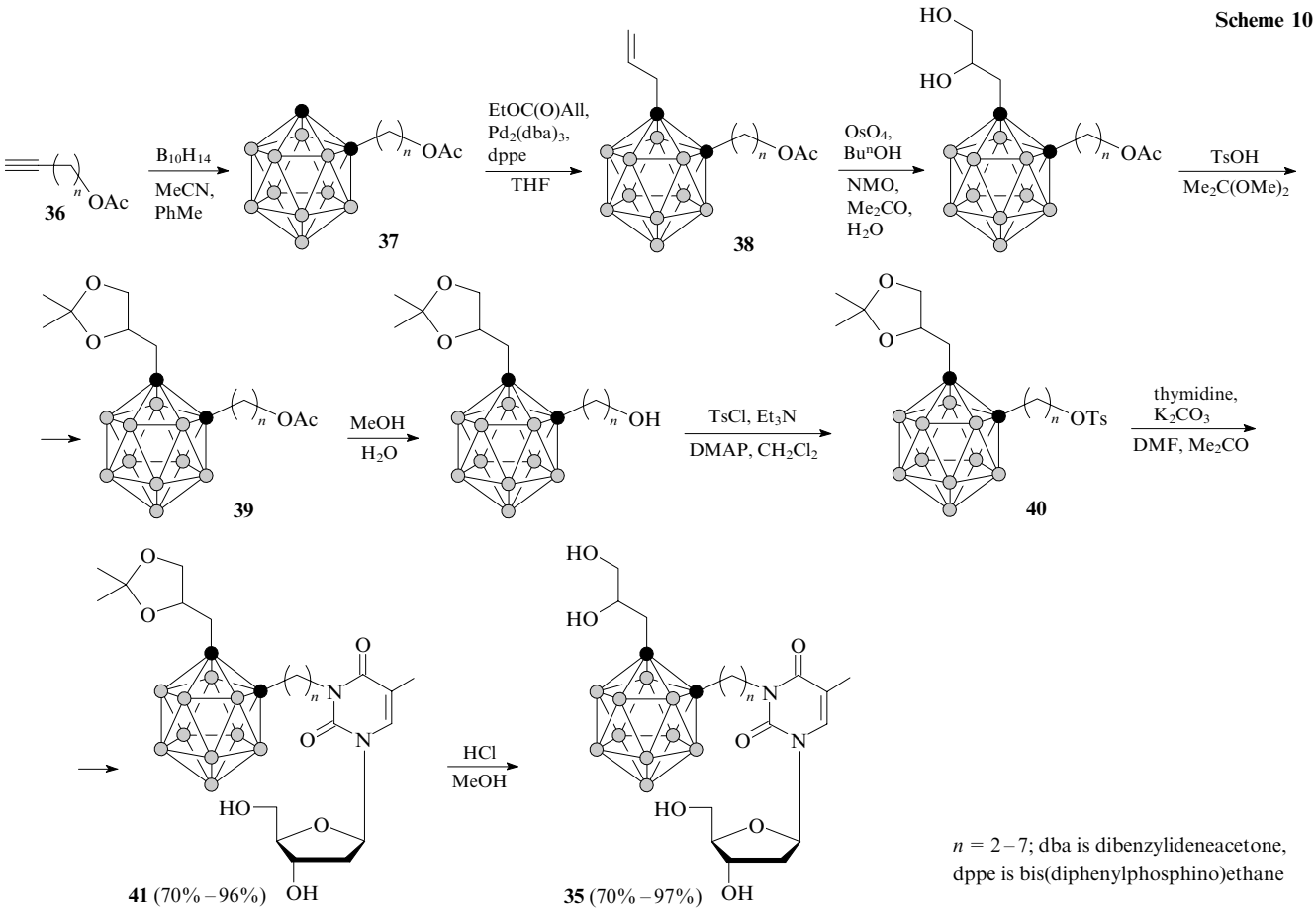
X = $(CH_2)_n$ (n = 2 – 6), $(CH_2)_2O(CH_2)_2$

tives **31**. The relatively low yield (14%) of the 3-oxapentane-1,5-diyl ditosylate derivative is likely to arise from both the electron-donating effect of the oxygen atom in the diethylene ether linker and the low solubility of the reagent in benzene. Temperatures below 10 °C and slow addition of a solution of the lithium salt of compound **30** to alkanediyl ditosylate in benzene are necessary conditions for increasing the yield of derivatives **31** and for suppressing the formation of side products. The subsequent condensation of compounds **31** with thymidine is carried out in the presence of K_2CO_3 to yield derivatives **32**. The *tert*-butoxycarbonyl group is eliminated by trifluoroacetic acid (TFA) to yield neutral *closo-m*-carboranyl thymidine analogues **33**; the treatment of the latter with Bu^n_4NF in THF and an acid yields zwitterion *nido-m*-carboranyl thymidines **34**.

As mentioned above, *o*-carboranyl deoxyuridine (**1a**, CDU) is poorly soluble in water. In laboratory animal experiments, 50% aqueous DMSO should be used; ~4% of the *closo*-carborane cluster in CDU degrades *in vitro* to *nido*-carborane, so dihydroxypropyl analogues of *o*-carboranyldeoxyuridine **35** were prepared (Scheme 10).[39] Alkynyl acetates **36** react with bis(acetonitrile) decaborane complex in toluene under reflux to yield carboranyl derivatives **37**, which yield compounds **38** upon palladium-catalyzed allylation. Then, the allyl groups in compounds **38** are dihydroxylated by OsO_4 and 4-methylmorpholine *N*-oxide (NMO). For inhibiting the undesired reactions during tosylation, isopropylidene-protected diols **39** are used to yield derivatives **40** upon deacylation and subsequent tosylation. The subsequent selective alkylation of thymidines at the N(3) atom yields compounds **41**; the alkylation of 3′- and 5′-hydroxy groups in the carbohydrate is not observed. After the isopropylidene protection is removed in acid medium, products **35** are formed.

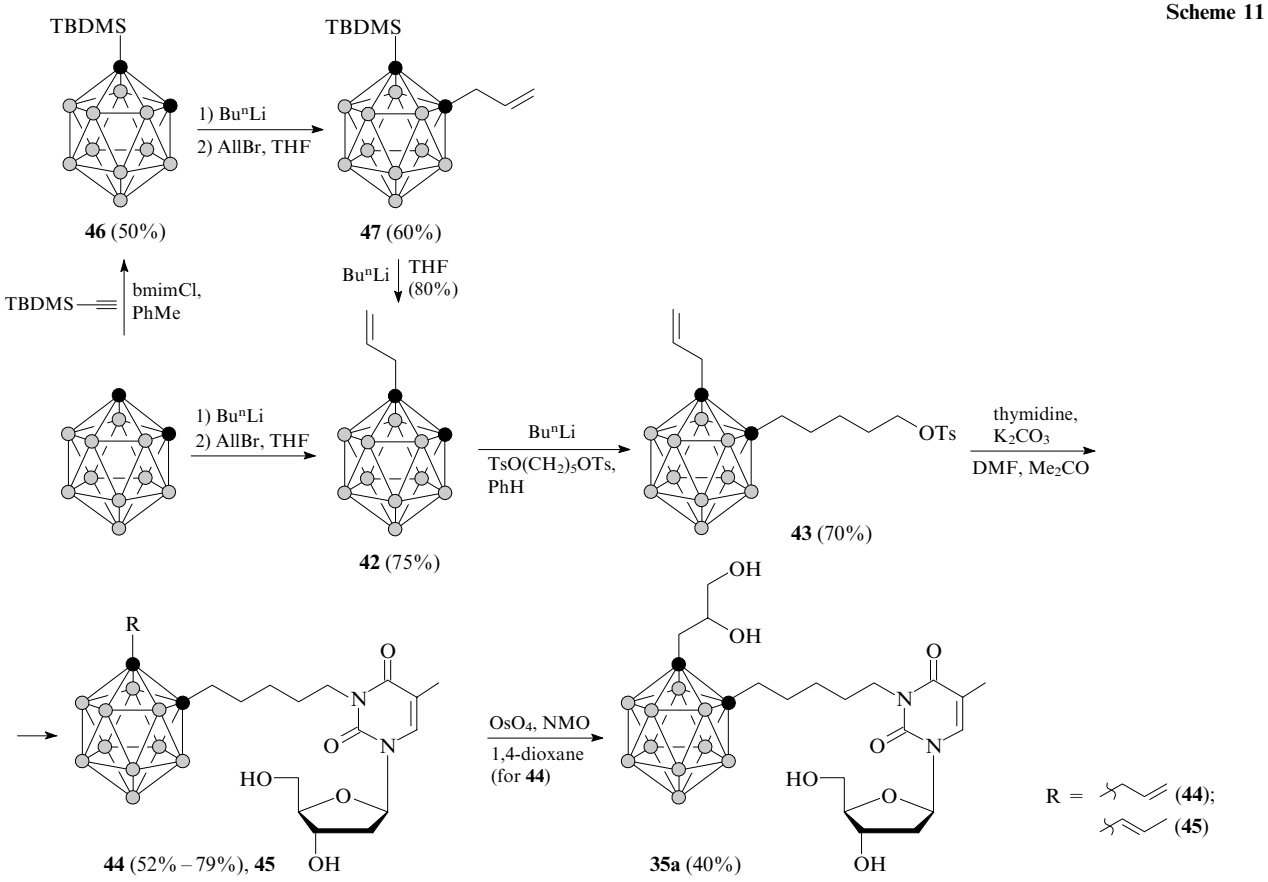
A similar compound was also derived from ^{10}B-enriched *o*-carborane. An improved strategy was developed to prepare product **35a** (n = 5) in four stages (Scheme 11).[40] First, the treatment of *o*-carborane by Bu^nLi yields a lithium salt of carborane, which then reacts with allyl bromide to yield compound **42**. Compound **42** is reacted with pentane-1,5-diyl ditosylate. For inhibiting disubstitution, the second synthesis stage comprises the dissolution of lithium carborane salt **42** in benzene, and the resulting solution is slowly added to a solution of $TsO(CH_2)_5OTs$ at 5 – 10 °C. Compound **43** is prepared in 70% yield under these conditions. The reaction of compound **43** with thymidine gives a

Scheme 10

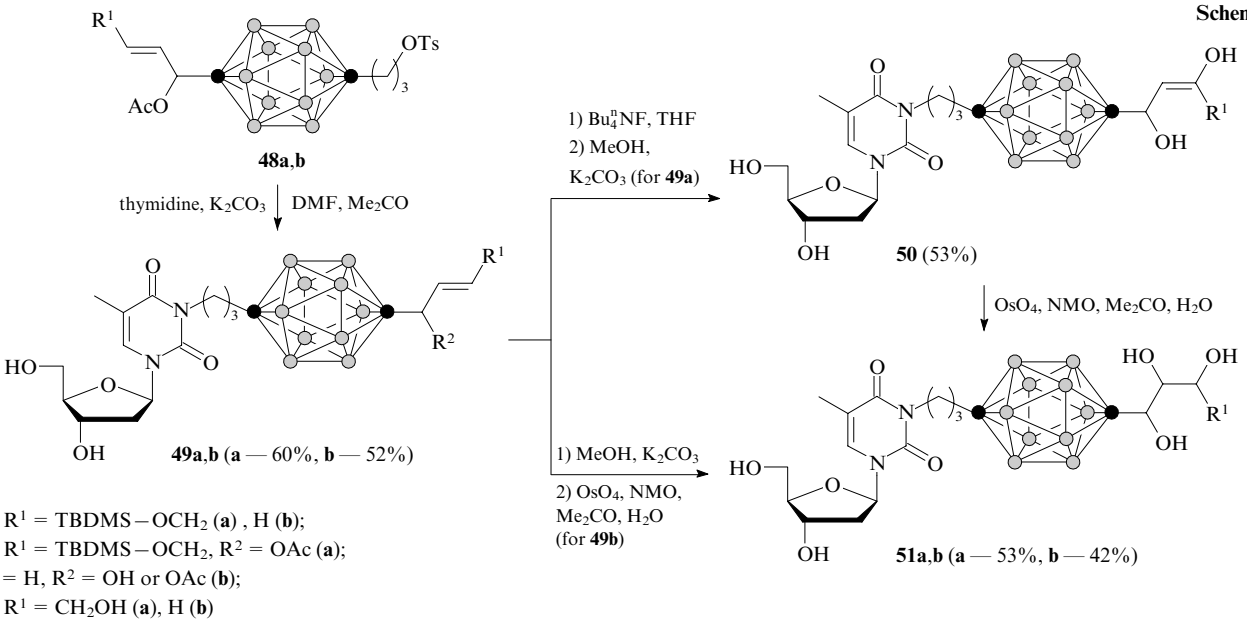


n = 2 – 7; dba is dibenzylideneacetone, dppe is bis(diphenylphosphino)ethane

Scheme 11



Scheme 12



48: R^1 = TBDMS–OCH_2 (**a**) , H (**b**);
49: R^1 = TBDMS–OCH_2, R^2 = OAc (**a**);
R^1 = H, R^2 = OH or OAc (**b**);
51: R^1 = CH_2OH (**a**), H (**b**)

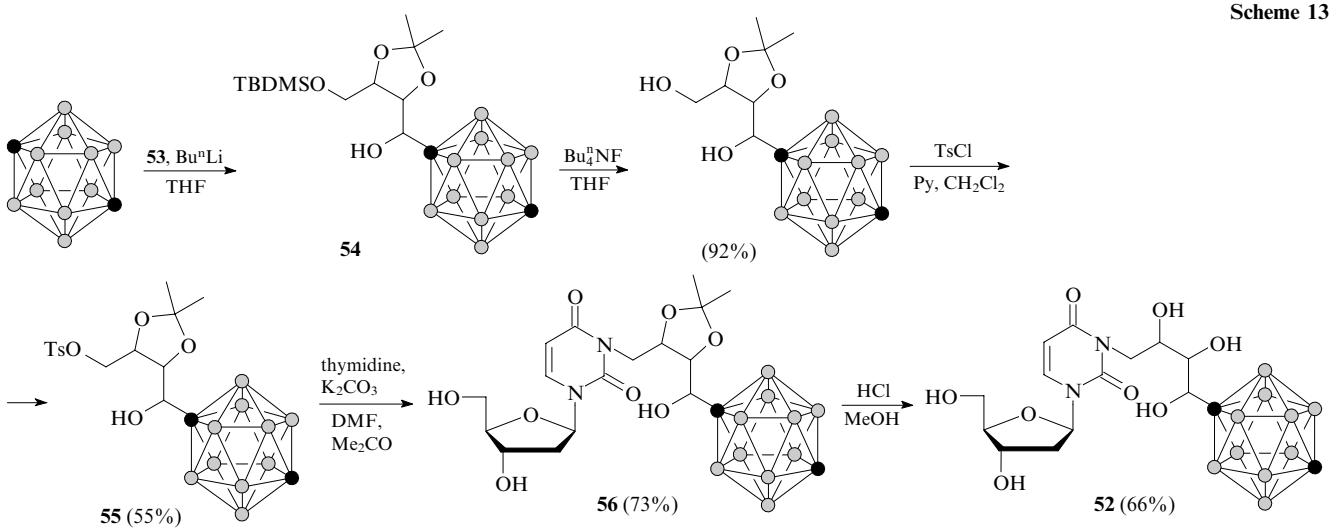
mixture of compound **44** and its isomer **45** (in the ratio 30 : 1). At a high temperature (50 °C) and the shortest reaction time (48 h), the ratio between product **44** and its isomer **45** is 1 : 1. When both products are treated with OsO_4 and 4-methylmorpholine *N*-oxide, only compound **44** is dihydroxylated to yield desired product **35a**. Isomer **45** is more resistant to hydroxylation due to the steric hindrances arising from the bulky *o*-carborane cluster.

Another route was proposed more recently to prepare compound **42** from ^{10}B-enriched decaborane using two-phase reaction conditions.[41] For example, the reaction of decaborane with *tert*-butyldimethylsilylacetylene in a mixture of 1-butyl-3-methylimidazolium chloride (bmimCl) and toluene produces compound **46** in 50% yield. Noteworthy, the reaction of the decaborane–acetonitrile adduct with TBDMS–C≡CH produces silylated derivative **46** in only 23% yield. The generation of a lithium salt of compound **46** under the action of Bu^nLi and subsequent addition of allyl bromide yield compound **47**. After the TBDMS group is removed from compound **47**, derivative **42** is formed (80%) to be then converted to target product **35a** as described above[40] (see Scheme 11).

Unlike *o*-carborane, *p*-carborane is stable *in vitro* and *in vivo*,[42] therefore, new *p*-carboran-1-ylthymidines having increased hydrophilicity due to the presence of hydroxy groups were prepared (Scheme 12).[43] The reaction of tosylates **48a**,**b** with thymidine yielded conjugates **49a**,**b**. Deprotection of derivative **49a** gave compound **50**; its subsequent hydroxylation by osmium(VIII) oxide in the presence of *N*-methylmorpholine oxide gave product **51a** in 53% yield. Compound **49b** was treated with K_2CO_3 in methanol and then with OsO_4 and *N*-methylmorpholine oxide to produce finally compound **51b** in 42% yield.

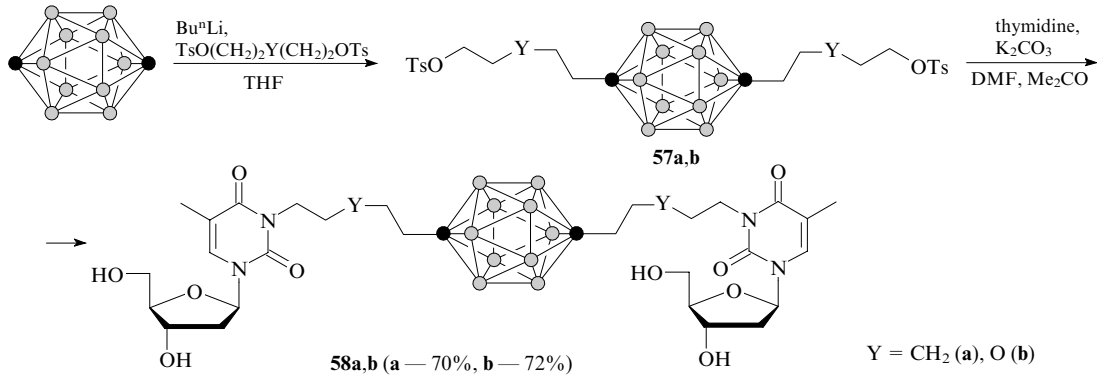
Conjugate **52** was prepared, where thymidine is attached to *p*-carborane through the C_4 spacer with three hydroxy groups (Scheme 13).[43] To the monolithium *p*-carborane salt, which was prepared by treating *p*-carborane with n-butyllithium, (2*S*,3*R*)-4-(*tert*-butyldimethylsilyloxy)-2,3-(isopropylidenedioxy)butanol (**53**) is added *in situ*[44] to yield compound **54**. A minor product is disubstituted

Scheme 13



Py is pyridine

Scheme 14

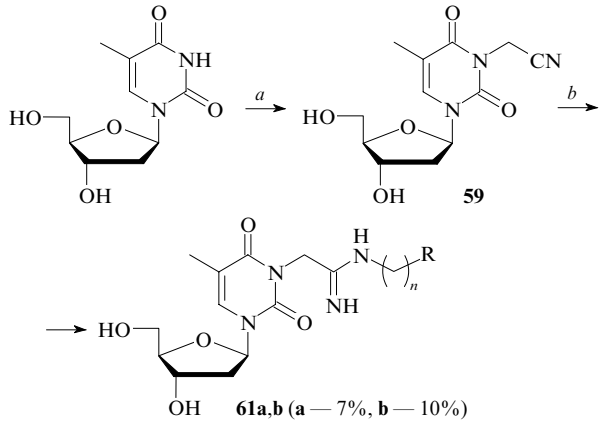


p-carborane (10%). The subsequent removal of protecting groups and reaction with tosyl chloride yield monotosylated alcohol **55**. Quite likely, the tosylation of the hydroxy group in position 1 of the spacer is hampered by steric hindrance generated by the bulky *p*-carborane cluster. The reaction of alcohol **55** with thymidine produces compound **56**, which then yields, after the elimination of isopropylidene group, desired product **52**.

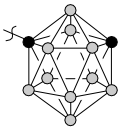
Boron-containing derivatives with two thymidine moieties attached through spacers in positions 1 and 12 of *p*-carborane have been prepared (Scheme 14).[43] The treatment of *p*-carborane with Bu^{n}Li in THF yields a dilithium salt, which then reacts with a solution of either pentane-1,5-diyl ditosylate,[37] or 3-oxapentane-1,5-diyl ditosylate to yield, respectively, compounds **57a**,**b**. Target products **58a**,**b** are produced by reaction of tosylates **57a**,**b** with thymidine in the presence of K_2CO_3.

Various N(3)-substituted thymidine analogues with an amidine unit have been prepared.[45] The selective alkylation of thymidine at the N(3) atom by iodoacetonitrile in the presence of K_2CO_3 generates 3-(cyanomethyl)thymidine (**59**); heating of the latter with *m*-carboranylalkylamines **60a**,**b** and 1 ml hexafluoroisopropyl alcohol at 120 °C leads to the complete evaporation of the solvent and gives compounds **61a**,**b** in low yields (Scheme 15).

Scheme 15

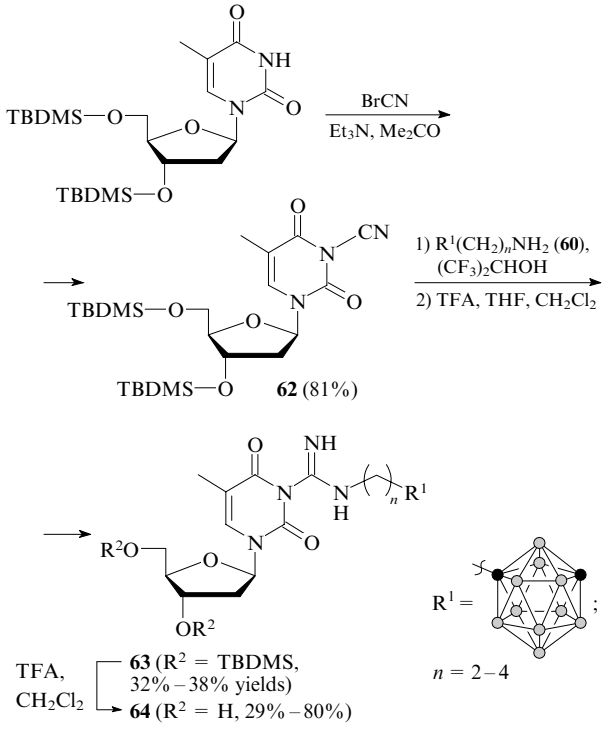


(*a*) ICH_2CN, K_2CO_3, DMF, Me_2CO; (*b*) $R(CH_2)_nNH_2$ (**60a**,**b**),

$(CF_3)_2CHOH$; R =  ; *n* = 2 (**a**), 3 (**b**)

Guanidine analogues were prepared as follows: cyanation at the N(3) position of 3′,5′-bis(*tert*-butyldimethylsilyl)thymidine in the presence of K_2CO_3 yields 3′,5′-bis(*tert*-butyldimethylsilyl)-3-cyanothymidine (**62**). The initial attempts to treat the unprotected thymidine with cyanogen bromide in the presence of K_2CO_3 yielded 3-cyanothymidine in as low as 5% yield. When compound **62** is further reacted with 1-(ω-aminoalkyl)-*m*-carboranes **60** in the presence of hexafluoroisopropyl alcohol under pressure, derivatives **63** are produced, and their stirring in trifluoroacetic acid and dichloromethane generates products **64** in 29% – 80% yields (Scheme 16).[45]

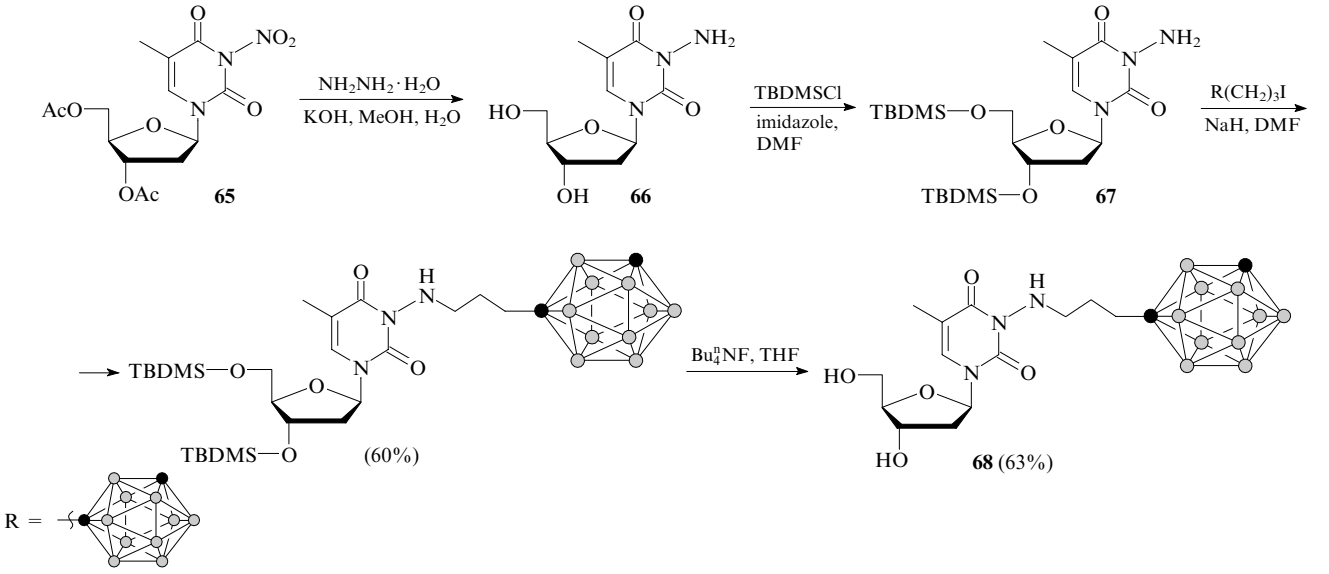
Scheme 16



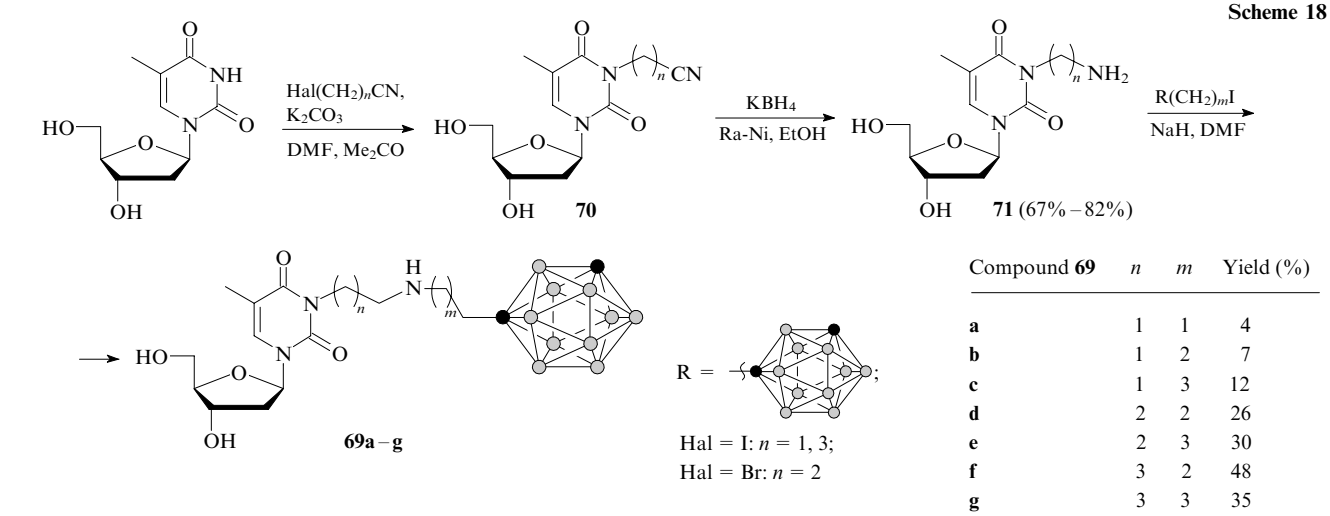
Boron-containing thymidine analogues with an NH group in the linker are obtained from 3′,5′-diacetyl-3-nitrothymidine (**65**). Treatment of the latter with hydrazine hydrate and KOH in a methanol – water mixture yields 3-aminothymidine (**66**). The N-alkylation of protected nucleoside **67** by 1-(3-iodopropyl)-*closo*-1,7-*m*-carborane in the presence of NaH in DMF with subsequent desilylation yields product **68** (Scheme 17).[46]

Compounds **69a** – **g** were prepared from 3-(ω-cyanoalkylthymidines **70**, which were in turn prepared by reacting 2′-deoxythymidine with haloalkanecarbonitriles in the pres-

Scheme 17

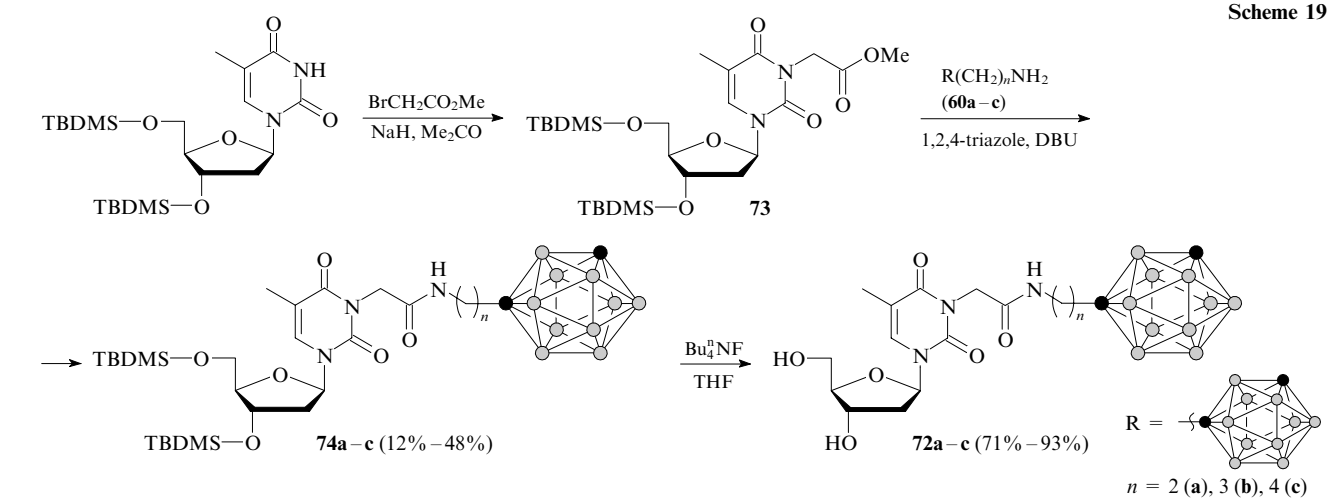


Scheme 18



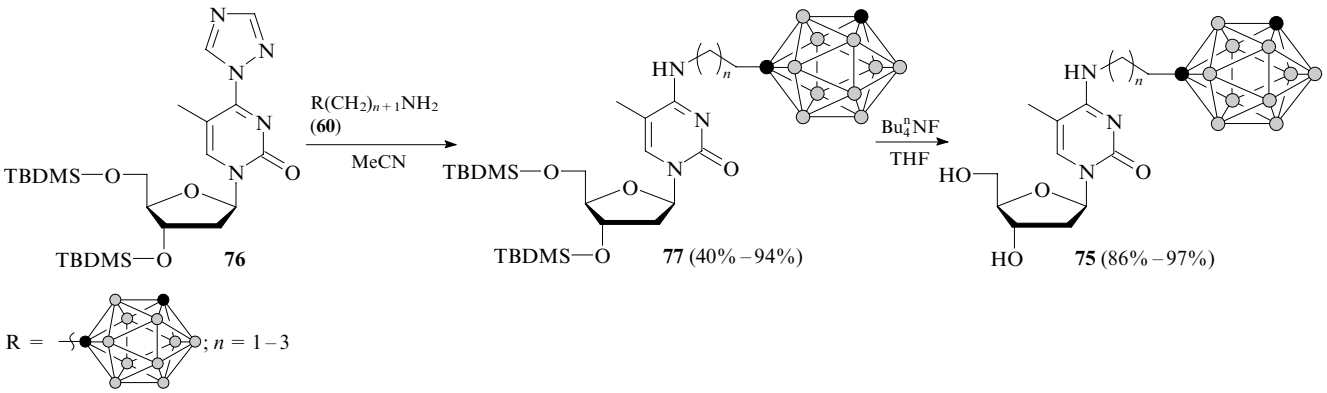
Compound **69**	*n*	*m*	Yield (%)
a	1	1	4
b	1	2	7
c	1	3	12
d	2	2	26
e	2	3	30
f	3	2	48
g	3	3	35

Scheme 19



ence of K_2CO_3.[46] The reduction of derivatives **70** by potassium borohydride over Raney nickel (Ra-Ni) yields compounds **71**. The latter are alkylated at the NH_2 group of nucleoside by 1-(ω-iodoalkyl-*closo*-1,7-*m*-carboranes in the presence of NaH in DMF to yield products **69a** – **g**. Despite the free hydroxy groups of nucleosides **71**, alkylation

Scheme 20



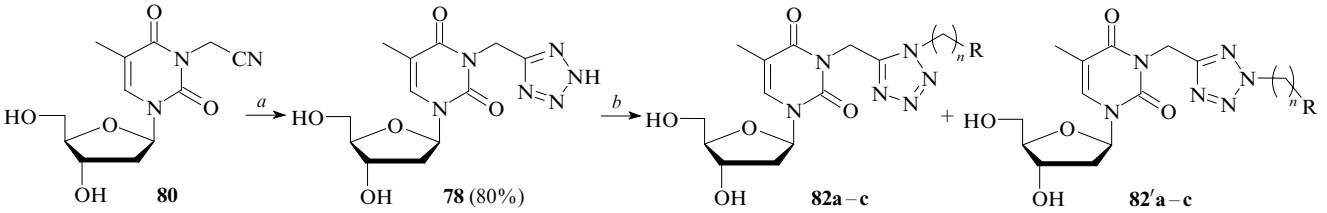
preferably yields the *N*-monoalkylated product; the *N*,*N*-dialkylated product is produced to a less extent. The low yields of compounds **69a** – **c** (4% – 12%) are due to their considerable degradation in the course of the reaction (Scheme 18).

Compounds **72a** – **c**, which contain an amide group in the linker, were prepared from 3′,5′-bis(*O*-*tert*-butyldimethylsilyl)thymidine. Its reaction with methyl bromoacetate in the presence of NaH yields ester **73**.[46] The subsequent acylation[47] of 1-(ω-aminoalkyl-*closo*-1,7-*m*-carboranes **60a** – **c** by modified nucleoside **73** using 1,2,4-triazole and 1,8-diazabicycloundec-7-ene (DBU) in the absence of solvent at 80 °C for 3 days yields compounds **74a** – **c**. After deprotection, products **72a** – **c** are generated in good yields (Scheme 19).

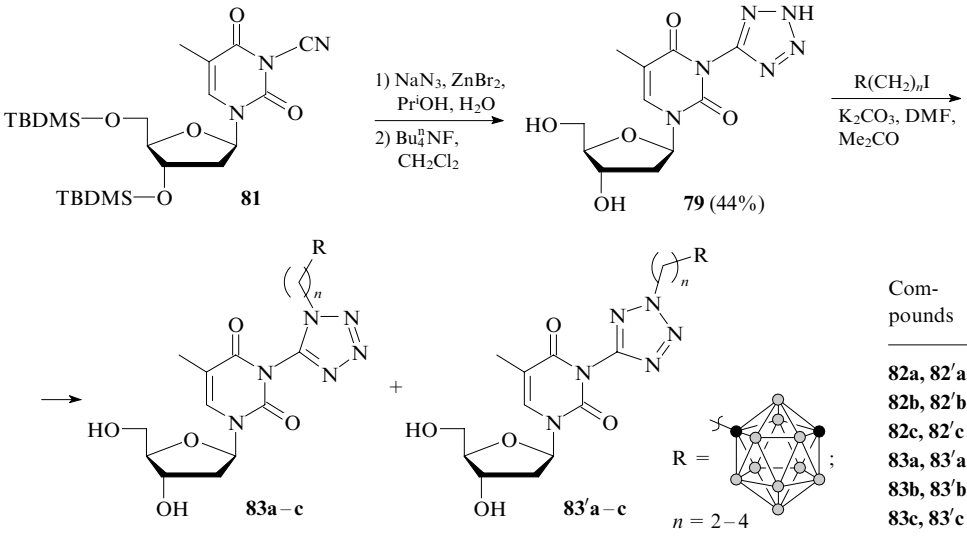
N(4)-*m*-Carboranylalkyl-5-methyl-2′-deoxycytidine analogues **75** were prepared by reacting substituted deoxycytidine **76** with 1-(ω -aminoalkyl)-*closo*-1,7-*m*-carboranes **60** in acetonitrile at 60 °C followed by deprotection of intermediate products **77** (Scheme 20).[46]

Carboranyl-substituted analogues of thymidine with the tetrazole ring in the spacer have been prepared.[45] The precursor tetrazolylmethylthymidine (**78**) and tetrazolylthymidine (**79**) were prepared by the [3 + 2] dipolar cycloaddition reaction (Scheme 21).[45] The treatment of compound **80** by NaN_3 in the presence of $ZnBr_2$ generates tetrazole **78**. Compound **81** when reacted under the same conditions yields a mixture of 3-(tetrazol-5-yl)thymidine **79**, 3′- and 5′-(*tert*-butyldimethylsilyl)- and 3′,5′-bis(*tert*-butyldimethylsilyl)-3-(tetrazol-5-yl)thymidines. The residual

Scheme 21



(*a*) NaN_3, $ZnBr_2$, Pr^iOH, H_2O; (*b*) $R(CH_2)_nI$, K_2CO_3, DMF, Me_2CO

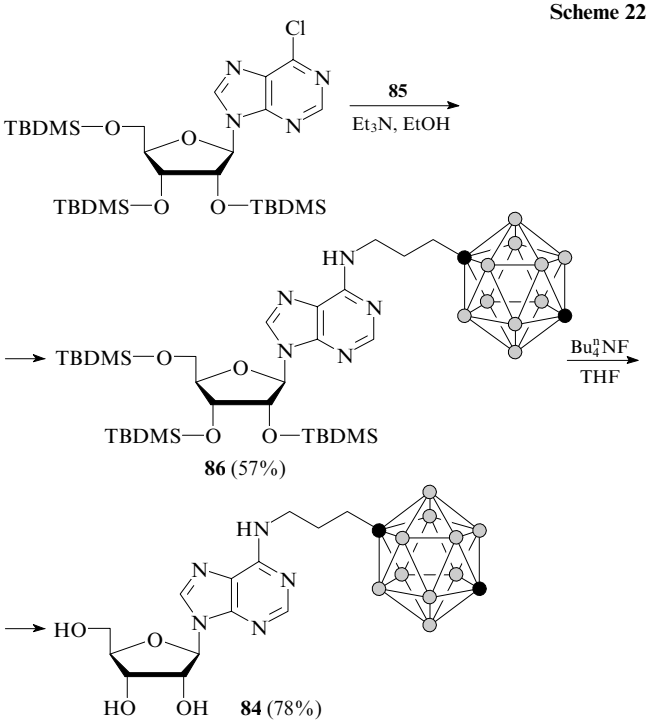


Compounds	*n*	Total yield (%)	Isomer ratio **82** (**83**) : **82′** (**83′**)
82a, 82′a	2	64	20 : 80
82b, 82′b	3	60	15 : 85
82c, 82′c	4	62	30 : 70
83a, 83′a	2	56	5 : 95
83b, 83′b	3	42	5 : 95
83c, 83′c	4	45	10 : 90

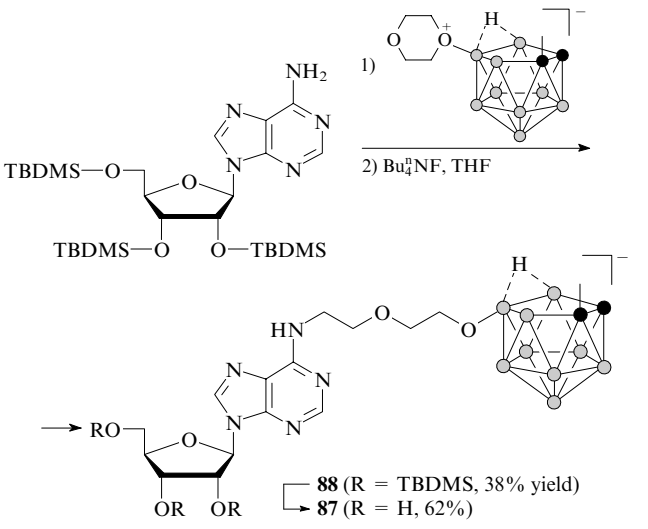
TBDMS groups are eliminated *in situ* by addition of trifluoroacetic acid in dichloromethane. The subsequent *N*-alkylation of the tetrazole ring in compounds **78** and **79** by 1-(ω-iodoalkyl)-*m*-carboranes in the presence of K_2CO_3 yields mixtures of isomers **82a – c**, **82′a – c** and **83a – c**, **83′a – c**, which differ from each other by the position of the carboranylalkyl substituent. Unfortunately, the separation of these isomers failed. Since *o*-carborane degrades under the condensation conditions, all carboranyl derivatives were prepared only with the more stable *m*-carborane.

Derivative **84**, where *p*-carborane is added at the position 6 of adenosine, was prepared by displacing the chlorine atom from 2′,3′,5′-tris(*O-tert*-butyldimethylsilyl)-6-chloroadenosine upon the reaction with 3-aminopropyl-*p*-carborane (**85**).[48] Subsequent removal of protecting groups in compound **86** yielded conjugate **84** (Scheme 22).[49]

Scheme 22



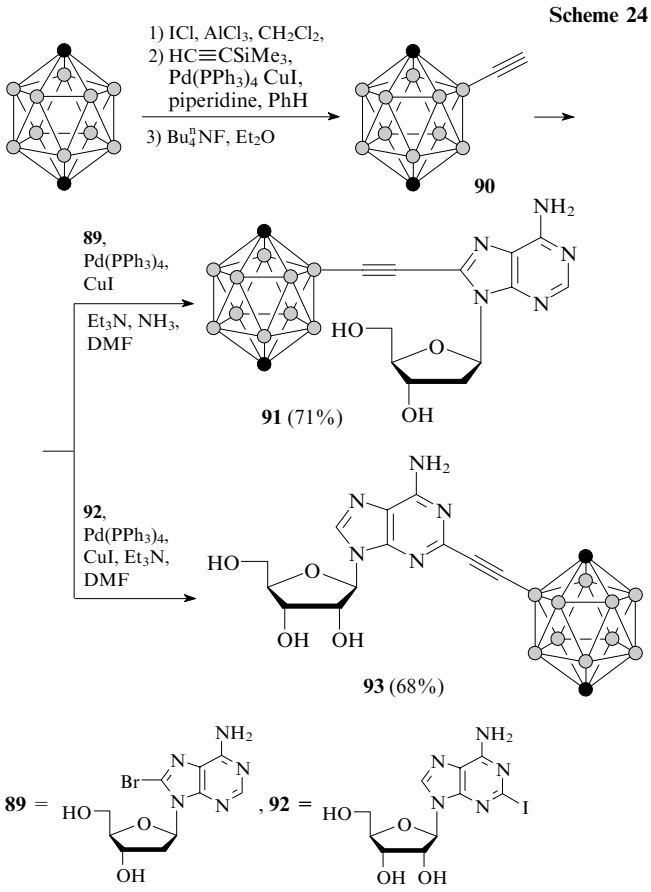
Scheme 23



6-*N*-{5-[7,8-*nido-o*-Carboran-10-yloxy]-3-oxapentyl}adenosine (**87**) was prepared by reaction of 2′,3′,5′-tris(*O-tert*-butyldimethylsilyl)adenosine protected at the carbohydrate moiety with 10-dioxonio-7,8-*nido-o*-carborane in the presence of NaH and subsequent removal of the protecting silyl group in compound **88** (Scheme 23).[50]

Conjugates where the *p*-carboran is attached to 2′-deoxyadenosine in position 8 of the nucleoside have been prepared (Scheme 24).[50] The catalysed cross-coupling

Scheme 24

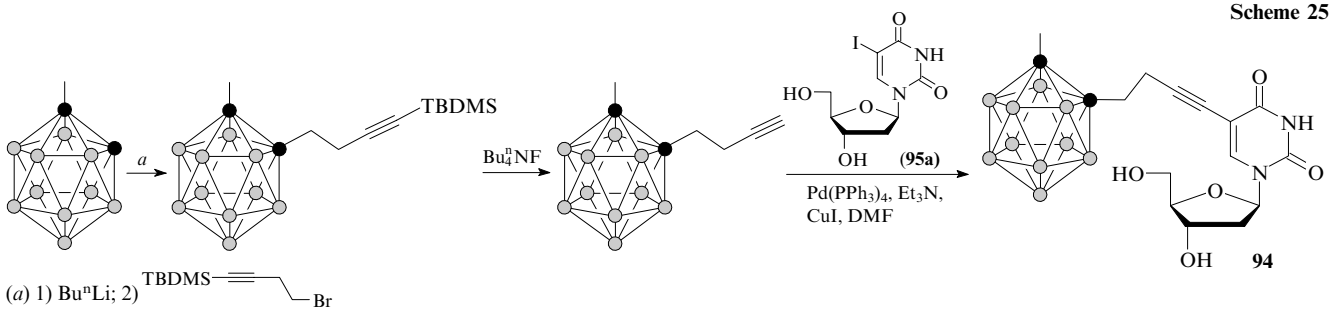


of 8-bromo-2′-deoxyadenosine (**89**)[51] and 2-ethynyl-*p*-carborane (**90**)[52] using $Pd(PPh_3)_4$, CuI in DMF or Et_3N produces 8-(*p*-carboran-2-ylethynyl)-2′-deoxyadenosine (**91**) in 71% yield. The Sonogashira reaction of 8-ethynyl-2′-deoxyadenosine with 2-iodo-*p*-carborane, however, produces expected product **91** in an as low as 27% yield. Noteworthy, the cross-coupling of unprotected 2-iodoadenosine (**92**)[53] with ethynylcarborane **90** under the same conditions proceeds to yield 2-(1,12-dicarba-*closo*-dodecaboran-2-ylethynyl)adenosine (**93**) (see Scheme 24).[54]

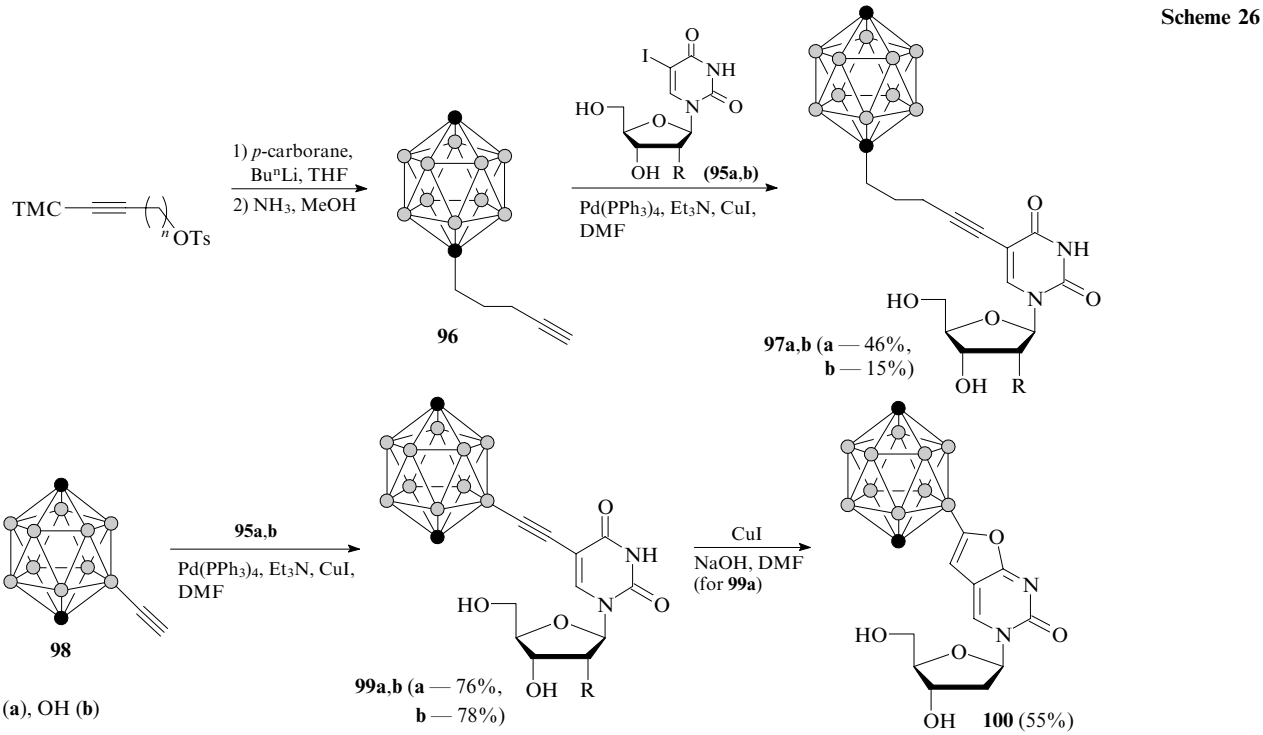
The synthesis of methyl-*o*-carborane 5-ethynyl-2′-deoxyuridine derivative **94** from 5-iodo-2′-deoxyuridine (**95a**) and the appropriate alkynyl-*o*-carborane has been described.[55] Noteworthy, conjugate **94** was mentioned in conference proceedings, and no experimental data were reported there (Scheme 25).

Similar conjugates with *p*-carborane were prepared two decades later.[56] Compounds **97a**,**b** are prepared in 46% and 15% yield, respectively, as a result of Sonogashira cross-coupling of 5-iodo-2′-deoxyuridine (**95a**) or 5-iodouridine (**95b**) with *p*-carborane **96**, which contains a triple terminal bond. Similar reactions of nucleosides **95a**,**b** with carborane

Scheme 25



Scheme 26

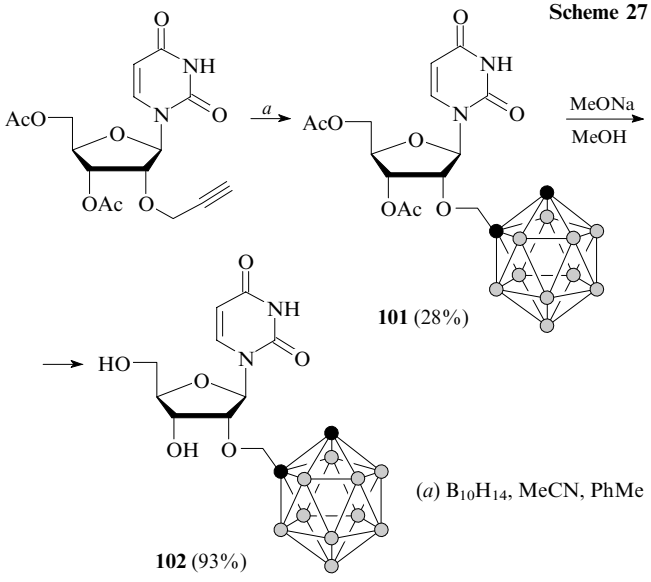


derivative **98**, where the ethynyl group is linked directly to the *p*-carborane cage at the boron atom, produces conjugates **99a**,**b**. The good yields of products **99a**,**b** in the Sonogashira reaction were achieved when the solvent was DMF and the catalyst was $Pd(PPh_3)_4$ in the presence of CuI and Et_3N.

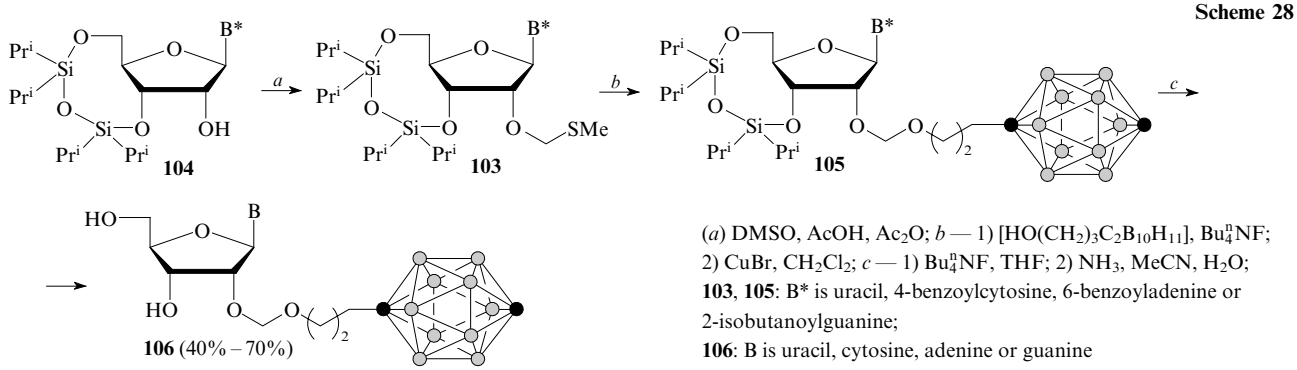
Compound **99a** undergoes intramolecular cyclization to fused bicyclic derivative **100**. A simple approach to the preparation of this product under standard conditions [57] using CuI and an organic base (triethylamine or $EtNPr^i_2$) did not give the expected result, so NaOH was used instead of organic bases.[58] However, neither the treatment of compounds **97a**,**b** and **99b** under standard conditions, nor the use of NaOH yielded the desired bicyclic products (Scheme 26).

The introduction of a bulky and hydrophobic carborane moiety into the sugar unit of the nucleoside considerably changes the natural conformation of the nucleoside, and this can expand the application of these modified compounds in many biological experiments. For this reason, conjugates were prepared where the boron cluster attaches to the nucleoside in position 2′ of the carbohydrate. The reaction of protected 2′-*O*-(3-prop-1-ynyl)uridine with the decaborane – acetonitrile complex in toluene yields derivative **101**, the removal of acetylene groups from which yields 2′-*O*-(*o*-carboran-1-yl)methyluridine (**102**) (Scheme 27).[59]

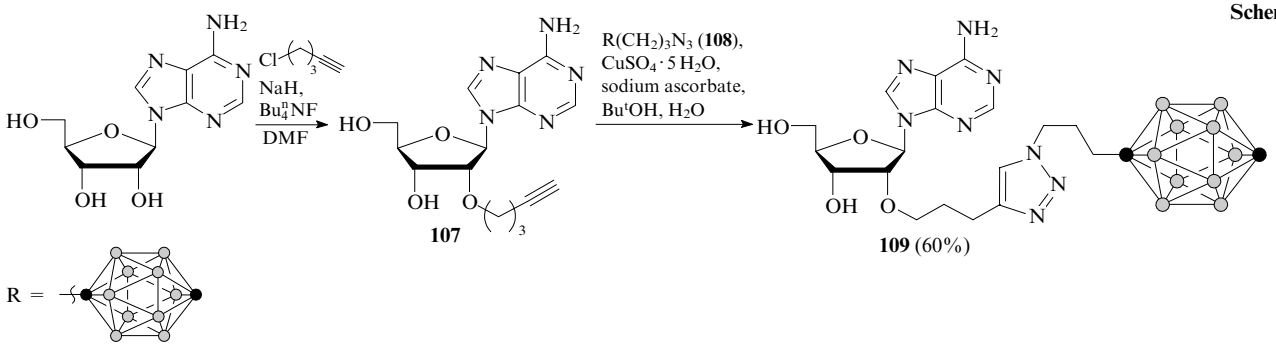
Scheme 27



Scheme 28



Scheme 29



Later, it was proposed to attach a modified unit comprising a *p*-carborane cluster to the nucleoside position 2′. Although *o*-carborane derivatives are available and have lower costs compared to *p*-carborane derivatives, an *o*-carborane degrades under basic conditions to the toxic *nido* form, so *p*-carborane was chosen to serve as the carborane species and synthetic strategy was developed to prepare 2′-*O*-[(*p*-carboran-1-yl)propyloxymethyl] derivatives with all nucleosides. The underlying idea of the strategy was to introduce a methylthiomethyl moiety in the carbohydrate position 2′ of a protected nucleoside (compound **103**) and then perform the nucleophilic substitution of the activated methylthio group by an alcohol containing the carborane cluster (Scheme 28).[60, 61] This synthesis uses the Markiewicz protection for the 3′- and 5′-hydroxy groups of the nucleoside. Starting compounds **104** are available and can be derived from nucleosides in high yields.[62] The treatment of compounds **104** by DMSO in a mixture of acetic acid and acetic anhydride yields key intermediates **103**,[63] which can then react with 1-(3-hydroxypropyl)-*p*-carborane to yield completely protected 3′,5′-*O*,*O*-tetra(isopropyl)disiloxane-1,3-diyl-2′-*O*-[(*p*-carboran-1-yl)propyloxymethyl] nucleosides. The elimination of the disiloxane group and N-acetyl group in derivatives **105** yields nucleosides **106** (see Scheme 28).

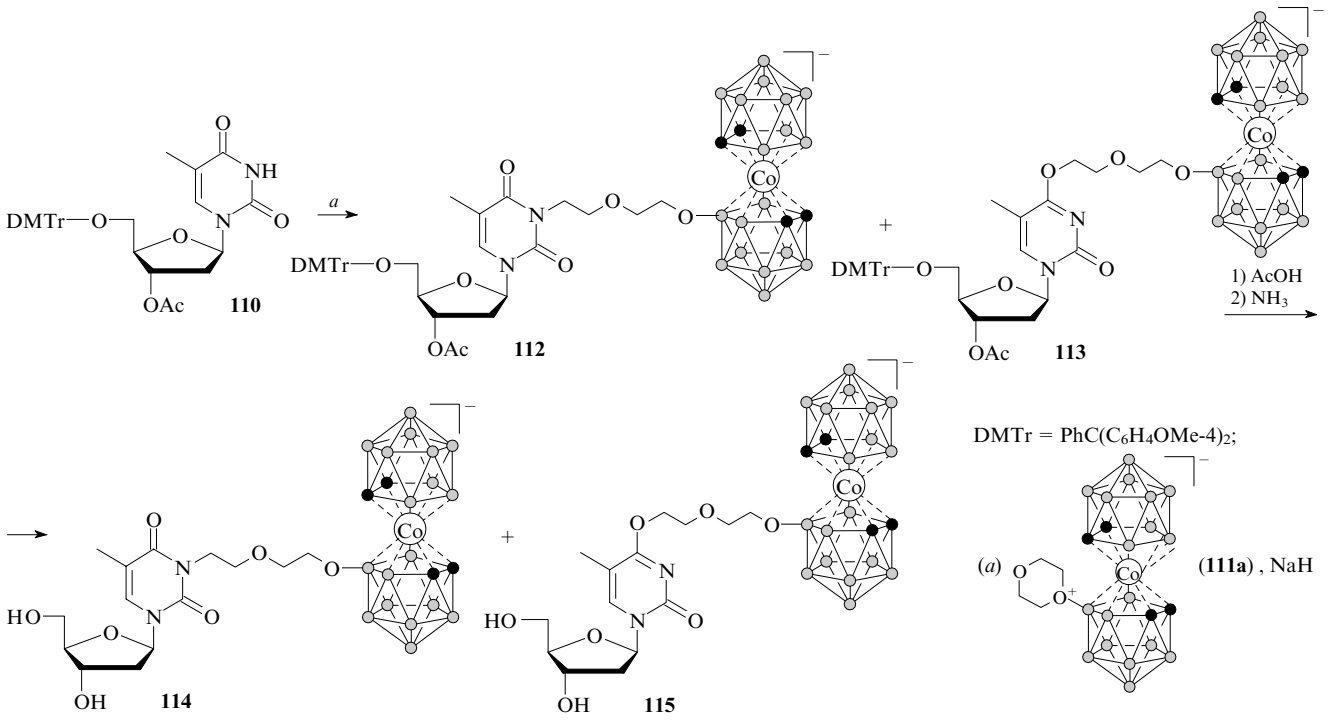
There is another approach to introduce a carborane moiety into the carbohydrate unit of the nucleoside, namely the [3 + 2] dipolar cycloaddition of azides to alkynes. As a result, 2′-*O*-(pent-4-yn-1-yl)adenosine (**107**), with its terminal triple bond, and derivative **108**, which can be prepared from 1-(3-hydroxypropyl)-1,12-dicarba-*closo*-*p*-dodecaborane and NaN_3 by the basic synthesis of azides from alcohols,[64] selectively yield product **109** (Scheme 29).[49]

Thus, the major methods for preparing conjugates of 12-vertex carboranes with nucleosides are nucleophilic substitution reactions and reactions of nucleoside-containing alkynes with the bis(acetonitrile)decaborane complex or decaborane. Both methods are laborious and frequently require using protecting groups. Conjugation methods are constantly being improved, but there are only few useful reactions because of appreciable limitations imposed: as a rule, the reaction should proceed in high yields and should not affect functional groups of the biomolecule. The cross-coupling reaction ideally satisfies these requirements, as alkynes are inert both toward the vast majority of functional groups and toward the reactants used in bioconjugation methods. The method uses only those functional groups that are introduced in the set positions and do not affect the rest of the biomolecule. Despite the few examples, the high potential of cross-coupling reactions has been efficiently shown in the preparation of carborane conjugates with nucleosides; the method has broad prospects, as it does not require protecting groups.

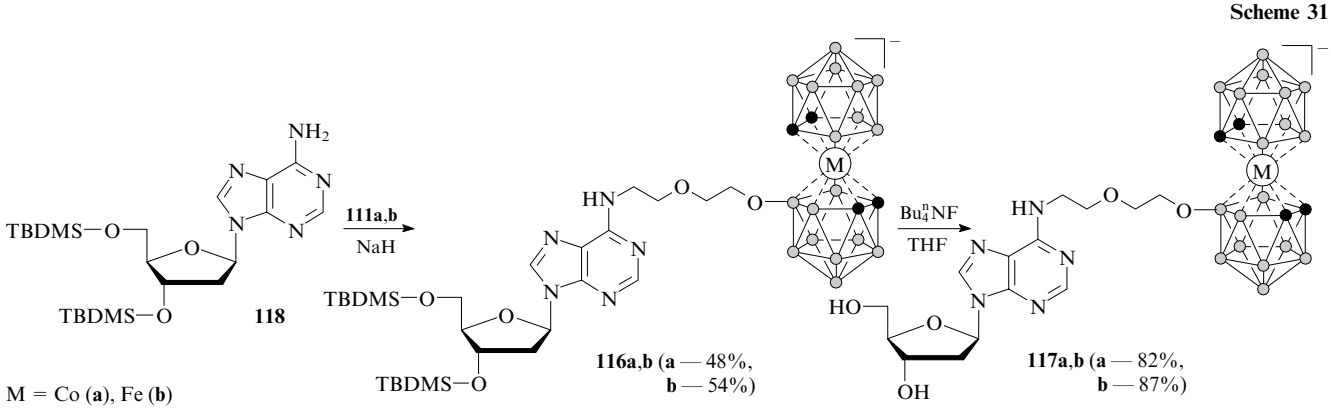
III. Conjugates with metallacarboranes

One major weakness of the carborane-containing nucleosides is their very high lipophilicity; *in vitro* studies at the cellular level are hampered by the water insolubility of conjugates. A series of metallacarborane-containing nucleosides with various hydrophilic substituents were prepared in order to overcome this weakness and to reach an acceptable hydrophilic–lipophilic balance. The first metallacarborane-containing nucleosides were prepared by Olejniczak *et al.*[65] in 2003. They reported that various products can be prepared by varying reaction parameters. For example, the reaction of carbohydrate-protected thymidine **110** with dioxonium-derivatized cobalt bis(1,2-dicarbollide) (**111a**) under severe conditions, *i.e.*, in the presence of NaH, yields two products of alkylation at the N(3) and O(4) thymidine ring atoms (compound **112** and compound **113**, respectively). The consecutive elimination of the acetyl protection

Scheme 30



Scheme 31

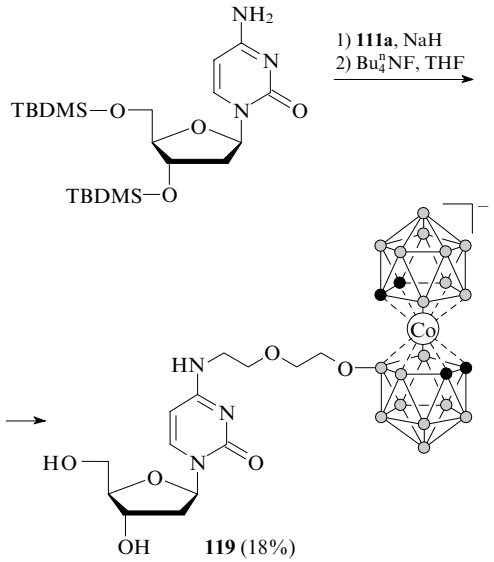


from 3′-OH groups and the trityl protection from 5′-OH groups yields the first isomeric thymidine metallacarborane conjugates (**114** and **115**) in the weight ratio 1 : 2 (Scheme 30). However, the authors were silent about the yields of these compounds, and it also remained unclear what cation they contained.

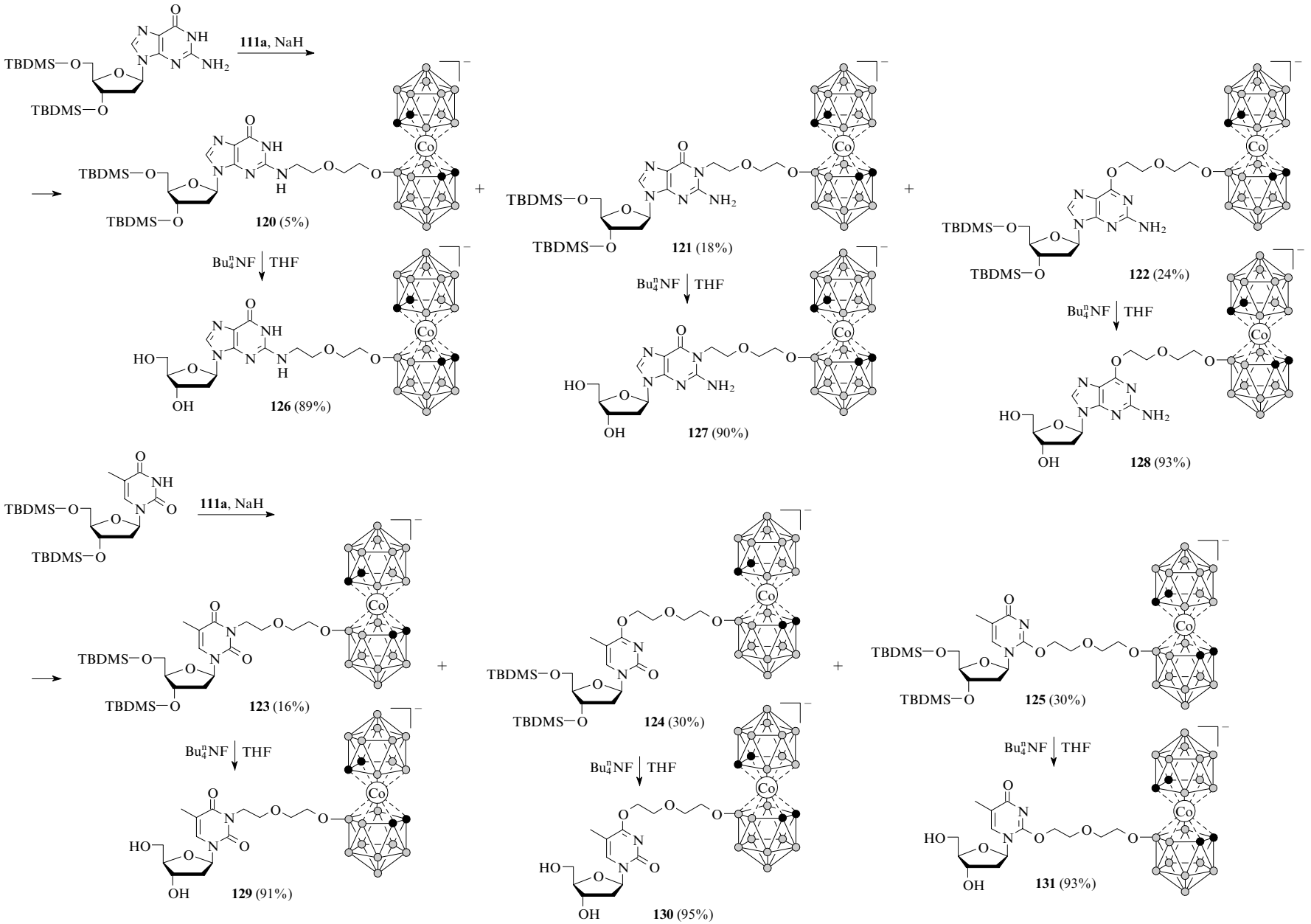
Similar reactions of opening of complex **111a** by the nucleophilic centres of all the four of 2′-deoxyribonucleosides with *tert*-butyldimethylsilyl protection in positions 3′ and 5′ of 2′-deoxyribose were studied more recently.[66] As a result, 2′-deoxyadenosine cobalt bis(1,2-dicarbollide) conjugate (**117a**), where the boron cluster is attached to the nucleoside at the N(6)-amino group, was prepared in two steps *via* protected intermediate **116a**. Later, product **117b**, the first 2 ′-deoxyadenosine iron bis(1,2-dicarbollide) conjugate, was prepared from 3′,5′-bis(*O*,*O*-*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**118**) and iron bis(1,2-dicarbollide) dioxonium complex (**111b**) in a similar way in two stages (Scheme 31).[67]

Olejniczak *et al.*[66] practised a similar approach with protected deoxycytidine, which generates the only N(4)-

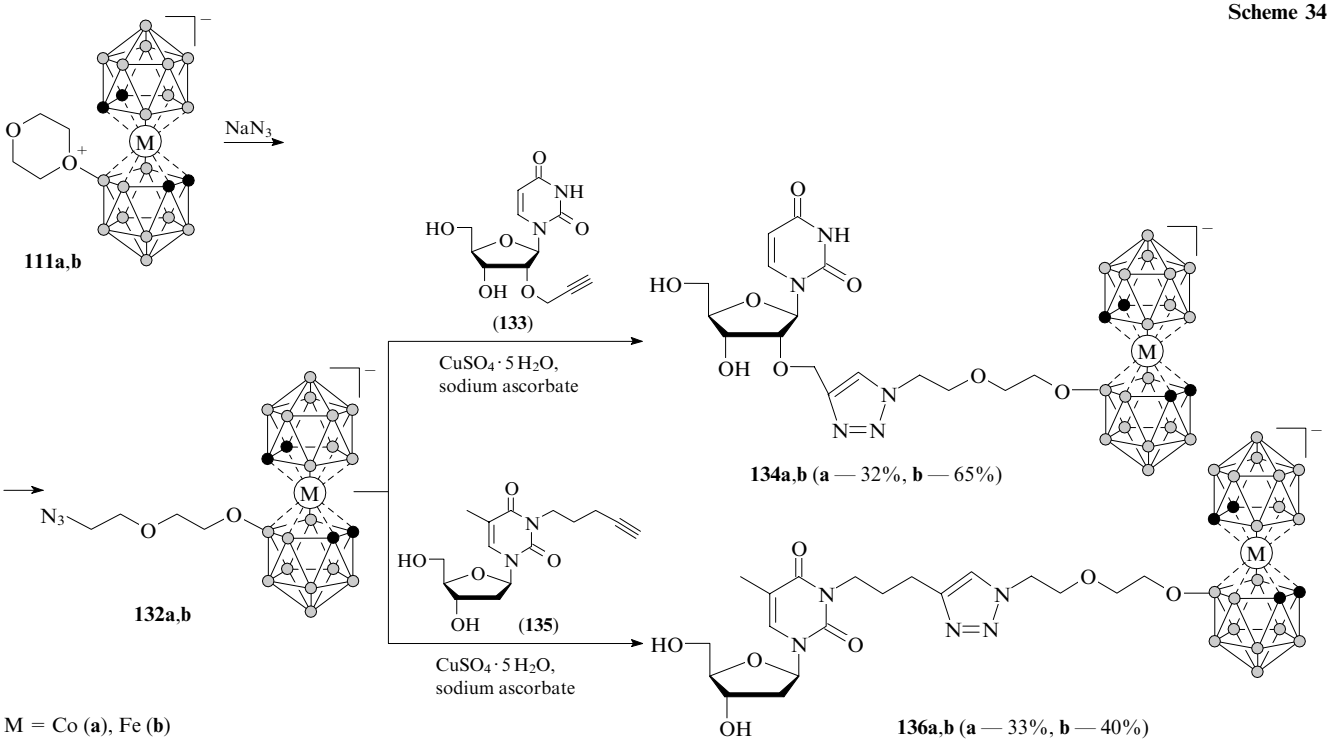
Scheme 32



Scheme 33


111a, NaH
Bu$_4^n$NF, THF
120 (5%)
121 (18%)
122 (24%)
126 (89%)
127 (90%)
128 (93%)
123 (16%)
124 (30%)
125 (30%)
129 (91%)
130 (95%)
131 (93%)

Scheme 34



alkylated product, namely cobalt bis(1,2-dicarbollide) 2′-deoxycytidine conjugate (**119**) (Scheme 32). In this reaction, the protected conjugate was not isolated from the reaction mixture and the protecting groups were removed *in situ*. The authors did not mention the cation that compensates for the (−1) charge of metallacarborane.

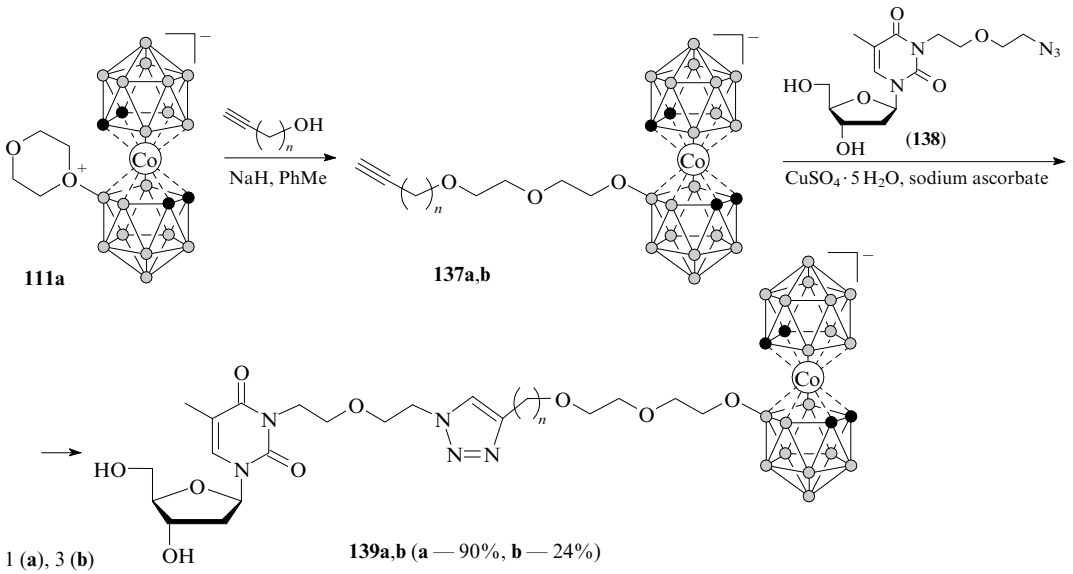
When other protected nucleosides are introduced into a similar process, however, mixtures of products are formed. For example, the reaction of dioxonium-derivatized cobalt bis(1,2-dicarbollide) **111a** with 3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-2′-deoxyguanosine in the presence of NaH in toluene yields the products of alkylation at the N(2), N(1) and O(6) atoms of purine base (conjugates **120** – **122**).[66] A similar reaction with 3′,5′-bis(*O*-*tert*-butyldimethylsilyl)thymidine yields a mixture of three isomeric products **123** – **125** as a result of alkylation at the N(3), O(4) and O(2) atoms of pyrimidine base. Conjugates **126** – **131** are formed upon removal of the *tert*-butyldimethylsilyl group by a routine method (Scheme 33).[66]

One more approach to the synthesis of metallacarborane-containing nucleosides consists of Cu^{I}-catalysed 1,3-dipolar cycloaddition of alkynes to azides. This is a universal method, as, unlike the non-catalytic process, the reaction in this case proceeds regiospecifically to yield 1,4-disubstituted 1,2,3-triazoles.[68] New boron-containing azides **132a**,**b** are generated upon the reaction of cobalt (iron) bis(1,2-dicarbollide) with NaN_3 under reflux in ethanol in the presence of $Bu^{n}_{4}NBr$. They react with 2′-*O*-propargyluridine (**133**) in the presence of aqueous copper sulfate and sodium ascorbate to yield 1,4-substituted triazoles **134a**,**b**, which are uridine cobalt (iron) bis(1,2-dicarbollide) conjugates, where the boron cluster is attached to the nucleoside at the 2′-O atom of deoxyribose.[69] Complexes **132a**,**b** were reacted with *N*(3)-(pent-4-yn-1-yl)thymidine (**135**) under the same conditions to prepare two more conjugates **136a**,**b**, where cobalt (iron) bis(1,2-dicarbollide) is linked to the nucleoside through the triazole ring at the N(3) atom of the pyrimidine base (Scheme 34).

Another dipolar cycloaddition version uses a metallacarborane as the alkyne component and thymidine as the azide component. The opening of complex **111a** by propargyl alcohol and pent-4-yn-1-ol in DMF in the presence of NaH yields terminal alkynes **137a**,**b** based on cobalt bis(1,2-dicarbollide), which can react with azido thymidine derivative **138** to yield 1,4-disubstituted triazoles **139a**,**b** (Scheme 35).[69]

As mentioned above, an important property of cyclic oxonium derivatives of cobalt dicarbollide is their ability to undergo nucleophile-induced ring opening.[70] The literature teaches that the ring opening in oxonium cation by tertiary amines produces ammonium salts in good yields.[71, 72] So, 2′-deoxyadenosines **140a**,**b**, which are modified by an (ω-dimethylaminoalkyl)amino group in position 8, react with dioxonium-derivatized cobalt bis(1,2-dicarbollide) **111a** in acetonitrile at room temperature to yield conjugates **141a**,**b**, where the nucleoside is linked to the boron cluster through position 8 of the purine base.[73, 74] 2′-Deoxyadenosine derivatives **140** can be prepared by refluxing 8-bromo-2′-deoxyadenosine with asymmetric *N*,*N*-dimethylethylenediamines and -propylenediamines for 5 h. Reactions of oxonium iron bis(1,2-dicarbollide) complexes **111b** and **142b** with modified 2′-deoxyadenosine **140a** also yield 2′-deoxyadenosine iron bis(1,2-dicarbollide) conjugates **143** and **144**.[75] Noteworthy, it was for the first time that researchers managed to prepare zwitterion derivatives of cobalt (iron) bis(1,2-dicarbollide) with 2′-deoxyadenosine, namely conjugates **141a**,**b**, **143** and **144**, where the 6-*exo*-NH_2 group of the nucleoside remains unaffected. An important advantage of the method for the preparation of such conjugates consists in that there is no need to protect the hydroxy groups of the carbohydrate, whereas the same cannot be said of the method used to prepare adenosine cobalt bis(1,2-dicarbollide) conjugate **145**, where a pro-

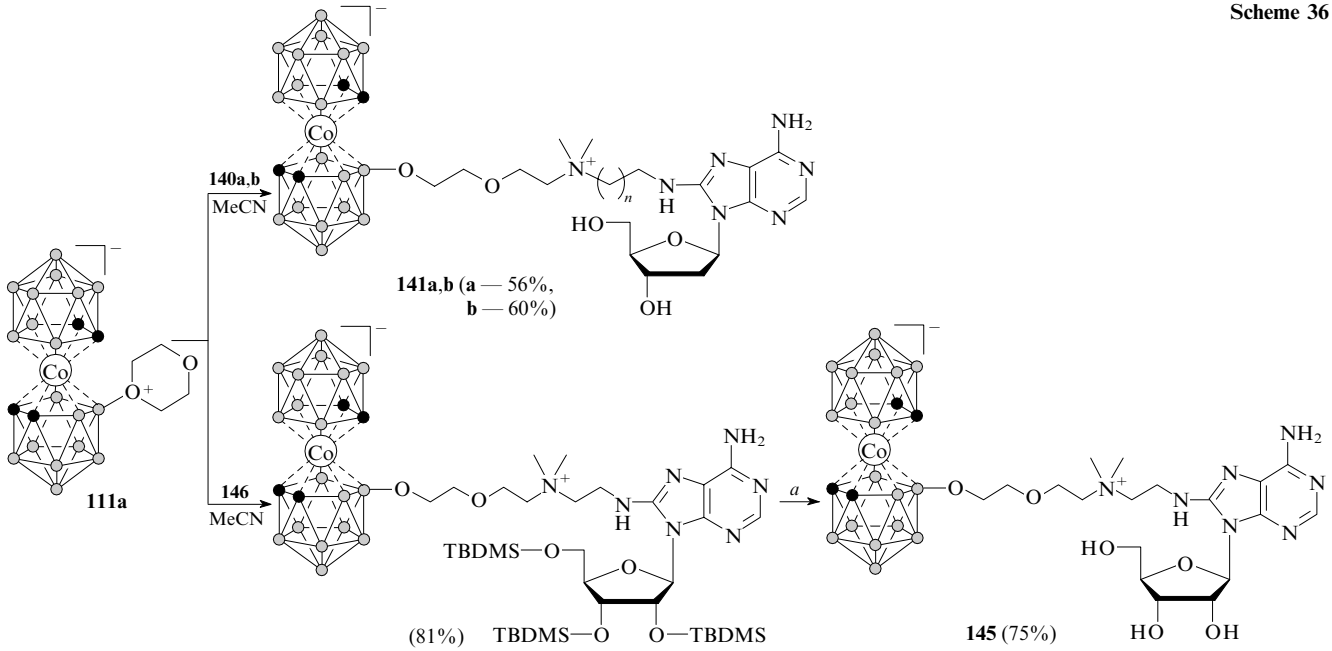
Scheme 35



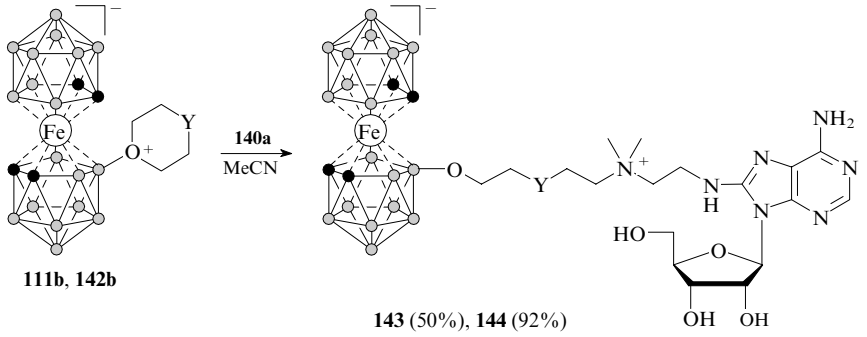
111a **137a**,**b** **139a**,**b** (**a** — 90%, **b** — 24%)

137, **139**: *n* = 1 (**a**), 3 (**b**)

Scheme 36



140a,**b** = ; **146** = ; (*a*) Bu^n_4NF, THF; **140**, **141**: *n* = 1 (**a**), 2 (**b**)



111b, **142b** **143** (50%), **144** (92%) Y = O (**111b**, **143**), CH_2 (**142b**, **144**)

tected derivative was used, namely, organic-soluble 8-(2-dimethylaminoetyhyl)amino-(2′,3′,5′-tris(*O*-*tert*-butyldimethylsilyl)adenosine (**146**). This derivative was prepared from 8-bromo-2′,3′,5′-tris(*tert*-butyldimethylsilyl)adenosine[76] and *N*,*N*-dimethylethylenediamine. Unlike the unprotected modified adenosine, its protected analogue **146** is soluble in polar organic solvents, and its reaction with boron cluster **111a** in MeCN at room temperature for 1 h, followed by the elimination of protecting groups, yields adenosine cobalt bis(1,2-dicarbollide) conjugate **145** (Scheme 36).[74]

The opening of oxonium derivatives of boron clusters by tertiary amines was also successfully employed to prepare cobalt bis(1,2-dicarbollide) conjugates with 5- ethynyl-2′-deoxyuridine.[77] First, a 5-ethynyl-2′-deoxyuridine derivative with NMe_2 group in the side chain was prepared by the Sonogashira reaction. Semioshkin *et al.*[77] discovered that two methyl groups in the α-position to the triple bond of the alkyne amine favour the smooth proceeding of the reaction avoiding the formation of the intramolecular cyclization side product (a furanopyrimidine derivative), which is frequent in this process. Reacting dioxonium derivative (**111a**) and tetrahydropyronium cobalt bis(1,2-dicarbollide) derivative (**142a**) with a small excess of modified nucleoside **147** in acetonitrile at room temperature for 3 h, followed by treatment with Bu^n_4NF, yields 5-ethynyl-2′-deoxyuridine cobalt bis(1,2-dicarbollide) conjugate (**148** and **149**, respectively) (Scheme 37).[77]

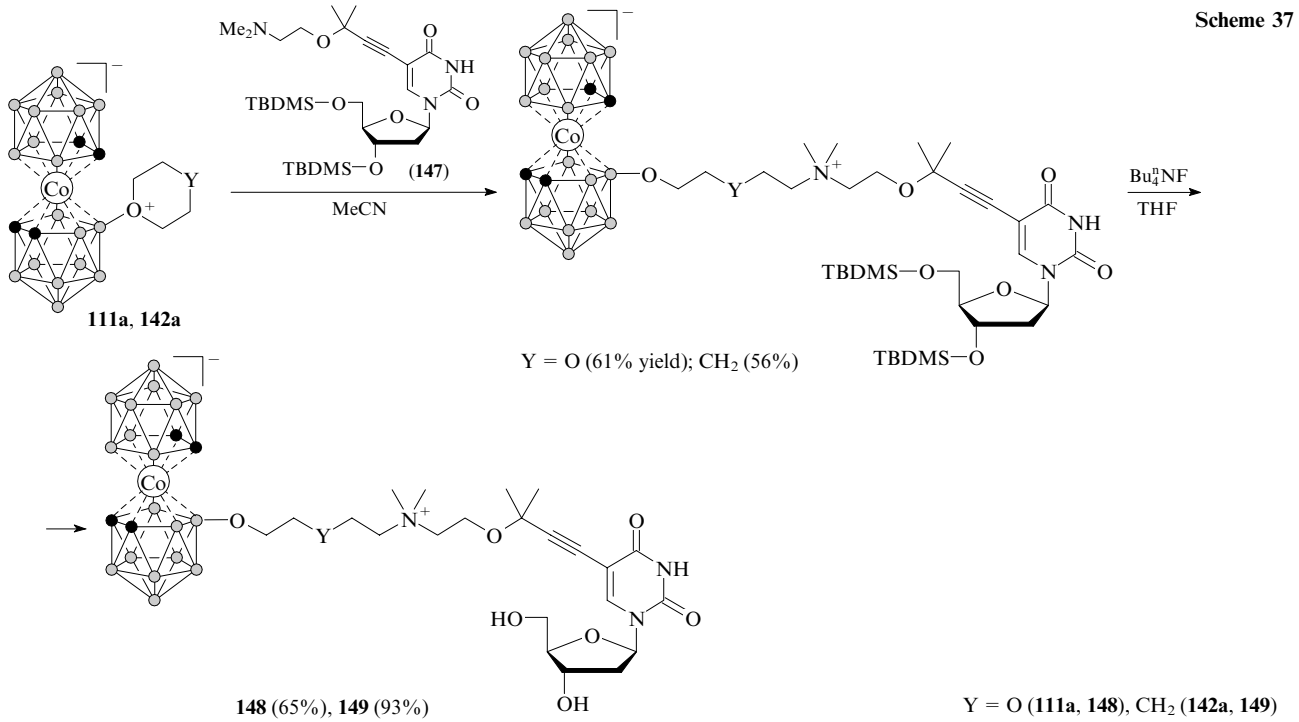
A far more facile and efficient method was developed later for preparing anionic conjugates of 5-ethynyl-2′-deoxyuridine and cobalt bis(1,2-dicarbollide) having a charge of −1.[78] This was the first time that the Sonogashira reaction was applied to cobalt bis(1,2-dicarbollide)-based alkynes. The cross-coupling of unprotected 5-iodo-2′-deoxyuridine (**95a**) with terminal cobalt bis(1,2-dicarbollide) alkynes (**137a**,**c** and **150a**,**b**) in DMF in the presence of $Pd(PPh_3)_4$ and Et_3N at room temperature for 24 h yielded conjugates **151a**,**b** and **152a**,**b**, respectively, in the form of water-soluble potassium salts (Scheme 38). Alkynes **137a**,**c** and **150a**,**b** were prepared by reacting oxonium cobalt bis(1,2-dicarbollide) derivatives with terminal alkyne alcohols in the presence of K_3PO_4.[79] Noteworthy, a furano[2,3-*d*]pyrimidine derivative was not formed in this reaction as an intramolecular cyclization side product even in trace amounts.[80] The advantage of DMSO consists in that, due to its high dissolution power, nucleosides with unprotected hydroxy groups can participate in the reaction. The reaction mixture should be treated with a saturated solution of K_2CO_3 to convert the conjugates from the triethylammonium to potassium salt.

Fused bicyclic derivatives of pyrimidine nucleosides, namely furano[2,3-*d*]pyrimidine 2′-deoxyribonucleosides and their pyrrolopyrimidine analogues, show a high promise for use in pharmaceutical chemistry; their antiviral activity was discovered recently[81,82] and gave impetus to the activities in the preparation and characterization of variously modified fused bicyclic nucleoside derivatives, including boron-containing species.

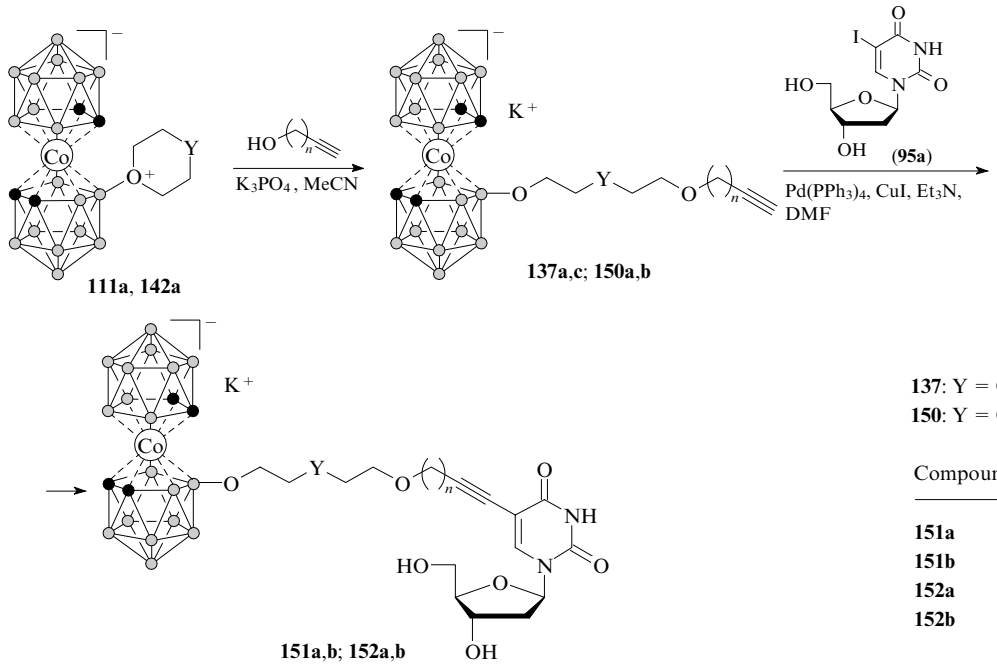
The main route to prepare furano[2,3-*d*]pyrimidin-2(3*H*)-one isomers of 5-ethynyl-2′-deoxyuridine is *via* the rearrangement of ethynyl-2′-deoxyuridines induced by Lewis acids, usually CuI, in the presence of Et_3N[82] or by mercury sulfate[83] or mercury chloride and zinc trifluoroacetate.[84] However, there is another method to prepare such cobalt bis(1,2-dicarbollide) derivatives. The direct cyclization of conjugates **153** and **154** in acetonitrile upon refluxing for 45 min with catalytic amounts of CuI and Et_3N yields furano[2,3-*d*]pyrimidine nucleosides derivatives with cobalt bis(1,2-dicarbollide) (**155**, **156**) in the form of potassium salts (Scheme 39).[78]

In the synthesis of conjugates **157** and **158**, where pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides are conjugated with cobalt bis(1,2-dicarbollide), metallic palladium on carbon, CuI and Et_3N were used to catalyze the addition of the alkyne to the base and subsequent cyclization. Reacting alkynes **137a**,**c** and **150a**,**b** with 3′,5′-di(*O*-acetyl)-

Scheme 37



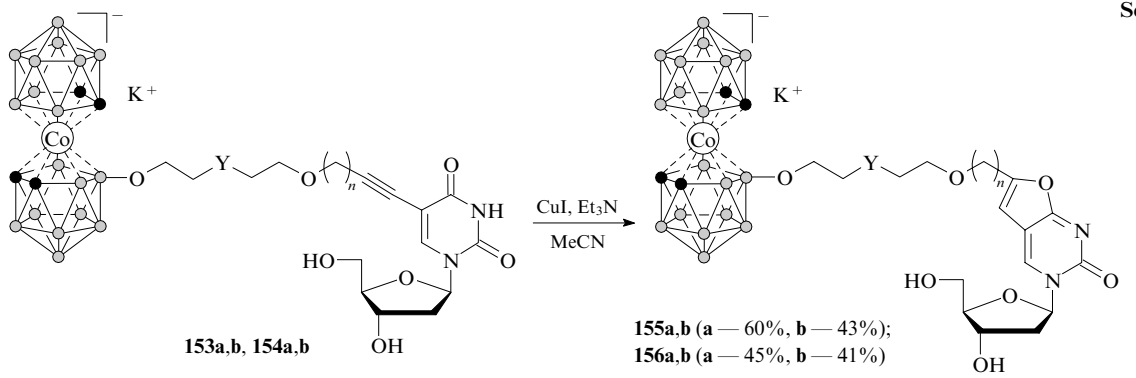
Scheme 38



137: Y = O: n = 1 (**a**), 2 (**c**);
150: Y = CH_2: n = 1 (**a**), 2 (**b**)

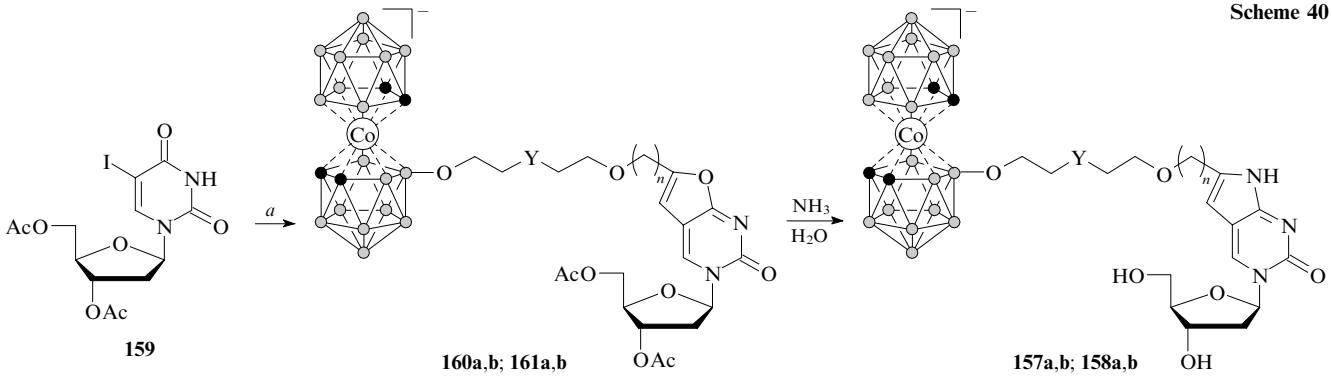
Compound	Y	n	Yield (%)
151a	O	1	81
151b	O	2	75
152a	CH_2	1	67
152b	CH_2	2	69

Scheme 39



Y = O (**153**, **155**), CH_2 (**154**, **156**); n = 1 (**a**), 2 (**b**)

Scheme 40



(*a*) **137a**, or **137c**, or **150a**, or **150b**; Pd/C, CuI, Et_3N, MeCN

Compound	Y	n	Yield (%)	Compound	Y	n	Yield (%)
160a	O	1	59	**157a**	O	1	96
160b	O	2	57	**157b**	O	2	93
161a	CH_2	1	40	**158a**	CH_2	1	95
161b	CH_2	2	40	**158b**	CH_2	2	96

5-iodo-2′-deoxyuridine (**159**) in boiling acetonitrile yields acylated conjugates of furano[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides with cobalt bis(1,2-dicarbollide) (**160a**,**b** and **161a**,**b**, respectively). The presence of Ph_3P in the reaction in this case does not affect the furanopyrimidinone yield. At the same time, the degree of cyclization is appreciably affected by the presence of 3′,5′-*O*-acetyl groups. Since the hydroxy groups of 2′-deoxyribose are protected, the reaction proceeds without complications. Further reacting these compounds with 25% aqueous ammonia at room temperature leads to the elimination of acetyl groups from the carbohydrate moiety and O – N exchange to yield new conjugates **157a**,**b** and **158a**,**b** of pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides with cobalt bis(1,2-dicarbollide) (Scheme 40).[78]

The main route to prepare metallacarborane-containing nucleosides is based on nucleophilic substitution reactions. For example, the opening of the oxonium ring of cobalt (iron) bis(1,2-dicarbollide) by nucleophilic centres of all the four nucleosides can generate desired derivatives. However, this method usually requires that protecting groups be introduced into the carbohydrate moiety of the nucleoside. Another route, which consists of Cu^{I}-catalysed 1,3-dipolar cycloaddition of alkynes to azides, is universal, as unlike in the non-catalyzed process, the reaction proceeds regiospecifically to yield 1,4-disubstituted 1,2,3-triazoles. A more facile two-step route to the preparation of anionic 5-ethynyl-2′-deoxyuridine conjugates with cobalt bis(1,2-dicarbollide) is opened by the Sonogashira reaction, which proceeds without complications and is a convenient method for preparing boron-containing 5-alkynylated pyrimidine nucleosides. This reaction does not produce furano[2,3-*d*]-pyrimidine derivatives as intramolecular cyclization side products even in trace amounts. From this, one can infer that the successful use of O-unprotected nucleosides in the coupling reaction with alkynes is due to the good choice of solvent (DMF) and not to the palladium catalyst. The advantage of this approach is that there is no need to protect the hydroxy groups of the carbohydrate moiety in the nucleoside to prepare the desired conjugates, and this appreciably simplifies the synthetic scheme. The feasibility to prepare the anionic forms of desired compounds is also of great importance, because of being important to biological studies. Noteworthy, the closing of a fused furan ring with participation of a triple bond is sterically hindered because of the linear configuration of the triple bond; in this process, however, this bond can be easily disturbed to attain the suitable transition state. A catalyst is needed for closing the furan ring. Many metals have catalytic properties to produce furans from compounds that contain a keto group and a triple bond in their structures. However, Cu^{I} salts are preferred for this process; the use of other metals gives rise to some problems. Some metals (palladium and mercury) are poisonous, which is impermissible for the reason that the compounds to be prepared are regarded as precursors for medicines. Silver salts have a drawback in that hydroxy groups should be obligatorily protected because of their ability to coordinate to Ag^{+} ions and the attendant appreciable decrease in product yield. So, studies of the intramolecular cyclization of boron-containing 5-ethynyl-2′-deoxyuridines gave rise to the preparation of their isomeric furano[2,3-*d*]pyrimidine derivatives. The latter were reacted with ammonia to replace the oxygen atom in position 7 of the bicyclic derivative by an NH group and to yield cobalt bis(1,2-dicarbollide) conjugates with pyrrolo[2,3-*d*]pyrimidine-2(3*H*) nucleosides.

IV. Conjugates with *closo*-dodecaborate

There are only few examples of conjugates of *closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ with nucleosides in the literature. Two routes were developed to prepare thymidine *closo*-dodecaborate conjugates. The first comprises the ring opening of oxonium *closo*-dodecaborate derivative **162a** in a reaction with 3′,5′-bis(*tert*-butyldimethylsilyl)-2′-deoxythymidine in the presence of K_2CO_3. As a result, regioselective alkylation at the N(3) atom yields protected adduct **163a** exclusively, whose treatment by $Bu^{n}_{4}NF$ yields thymidine *closo*-dodecaborate conjugate **164a** (Scheme 41).[85] However, the reaction of protected thymidine with dioxonium *closo*-dodecaborate derivative **162a** in toluene in the presence of NaH produces three isomers, which can hardly be separated chromatographically. The production of N(3)-isomer **164a** exclusively is likely due to the fact that K_2CO_3 (a weak base) selectively deprotonates thymidine at N(3) (the highest acidity centre), and NaH (a stronger base) converts it to three possible sodium salts [N(3)Na, O(2)Na and O(4)Na].

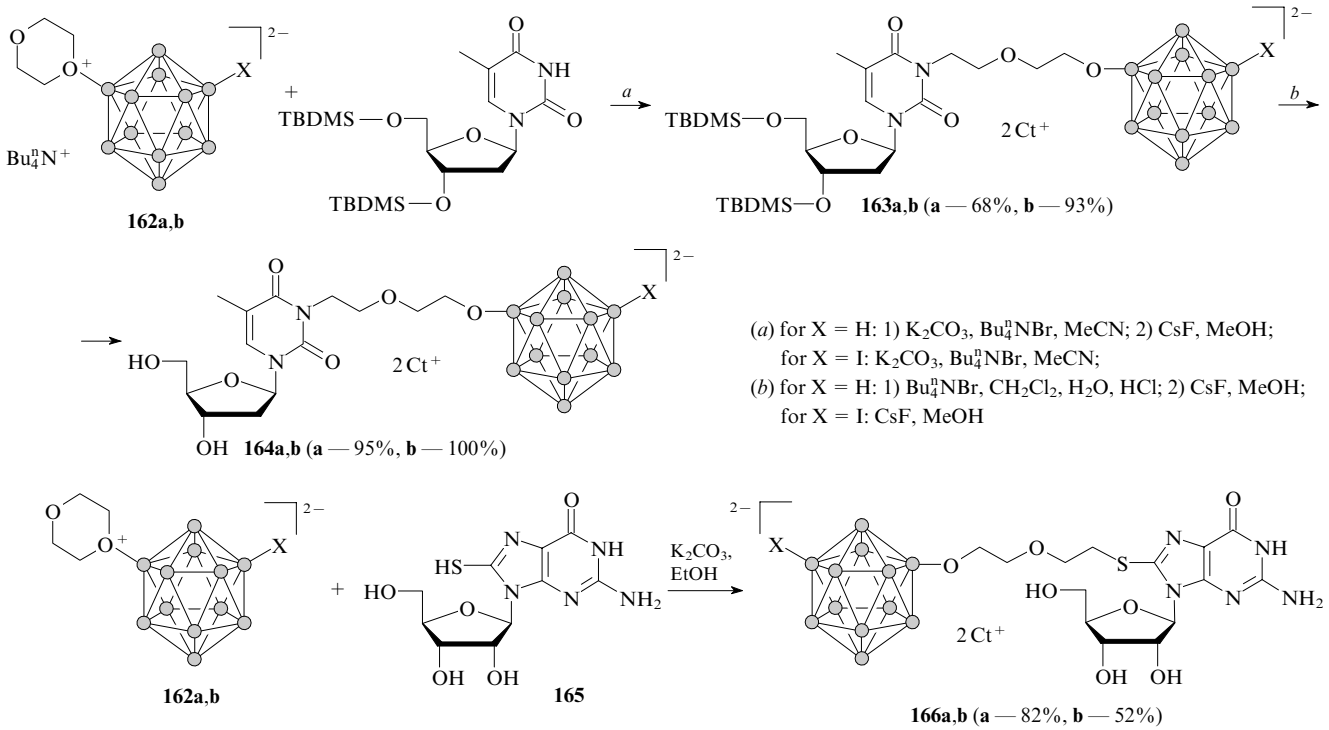
A similar method in the presence of K_2CO_3 was used to prepare a conjugate of a substituted *closo*-dodecaborate with thymidine, namely 1-iodo-7-dioxoniodecahydro-*closo*-dodecaborate (**162b**). Compound **162b** can easily be prepared regioselectively by the procedure described by Semioshkin *et al.*[86] Interestingly, in the case of iodinated cluster **162b**, the reaction with protected thymidine proceeds more rapidly (the full conversion is in 2 h at room temperature) than in the case of non-iodinated oxonium derivative **162a** (boiling is required; the reaction does not proceed at room temperature). The elimination of silyl protecting groups in compound **163b** by caesium fluoride yields conjugate **164b**.[87]

The opening of oxonium *closo*-dodecaborate derivatives by 8-sulfanylguanosine (**165**), prepared from 8-bromoguanosine,[88] was used to prepare the first guanosine $[B_{12}H_{12}]^{2-}$ conjugates **166a**,**b** (see Scheme 41).[87,89] When unsubstituted *closo*-dodecaborate derivative **162a** is refluxed with 8-sulfanylguanosine in absolute ethanol in the presence of K_2CO_3, full conversion is observed in 16 h. The reaction of iodinated *closo*-dodecaborate derivative **162b** proceeds under similar conditions, with full conversion achieved far more quickly, in 5-h refluxing.

There is one more strategy to prepare such derivatives. As mentioned above, *N*(3)-(pent-4-yn-1-yl)thymidine undergoes a regioselective [3 + 2] cycloaddition with azides based on cobalt (iron) bis(1,2-dicarbollide) to yield triazoles.[69] This strategy is also suitable for preparing a thymidine *closo*-dodecaborate conjugate. The reaction of $[B_{12}H_{11}O(CH_2)_2O(CH)_2N_3]^{2-}$ (**167**) with *N*(3)-(pent-4-yn-1-yl)thymidine (**135**) catalyzed by a mixture of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate yields conjugate **168**, where the *closo*-dodecaborate is linked to nucleoside through a stable triazole ring at the N(3) atom of the thymidine (Scheme 42).[90]

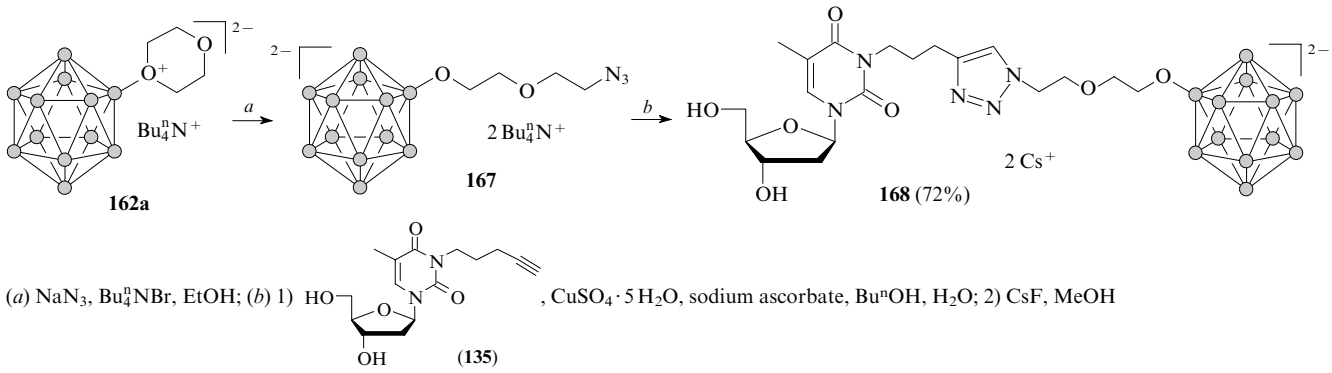
Oxonium *closo*-dodecaborate derivatives are known to react with aliphatic amines to yield ammonium salts.[71] However, $[B_{12}H_{11}O^{+}(CH_2CH_2)_2O]^{-}$ (**162a**) is not opened by the *exo*-amino groups of adenosine, so a suitable nucleoside derivative, namely 2′,3′,5′-tris-(*O*-*tert*-butyldimethyl-

Scheme 41



X = H (**a**), I (**b**); Ct = Cs (**163a**, **164a**, **166a**), Bu$^n_4$N (**163b**, **164b**, **166b**)

Scheme 42

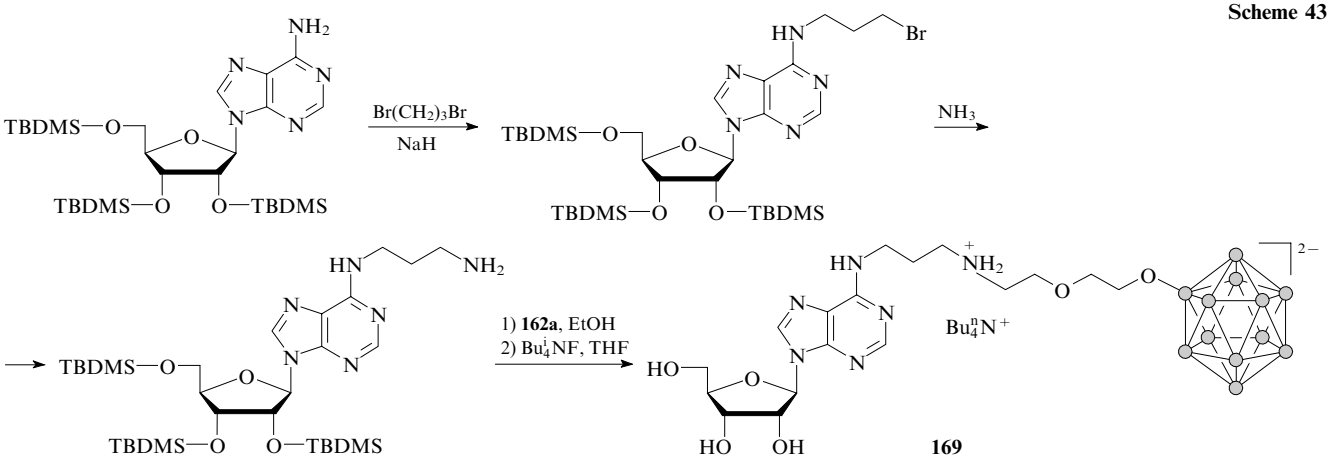


silyl)-*N*(6)-(3-aminopropyl)adenosine, was prepared from 2′,3′,5′-tris(*O*-*tert*-butyldimethylsilyl)adenosine in two steps.[91] Nucleophilic ring opening in oxonium *closo*-dodecaborate **162a** by the reaction product, followed by desilylation *in situ*, yields adenosine conjugate **169** (Scheme 43).

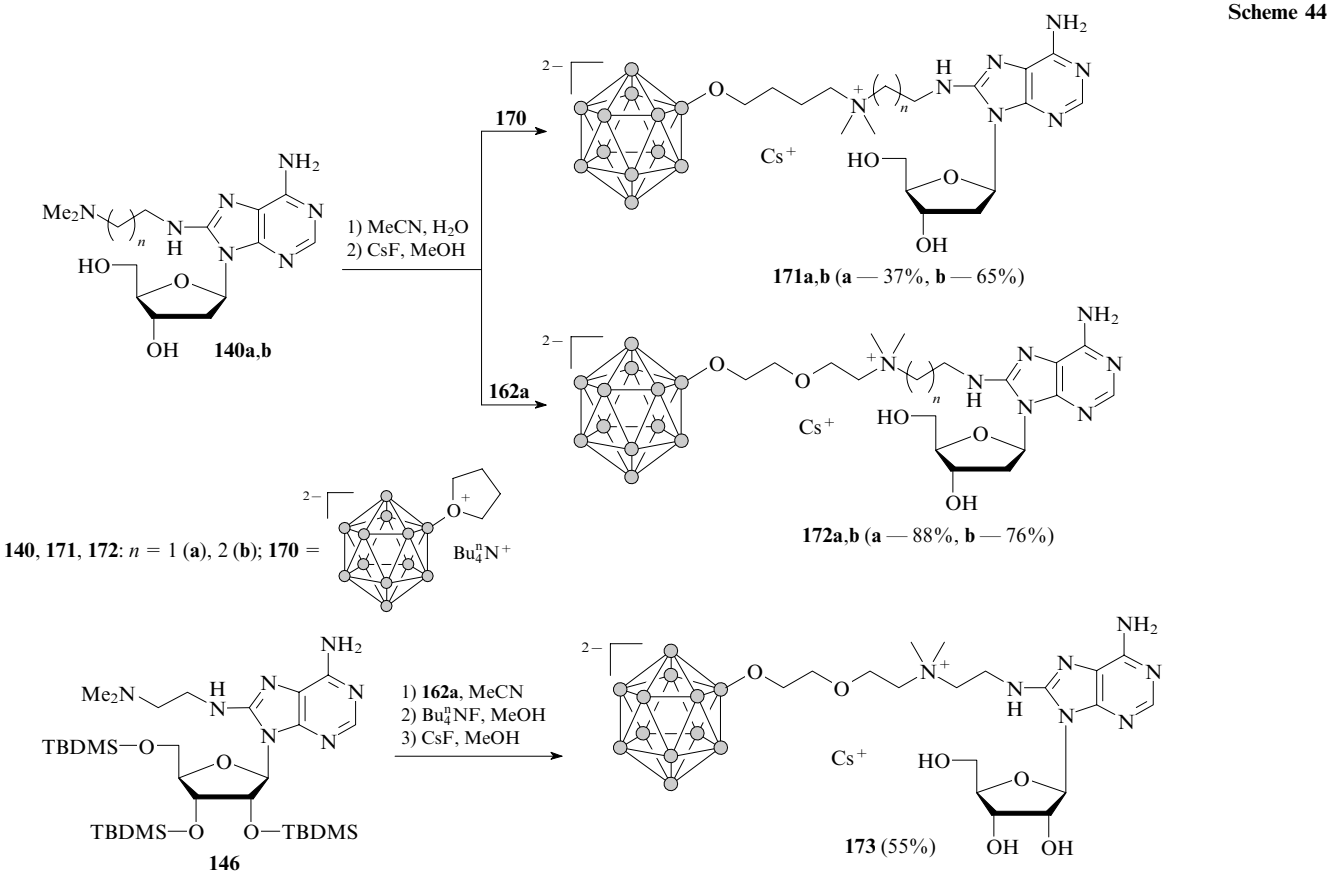
Reacting cyclic oxonium *closo*-dodecaborate derivatives with amines appeared a fruitful strategy to prepare various derivatives of this boron cluster. Reactions with tertiary amines are of special interest for the preparation of nucleoside *closo*-dodecaborate conjugates.[71] The advantage of this method lies in that the reaction produces stable quaternary ammonium salts in good yields and in the feasibility to use tertiary amines in the ratio 1 : 1 with boron-containing electrophiles. The universal character of the strategy made it possible to prepare new 2′-deoxyadenosine *closo*-dodecaborate conjugates, where the nucleoside is linked to the boron cluster at the C(8) atom of the purine base. The reactions of 8-bromo-2′-deoxyadenosine with asymmetric *N*,*N*-dimethylethylenediamines or -propylenediamines yield 2′-deoxyadenosine derivatives **140a**,**b** with an NMe_2 group in the side chain. The optimal conditions for these reactions are to reflux 8-bromo-2′-deoxyadenosine [92, 93] in the proper amine [94] for 5 h. Upon the nucleophilic opening of 2′-deoxyadenosine-modified cyclic oxonium *closo*-dodecaborates **170** and **162a** in MeCN under reflux, 2′-deoxyadenosine *closo*- dodecaborate conjugates **171a**,**b** and **172a**,**b** are produced in the form of caesium salts (Scheme 44).[73, 74] Adenosine *closo*-dodecaborate conjugate **173**, as the cobalt bis(1,2-dicarbollide) conjugate,[74] was prepared from 8-(2-dimethylaminoetyhyl)amino-2′,3′,5′-tris(*tert*-butyldimethylsilyl)adenosine (**146**). The reaction of boron cluster **162a** with nucleoside **146** under reflux in MeCN for 5 h, followed by the *in situ* elimination of protecting groups, generates conjugate **173**, which is isolated in the form of a caesium salt (see Scheme 44).[74]

The opening of oxonium derivatives of boron clusters by tertiary amines was also successfully used to prepare 5-ethynyl-2′-deoxyuridine *closo*-dodecaborate conjugates.

Scheme 43



Scheme 44

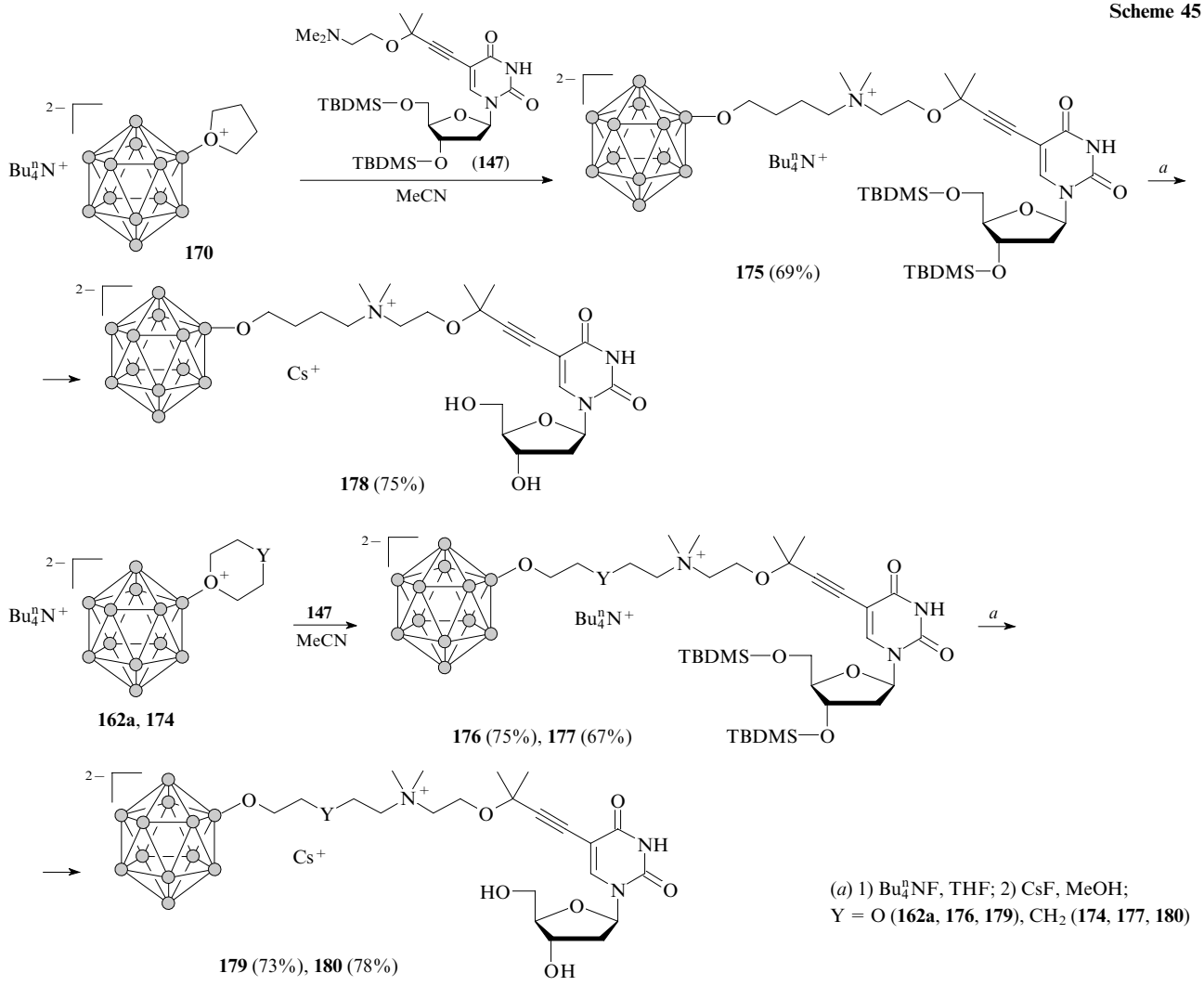


The reactions of cyclic oxonium *closo*-dodecaborate derivatives **162a**, **170** and **174** with a small excess of amine **147** under reflux in acetonitrile proceeds to yield protected derivatives **175** – **177**, which can be desilylated by Bu_4^nNBr to yield 5-ethynyl-2′-deoxyuridine *closo*-dodecaborate conjugates **178** – **180** (Scheme 45). NMe_2-Modified 5-ethynyl-2′-deoxyuridine **147** can be prepared by the Sonogashira reaction from an alkyne amine, as considered for its conjugate with cobalt bis(1,2-dicarbollide).[77]

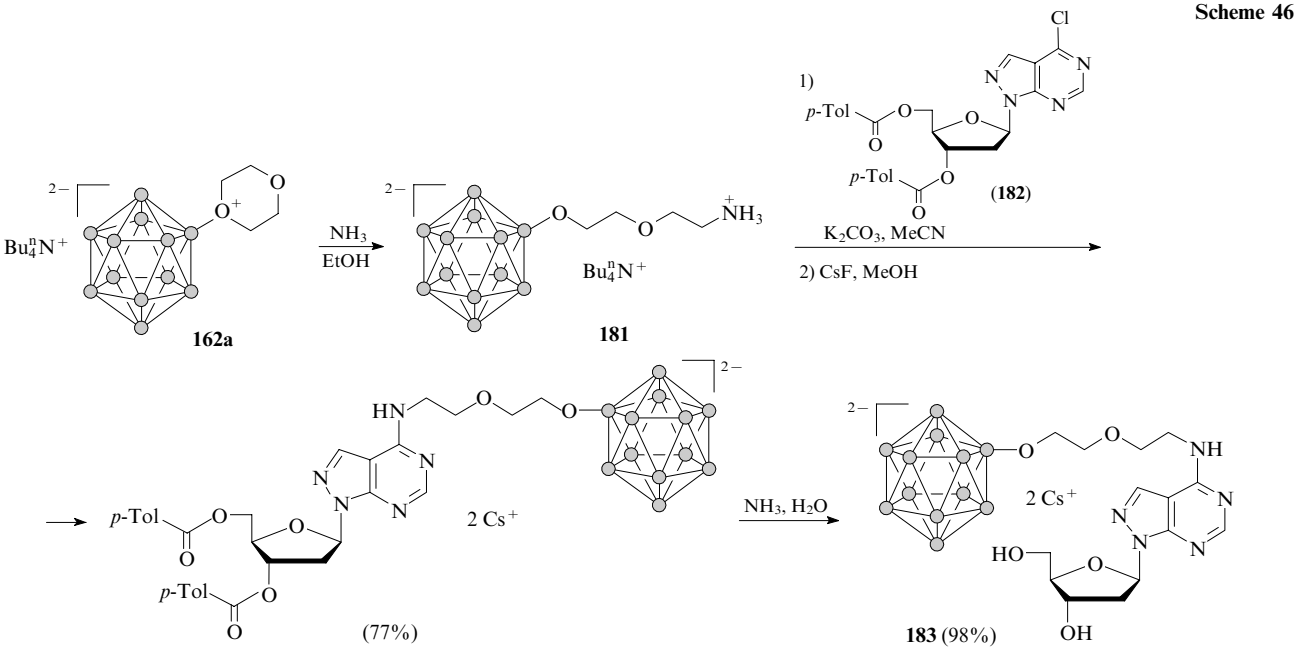
The reaction of primary ammonium salt **181** with non-natural nucleoside analogue **182** in the presence of K_2CO_3, followed by the elimination of protecting groups from the carbohydrate moiety, served to prepare the first 8-aza-7-deaza-2′-deoxyadenosine *closo*-dodecaborate conjugate **183** (Scheme 46).[95] Primary ammonium salt **181** was prepared from cyclic oxonium *closo*-dodecaborate **162a** and ammonia in ethanol.

The nucleophilic opening of the oxonium moiety of polyhedral boron hydride is used to prepare nucleoside *closo*-dodecaborate derivatives. This universal method can serve to produce large amounts of desired *closo*-dodecaborate derivatives for libraries of such compounds with varied boron polyhedron structures and linker unit lengths. As mentioned above, the regioselective [3 + 2] cycloaddition of azides to alkynes yielding 1,4-disubstituted 1,2,3-triazoles is used to synthesize cobalt (iron) bis(1,2-dicarbollide) conjugates. This method is also suitable for preparing a thymidine *closo*-dodecaborate conjugate, and it is very

Scheme 45



Scheme 46



efficient as it does not require introducing and then eliminating protecting groups in the carbohydrate moiety of the nucleoside and requires fewer steps.

V. Conclusion

The reviewed pieces of data show that the synthesis of nucleoside conjugates with polyhedral boron compounds, a relatively new line of research in the chemistry of modified nucleosides, in the latest decades has been of great interest to both synthetic chemists and biologists. These boron compounds can serve as the basis for the design of medicines for diverse purposes.[96, 97] In the latest two decades, a great many new conjugates of polyhedral boron compounds were prepared, such as *closo*-carboranes, *nido*-carboranes, metallacarboranes, and *closo*-dodecaborates, with all canonical nucleosides and with their non-native analogues. A nucleoside was modified with boron polyhedra both at the purine or pyrimidine base and at the carbohydrate unit.

The detailed consideration of the main approaches to the preparation of conjugates of polyhedral boron compounds with nucleosides allows us to conclude the following: in most cases, nucleophilic substitution reactions are used at the stage of adding the boron polyhedron to the nucleoside. In this case, the key role is played by the nature of the boron polyhedron and its chemical properties; the synthesis frequently comprises many steps and is laborious. Cross-coupling and [3 + 2] dipolar cycloaddition reactions are used far less frequently at the step of addition of the boron polyhedron to the nucleoside. At the same time, these two approaches are universal; that is, their use is independent of the nature of the boron polyhedron; further, they usually comprise one to three simple steps. One recent study[98] showed that the [3 + 2] dipolar cycloaddition of carboranylalkyl azides to alkynylated nucleosides makes it possible to prepare some conjugates in one or two steps virtually avoiding the use of protecting groups, which is incommensurately less laborious than the earlier multistep approaches to the preparation of nucleoside carborane conjugates. We hold the opinion that just these methods will in future help to prepare a wide spectrum of compounds of this type, which can serve as the basis for the design of a new generation of medicines.

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References

1. D L Nelson, M M Cox, in *Lehninger Principles of Biochemistry. Nucleotides and Nucleic Acids* (5th Edn) (New York: Worth Publishers, 2008) p. 271
2. J Niziol, W Rode, T Ruman *Mini-Rev. Org. Chem.* **9** 418 (2012)
3. A R Martin, J-J Vasseur M Smietana *Chem. Soc. Rev.* **42** 5684 (2013)
4. W Tjarks, R Tiwari, Y Byun, S Narayanasamy, R F Barth *Chem. Commun.* 4978 (2007)
5. H Nakamura, M Kirihata, in *Neutron Capture Therapy* (Ed. W A G Sauerwein) (Berlin, Heidelberg: Springer, 2012) p. 99
6. M F Hawthorne *Angew. Chem., Int. Ed. Engl.* **32** 950 (1993)
7. C Morin *Tetrahedron* **50** 12521 (1994)
8. W Tjarks *J. Organomet. Chem.* **614 – 615** 37 (2000)
9. Y Byun, S Narayanasamy, J Johnsamuel, A K Bandyopadhyaya, R Tiwari, A S Al-Madhoun, R F Barth, S Eriksson, W Tjarks *Anti-Cancer Agents Med. Chem.* **6** 127 (2006)
10. P Li, Z A Sergueeva, M Dobrikov, B R Shaw *Chem. Rev.* **107** 4746 (2007)
11. A Khalil, K Ishita, T Ali, W Tjarks *Future Med. Chem.* **5** 677 (2013)
12. Z J Lesnikowski, J Shi, R F Schinazi *J. Organomet. Chem.* **581** 156 (1999)
13. J F Valliant, K J Guenther, A S King, P Morel, P Schaffer, O O Sogbein, K A Stephenson *Coord. Chem. Rev.* **232** 173 (2002)
14. Z J Lesnikowski *Eur. J. Org. Chem.* 4489 (2003)
15. Z J Lesnikowski *Collect. Czech. Chem. Commun.* **72** 1646 (2007)
16. Z J Lesnikowski *J. Organomet. Chem.* **694** 1771 (2009)
17. I B Sivaev, V I Bregadze *Ros. Khim. Zh.* **48** (4) 109 (2004)
18. R F Schinazi, W H Prusoff *J. Org. Chem.* **50** 841 (1985)
19. Y Yamamoto, T Seko, H Nemoto *J. Org. Chem.* **54** 4734 (1989)
20. A M Yurkevich, I I Kolodkina, L S Varshavskaya, V I Borodulina-Shwetz, I P Rudakova, N A Preobrazhenski *Tetrahedron* **25** 477 (1969)
21. S X Cai, J F W Keana *Bioconjug. Chem.* **2** 317 (1991)
22. A R Martin, K Mohanan, D Luvino, N Floquet, C Baraguey, M Smietana, J-J Vasseur *Org. Biomol. Chem.* **7** 4369 (2009)
23. C El Amri, A R Martin, J-J Vasseur, M Smietana *ChemBioChem* **13** 1605 (2012)
24. A Sood, B F Spielvogel, B R Shaw *J. Am. Chem. Soc.* **111** 9234 (1989)
25. J-C Zhuo, A H Soloway, J C Beeson, W Ji, B A Barnum, F-G Rong, W Tjarks, G T Jordan, J Liu, S G Shore *J. Org. Chem.* **64** 9566 (1999)
26. N A Petasis *Aust. J. Chem.* **60** 795 (2007)
27. W E Hill, F A Johnson, R W Novak *Inorg. Chem.* **14** 1244 (1975)
28. Y Yamamoto, T Seko, H Nakamura, H Nemoto, H Hojo, N Mukai, Y Hashimoto *J. Chem. Soc., Chem. Commun.* 157 (1992)
29. Y Yamamoto, T Seko, H Nakamura, H Nemoto *Heteroat. Chem.* **3** 239 (1992)
30. R N Grimes *Carboranes* (2nd Edn) (Amsterdam: Elsevier, 2011)
31. M F Hawthorne, D C Young, P M Garrett, D A Owen, S G Schwerin, F N Tebbe, P A Wegner *J. Am. Chem. Soc.* **90** 862 (1968)
32. L I Zakharkin, A V Grebennikov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2019 (1966)
33. F-G Rong, A H Soloway *Nucleosides Nucleotides* **13** 2021 (1994)
34. F-G Rong, A H Soloway, S Ikeda, D H Ives *Nucleosides Nucleotides* **14** 1873 (1995)
35. A J Lunato, J Wang, J E Woollard, A K M Anisuzzaman, W Ji, F-G Rong, S Ikeda, A H Soloway, S Eriksson, D H Ives, T E Blue, W Tjarks *J. Med. Chem.* **42** 3378 (1999)
36. G W Kabalka, M Varma, R S Varma, P C Srivastava, F F Knapp Jr *J. Org. Chem.* **51** 2386 (1986)
37. Y Byun, J Yan, A S Al-Madhoun, J Johnsamuel, W Yang, R F Barth, S Eriksson, W Tjarks *J. Med. Chem.* **48** 1188 (2005)
38. Y Byun, J Yan, A S Al-Madhoun, J Johnsamuel, W Yang, R F Barth, S Eriksson, W Tjarks *Appl. Radiat. Isot.* **61** 1125 (2004)

39. A S Al-Madhoun, J Johnsamuel, J Yan, W Ji, J Wang, J-C Zhuo, A J Lunato, J E Woollard, A E Hawk, G Y Cosquer, T E Blue, S Eriksson, W Tjarks *J. Med. Chem.* **45** 4018 (2002)
40. Y Byun, B T S Thirumamagal, W Yang, S Eriksson, R F Barth, W Tjarks *J. Med. Chem.* **49** 5513 (2006)
41. U Kusari, Y Li, M G Bradley, L G Sneddon *J. Am. Chem. Soc.* **126** 8662 (2004)
42. D C Busby, M F Hawthorne *Inorg. Chem.* **21** 4101 (1982)
43. S Narayanasamy, B T S Thirumamagal, J Johnsamuel, Y Byun, A S Al-Madhoun, E Usova, G Y Cosquer, J Yan, A K Bandyopadhyaya, R Tiwari, S Eriksson, W Tjarks *Bioorg. Med. Chem.* **14** 6886 (2006)
44. P Davoli, A Spaggiari, L Castagnetti, F Prati *Org. Biomol. Chem.* **2** 38 (2004)
45. H K Agarwal, C A McElroy, E Sjuvarsson, S Eriksson, M V Darby, W Tjarks *Eur. J. Med. Chem.* **60** 456 (2013)
46. H K Agarwal, A Khalil, K Ishita, W Yang, R J Nakkula, L-C Wu, T Ali, R Tiwari, Y Byun, R F Barth, W Tjarks *Eur. J. Med. Chem.* **100** 197 (2015)
47. H J Jessen, W Fendrich, C Meier *Eur. J. Org. Chem.* 924 (2006)
48. J G Wilson, A K M Anisuzzaman, F Alam, A H Soloway *Inorg. Chem.* **31** 1955 (1992)
49. K Bednarska, A B Olejniczak, A Piskala, M Klink, Z Sulowska, Z J Lesnikowski *Bioorg. Med. Chem.* **20** 6621 (2012)
50. K Bednarska, A B Olejniczak, B A Wojtczak, Z Sułowska, Z J Leśnikowski *ChemMedChem.* **5** 749 (2010)
51. M Ikehara, M Kaneko *Chem. Pharm. Bull.* **18** 2441 (1970)
52. W Jiang, C B Knobler, C E Curtis, M D Mortimer, M F Hawthorne *Inorg. Chem.* **34** 3491 (1995)
53. M J Robins, B Uznański *Can. J. Chem.* **59** 2601 (1981)
54. A Olejniczak, B Wojtczak, Z J Lesnikowski *Nucleosides, Nucleotides Nucleic Acids* **26** 1611 (2007)
55. G W Kabalka, R N Kesavulu, C Narayana, in *Cancer Neutron Capture Therapy* Vol. 21 (Ed. Y Mishima) (New York: Plenum Press, 1996) p. 157
56. M Białek-Pietras, A B Olejniczak, E Paradowska, M Studzińska, P Suski, A Jabłońska, Z J Leśnikowski *J. Organomet. Chem.* **798** 99 (2015)
57. C McGuigan, C J Yarnold, G Jones, S Velázquez, H Barucki, A Brancale, G Andrei, R Snoeck, E De Clercq, J Balzarini *J. Med. Chem.* **42** 4479 (1999)
58. R Kumar, L I Wiebe, E E Knaus *Can. J. Chem.* **74** 1609 (1996)
59. W Tjarks, A K M Anisuzzaman, L Liu, A H Soloway, R F Barth, D J Perkins, D A Adams *J. Med. Chem.* **35** 1628 (1992)
60. B Wojtczak, A Semenyuk, A B Olejniczak, M Kwiatkowski, Z J Lesnikowski *Tetrahedron Lett.* **46** 3969 (2005)
61. A B Olejniczak, A Semenuk, M K iatkowski, Z J Lesnikowski *J. Organomet. Chem.* **680** 124 (2003)
62. B S Sproat, in *Methods in Molecular Biology* Vol. 20 (Ed. S Agraval) (Totowa, NJ: Humana, 1993) p. 115
63. J Hovinen, E Azhayeva, A Azhayev, A Guzaev, H Lönberg *J. Chem. Soc., Perkin Trans. 1* 211 (1994)
64. B A Wojtczak, A B Olejniczak, Z J Lesnikowski *Curr. Protoc. Nucleic Acid Chem.* Suppl. **38** 4.37.1 (2009)
65. A B Olejniczak, J Plešek, O Kříž, Z J Lesnikowski *Angew. Chem., Int. Ed.* **42** 5740 (2003)
66. A B Olejniczak, J Plešek, Z J Leśnikowski *Chem. – Eur. J.* **13** 311 (2007)
67. A B Olejniczak, P Mucha, B Grüner, Z J Lesnikowski *Organometallics* **26** 3272 (2007)
68. C W Tornøe, C Christensen, M Meldal *J. Org. Chem.* **67** 3057 (2002)
69. B A Wojtczak, A Andrysiak, B Crüner, Z J Lesnikowski *Chem. – Eur. J.* **14** 10675 (2008)
70. A A Semioshkin, I B Sivaev, V I Bregadze *Dalton Trans.* 977 (2008)
71. A Semioshkin, E Nizhnik, I Godovikov, Z Starikova, V Bregadze *J. Organomet. Chem.* **692** 4020 (2007)
72. I B Sivaev, Z A Starikova, S Sjöberg, V I Bregadze *J. Organomet. Chem.* **649** 1 (2002)
73. A Semioshkin, V Bregadze, I Godovikov, A Ilinova, Z J Lesnikowski, I Lobanova *J. Organomet. Chem.* **696** 3750 (2011)
74. A A Ilinova, V I Bregadze, A N Bogomazova, I A Lobanova, A F Mironov, A A Semioshkin *Russ. Chem. Bull., Int. Ed.* **62** 1115 (2013) [*Izv. Akad. Nauk, Ser. Khim.* 1115 (2013)]
75. I Lobanova, I Kosenko, J Laskova, I Ananyev, A Druzina, A Godovikov, V I Bregadze, S Qi, Z J Leśnikowski, A Semioshkin *Dalton Trans.* **44** 1571 (2015)
76. L-L Gundersen *Acta Chem. Scand.* **50** 58 (1996)
77. A Semioshkin, A Ilinova, I Lobanova, V Bregadze, E Paradowska, M Studzińska, A Jablońska, Z J Lesnikowski *Tetrahedron* **69** 8034 (2013)
78. A Ilinova, A Semioshkin, I Lobanova, V I Bregadze, A F Mironov, E Paradowska, M Studzińska, A Jablońska, M Białek-Pietras, Z J Leśnikowski *Tetrahedron* **70** 5704 (2014)
79. I D Kosenko, I A Lobanova, I A Chekulaeva, I A Godovikov, V I Bregadze *Russ. Chem. Bull., Int. Ed.* **62** 497 (2013) [*Izv. Akad. Nauk, Ser. Khim.* 496 (2013)]
80. M J Robins, R S Vinayak, S G Wood *Tetrahedron Lett.* **31** 3731 (1990)
81. J Balzarini, C McGuigan *J. Antimicrob. Chemother.* **50** 5 (2002)
82. M J Robins, I Nowak, V K Rajwanski, K Miranda, J F Cannon, M A Peterson, G Andrei, R Snoeck, E De Clercq, J Balzarini *J. Med. Chem.* **50** 3897 (2007)
83. M J Robins, P J Barr *J. Org. Chem.* **48** 1854 (1983)
84. A Sniady, A Durham, M S Morreale, A Marcinek, S Szafert, T Lis, K R Brzezinska, T Iwasaki, T Ohshima, K Mashima, R Dembinski *J. Org. Chem.* **73** 5881 (2008)
85. A Semioshkin, J Laskova, B Wojtczak, A Andrysiak, I Godovikov, V Bregadze, Z J Lesnikowski *J. Organomet. Chem.* **694** 1375 (2009)
86. A Semioshkin, V Bregadze, I Godovikov, A Ilinova, J Laskova, Z Starikova *J. Organomet. Chem.* **696** 2760 (2011)
87. A A Ilinova, V I Bregadze, J N Laskova, A Semioshkin, A F Mironov *Russ. Chem. Bull., Int. Ed.* **61** 1663 (2012) [*Izv. Akad. Nauk, Ser. Khim.* 1646 (2012)]
88. R E Holmes, R K Robins *J. Am. Chem. Soc.* **86** 1242 (1964)
89. A Semioshkin, J Laskova, A Ilinova, V Bregadze, Z J Lesnikowski *J. Organomet. Chem.* **696** 539 (2011)
90. A A Semioshkin, S N Osipov, J N Grebenyuk, E A Nizhnik, I A Godovikov, G T Shchetnikov, V I Bregadze *Collect. Czech. Chem. Commun.* **72** 1717 (2007)
91. A Semioshkin, J Grebenyuk, B Wojtczak, A Andrysiak, Z J Lesnikowski, in The *XIIIth International Conference on Boron Chemistry, Platja d'Aro, 2008* p. OC-A14
92. G Butora, C Schmitt, D A Levorse, E Streckfuss, G A Doss, M MacCoss *Tetrahedron* **63** 3782 (2007)
93. L Clima, W Bannwarth *Helv. Chim. Acta* **91** 165 (2008)
94. E Halbfinger, D T Major, M Ritzmann, J Ubl, G Reiser, J L Boyer, K T Harder, B Fischer *J. Med. Chem.* **42** 5325 (1999)
95. J Laskova, A Kozlova, M Białek-Pietras, M Studzińska, E Paradowska, V Bregadze, Z J Leśnikowski, A Semioshkin *J. Organomet. Chem.* **807** 29 (2016)
96. Z J Leśnikowski *Expert Opin. Drug Discov.* **11** 569 (2016)
97. Z J Leśnikowski *J. Med. Chem.* **59** 7738 (2016)
98. M Matuszewski, A Kiliszek, W Rypniewski, Z J Lesnikowski, A B Olejniczak *New J. Chem.* **39** 1202 (2015)