From sugars to modified nucleosides

Eva Hýrošová,[a] Lubor Fišera,[a]* Michal Medvecký,[a] Hans-Ulrich Reissig,[b] Ahmed Al-Harrasi,[b] and Miroslav Kóóš [c]

[a]*Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic*
[b]*Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany*
[c]*Institute of Chemistry, Slovak Academy of Sciences, 84538 Bratislava, Slovak Republic*
E-mail: lubor.fisera@stuba.sk

Abstract

Two strategies are reported for the diastereoselective synthesis of isoxazolidinyl nucleosides, as potential antiviral agents — a one-step approach based on 1,3-dipolar cycloaddition of sugar-derived nitrones with vinyl nucleobases derived from uracil and adenine, as well as a two-step methodology based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines. The 1,3-dipolar cycloadditions of sugar-derived nitrones with vinyl acetate proceed with very good diastereoselectivity to give the diastereoisomeric isoxazolidines. Condensation of the major diastereomerically pure acetoxyisoxazolidines with silylated uracil, thymine, cytosine, *N*-acetylguanine and purines occurs with moderate to excellent stereoselectivity with the formation of the expected isoxazolidinyl nucleosides. The stereoselectivity of the addition of the silylated nucleobase is dependent on the structure of the substituent at C-3 originating from the starting chiral nitrone and on the attacking nucleobase.

Keywords: Nucleosides, 1,3-dipolar cycloadditions, chiral nitrones, carbohydrates, isoxazolidines, stereoselectivity

Contents

 ©ARKAT USA, Inc.

1. Introduction

Nitrogen-containing heterocycles and their derivatives have broad application in synthetic materials, and biological chemistry and, as a result, their synthesis and reactivity is subject of considerable interest. Over the years, nitrones have become important building blocks in organic synthesis.[1-10] Nucleosides are generally defined as DNA or RNA subunits and consist of both a base moiety such as adenine, thymine, guanine, cytosine and uracil, and a sugar moiety such as D-ribose or 2-deoxy-D-ribose.[11] Many nucleoside analogues have been synthesized with modification of the base, sugar, and phosphate moieties. In particular, nucleoside analogues in which the furanose ring has been replaced by different carbon or heterocyclic systems, have attracted special interest by virtue of their biological action as antiviral and/or anti-cancer agents.[12] Among these, the uracil-, thymine-, cytosine-, and adenine- nucleosides **1** possessing an isoxazolidinyl moiety (carbocyclic-2′-oxo-3′-azanucleosides) are emerging as an interesting class of dideoxynucleoside analogues with potential pharmacological activity.[12] For the synthesis of modified isoxazolidinyl nucleosides **1** two strategies can be used — in particular, a one-step approach based on the 1,3-dipolar cycloaddition of nitrones with vinyl nucleobases, and a two-step methodology based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines.[13-20]

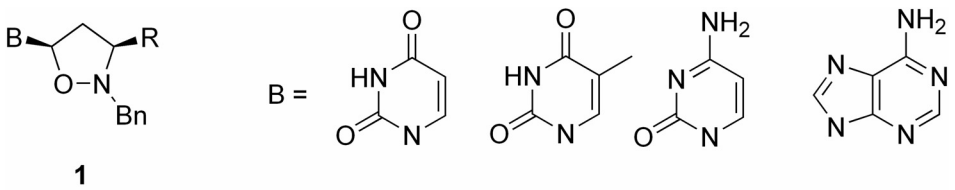
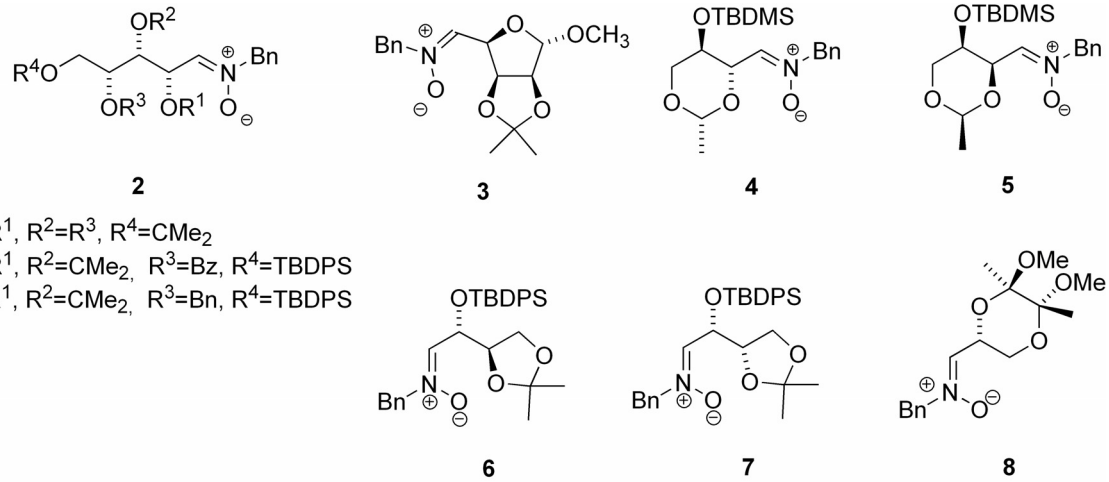


Figure 1

2. Sugar-derived Nitrones

Glycosides are important as enzyme inhibitors, and as chiral synthons suitable for the synthesis of many natural products. Since the 1,3-dipolar cycloaddition has a nearly singular capability of establishing large numbers of stereogenic centers in one synthetic step in recent years attention has been focused on the preparation of chiral sugar- derived nitrones. The configuration of the newly generated stereogenic centers would be determined by the nitrone. Asymmetric induction in 1,3-dipolar cycloaddition has been achieved efficiently by using nitrones with chiral groups at either the nitrogen atom or the carbon atom.[4] Among nitrones, the sugar- derived nitrones represent versatile substrates as they provide a polyhydroxylated carbon framework with multiple avenues of chirality.[9] During recent years we have gained knowledge of the preparation of optically active nitrone templates for the asymmetric 1,3-dipolar cycloadditions and samarium diiodide- induced couplings.[21-27] In connection with our synthetic studies on the utility of chiral nitrones for the synthesis of biologically interesting compounds, we have prepared the sugar-derived nitrones **2-8** possessing structures suitable for building nitrogen-containing heterocycles (Scheme 1).

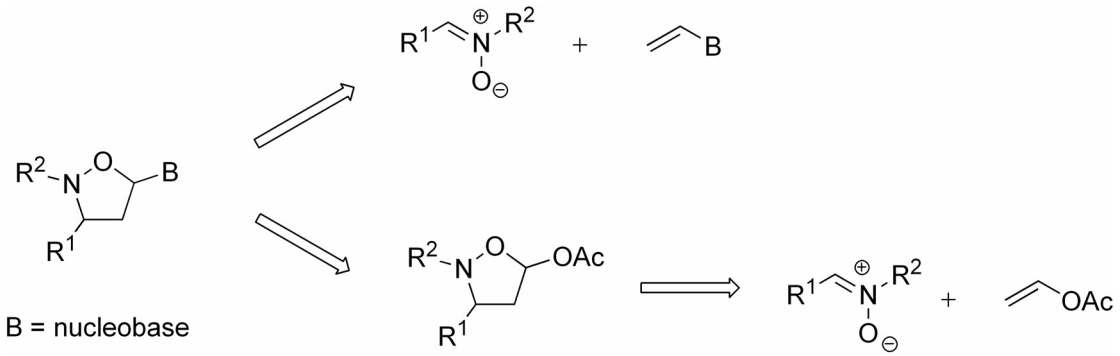
The aim of the present account is to describe the diastereoselective synthesis of isoxazolidinyl nucleosides by means of a 1,3-dipolar cycloaddition of chiral sugar- derived nitrones as the key step. The use of *C*-chiral nitrones allows diastereoselective synthetic access to homochiral isoxazolidinyl nucleosides. The enantioselective synthesis of isoxazolidinyl nucleosides by using chiral *N*-glycosyl nitrones is not included in this account.[15,20,28]



Scheme 1

3. Isoxazolidinyl Nucleosides

For the synthesis of modified isoxazolidinyl nucleosides **1**, two strategies can be used: a one-step approach based on the 1,3-dipolar cycloaddition of nitrones with vinyl nucleobases, and a two-step methodology based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines (Scheme 2).[15-20]



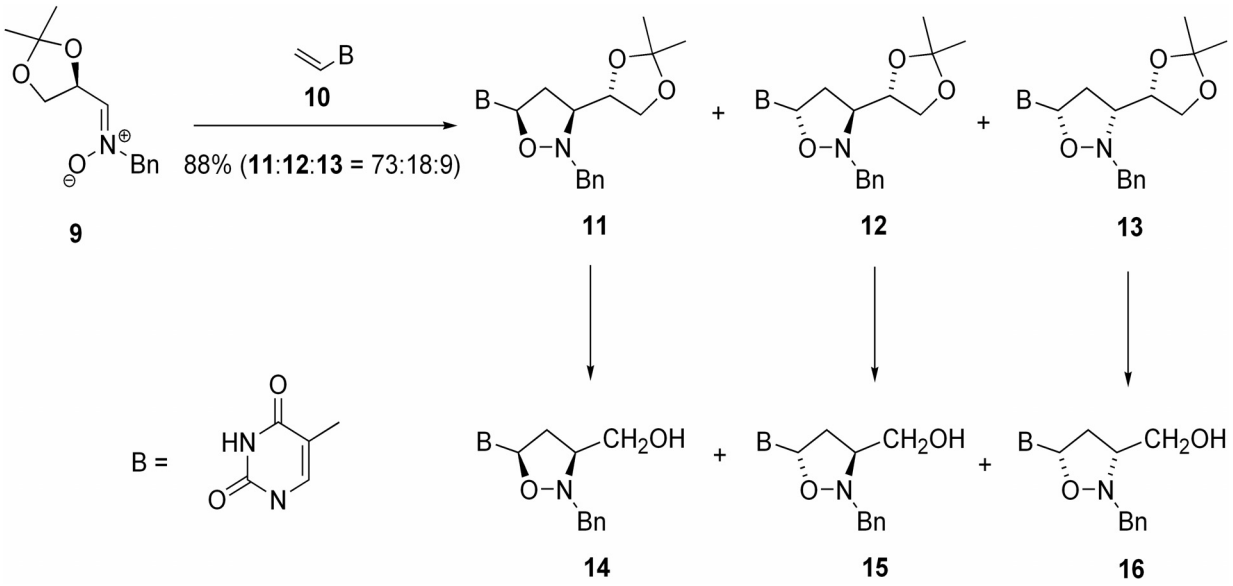
Scheme 2

3.1. From D-*glycero* nitrone and vinylthymine

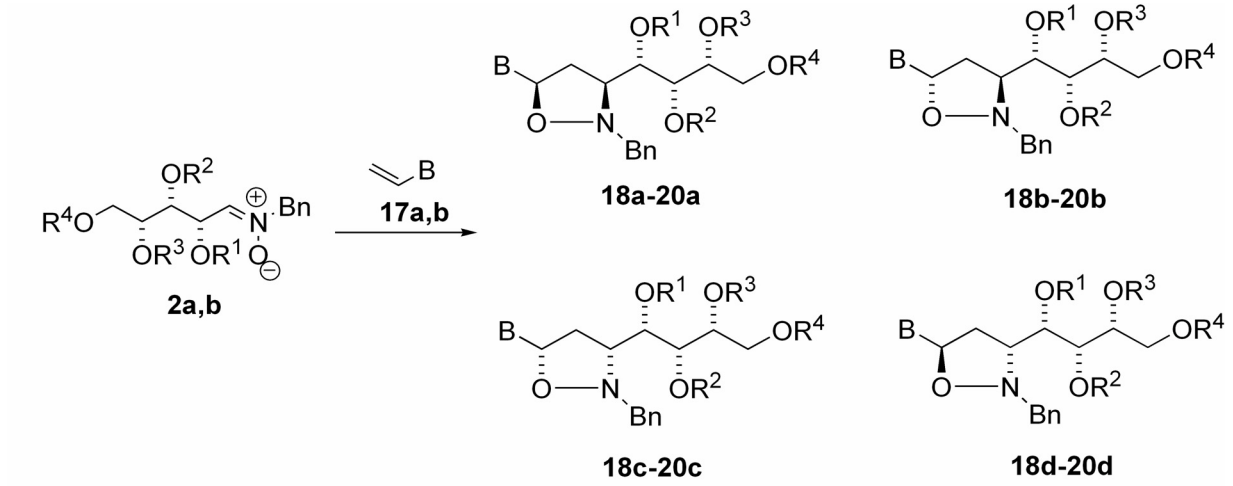
The 1,3-dipolar cycloaddition between an achiral nitrone and a vinyl base has been applied to the synthesis of isoxazolidinyl nucleosides.[19,29-31] This approach should be a highly promising reaction for the straightforward synthesis of a variety of isoxazolidinyl nucleosides. The first chiral version of that reaction has been investigated by Merino.[16] The cycloaddition of the nitrone **9**, which is readily available from 2,3-*O*-isopropylidene-D-glyceraldehyde, with vinylthymine (**10**) in refluxing toluene proceeded smoothly to give a 73:18:9 mixture of three adducts **11-13** in 88% yield (Scheme 3). Deprotection of the separated anomers was achieved by using catalytic *p*-TsOH in MeOH. The resulting 1,2-diols were treated sequentially with sodium periodate and sodium borohydride to give the hydroxymethyl- substituted isoxazolidinyl nucleosides **14-16** in good yields.

3.2. From D-*xylo* nitrones and vinyluracil and vinyladenine

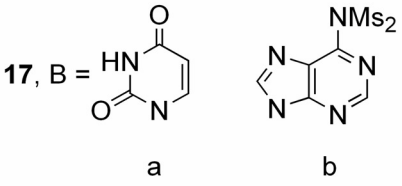
We have prepared from D-xylose the new sugar-derived nitrones **2a** and **2b** possessing structures suitable for the building of pyrrolidines.[32] Their cycloadditions to vinylated nucleobases **17**, derived from uracil and adenine, proceeded regioselectively and led to the isoxazolidines **18-20** as a mixture of four diastereoisomers in all cases (Scheme 4). In the case of cycloadditions of nitrones **2a** and **2b** with 9-vinyladenine **17b** an inseparable mixture of the adenosine diastereoisomers has been obtained. To improve the separation the free amino group of the adenine moiety was protected. The cycloaddition of nitrone **2a** with *N,N*-dimesylated 9-vinyladenine **17b** proceeded with better selectivity, in favor of the major *anti-cis* isomer **20a**.[32]



Scheme 3



2a R^1,R^2 = R^3,R^4 = CMe_2
2b R^1,R^2 = CMe_2, R^3 = Bz, R^4 = TBDPS
18 R^1,R^2 = R^3,R^4 = CMe_2, B = uracil 63:17:15:5
19 R^1,R^2 = CMe_2, R^3 = Bz, R^4 = TBDPS, B = uracil 59:24:11:16
20 R^1,R^2 = R^3,R^4 = CMe_2, B = adenine, 73:13:9:5



Scheme 4

X-ray analysis of the major diastereoisomer **18a** prepared from uracil reveals a C-3/C-1' *anti*- and C-3/C-5 *cis*- configuration, and therefore indicates that the cycloaddition arises from the more sterically accessible *si* face of the *Z*-nitrone **2a**, via an *exo*-transition state for the *anti-cis* diastereoisomer **18a** and *via* an *endo* transition state for the *anti-trans* **19a** isomer (Fig. 2).

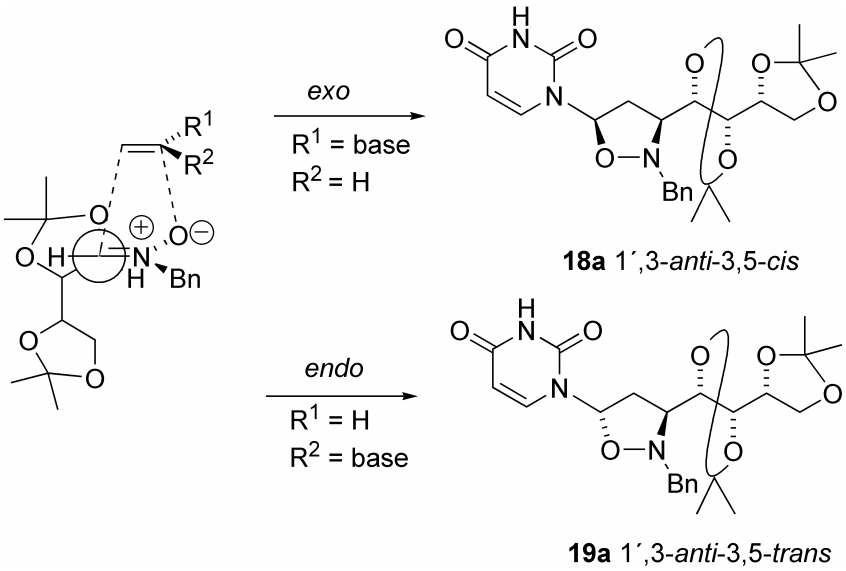


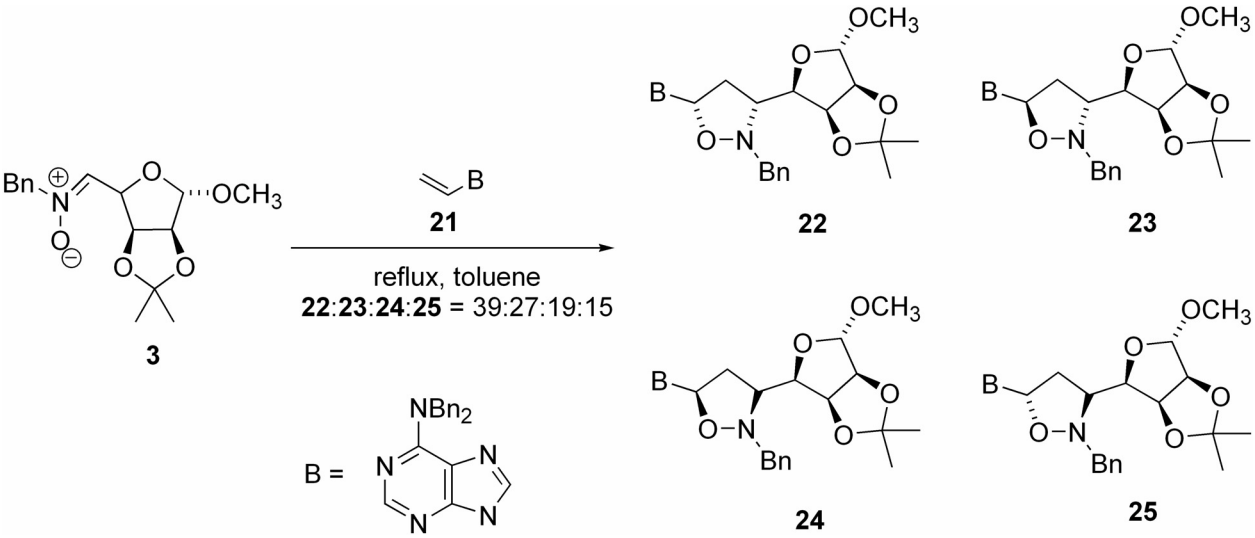
Figure 2

3.3. From D-*lyxo* nitrone and vinyladenine

The 1,3-dipolar cycloaddition of the readily available chiral sugar- derived D-lyxosyl nitrone **3**, with *N,N*-dibenzyl-9-vinyladenine has been also investigated in our group.[33] Nitrone **3** reacted with *N,N*-dibenzyl-9-vinyladenine to give a mixture of all possible 5-substituted isoxazolidines **22-25** in the ratio of 39:27:19:15 in 98% yield, the *anti-cis* isomer **22** being the major product (Scheme 5). Two of them, with a C-3/C-5 *trans* configuration of the isoxazolidine moiety, are α-anomers and the other two possess a C-3/C-5 *cis* configuration of the isoxazolidine moiety are β-anomers. Whereas the regioselectivity of the reaction was very high, the corresponding 4-substituted regioisomers were not detected, and both the *cis/trans* selectivity (*cis/trans* ratio 58:42) and the diastereofacial selectivity (*anti/syn* ratio 66:34) were rather low.

4. Acetoxyisoxazolidines prepared from Sugar- derived Nitrones

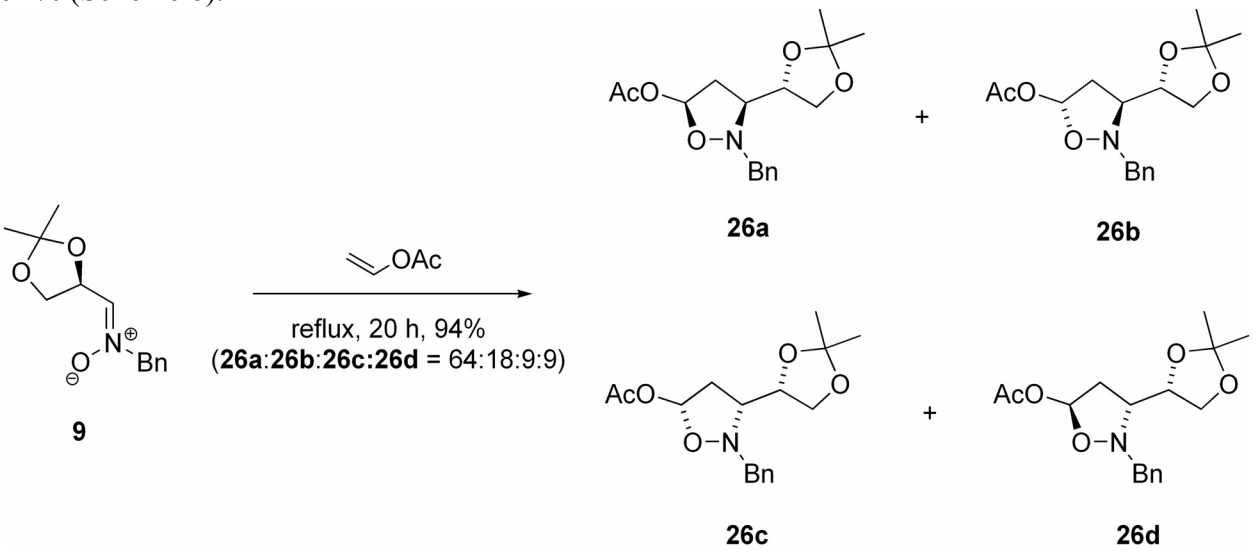
Since we found that the cycloadditions of chiral sugar- derived nitrones to vinylated nucleobases derived from uracil and adenine led to the isoxazolidines as a mixture of four diastereoisomers in all cases, for the synthesis of modified isoxazolidinyl nucleosides we have chosen a two-step methodology based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines. Therefore, the cycloaddition of the chiral nitrones **2-8** with vinyl acetate was investigated. The reaction of the nitrone **9** with vinyl acetate has been described by Merino *et al*.[16] It is known that 1,3-dipolar cycloadditions of electron-rich alkenes to chiral α-alkoxy nitrones give preferentially *anti*-adducts as a result of dipolarophile attack from the less sterically hindered *si* diastereotopic face of the nitrone.[9,16]



Scheme 5

4.1. 1,3-Dipolar cycloaddition of D-*glycero* nitrone with vinyl acetate

The cycloaddition of **9** with vinyl acetate took place without solvent to give a mixture of four stereoisomeric isoxazolidines **26a–26d** in an isomer ratio of 64:18:9:9 and a combined yield of 94% (Scheme 6).[16]

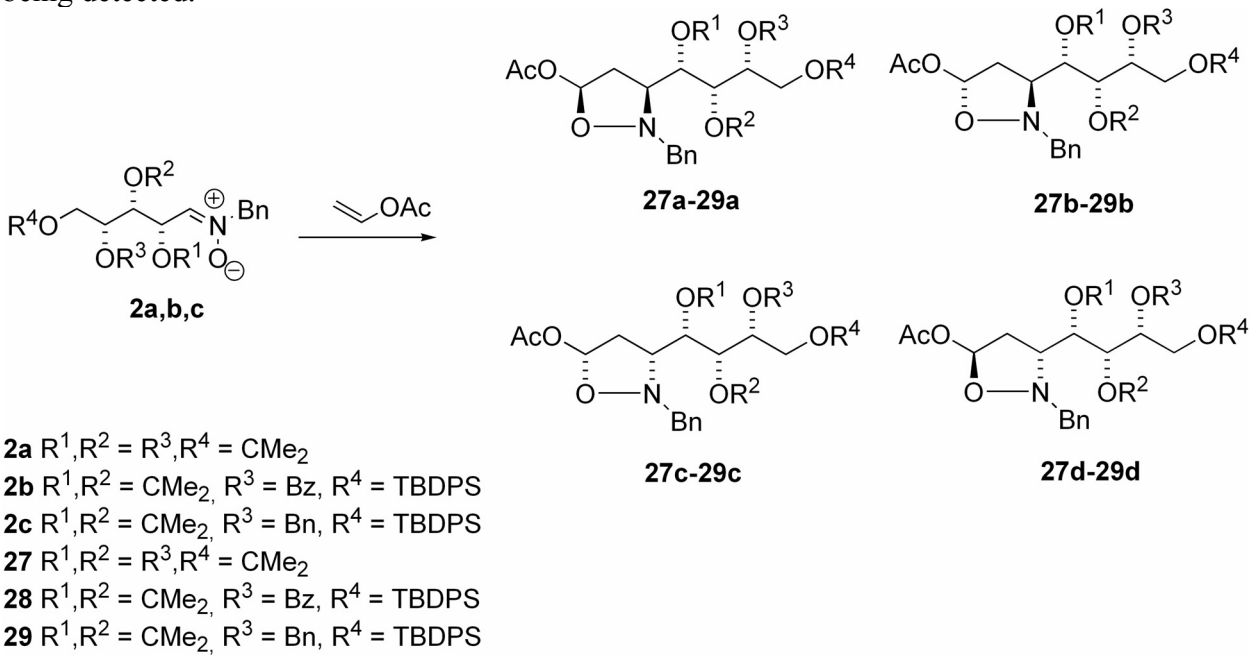


Scheme 6

4.2. 1,3-Dipolar cycloaddition of sugar- derived nitrones 2–8 with vinyl acetate

The 1,3-dipolar cycloaddition of the D-*xylo* nitrones **2a** and **2b** with vinyl acetate at reflux leads to the 5-acetoxy- substituted isoxazolidines as a mixture of diastereoisomers **27a**–**d** and **28a**,**b**,**d** respectively (Scheme 7).[34] In contrast to the cycloadditions of these nitrones with vinylated nucleobases, the *anti-trans* isoxazolidines **27b** and **28b**, are respectively the major products,

(entries 1,2, Table 1). The attack of the dipolarophile on the *Z* configuration of the nitrones **2a-c** proceeded preferentially through an *endo* transition state (Fig. 2, R^2 = OAc). The activation energy of the possible *Z*/*E*- isomerization for the sugar- derived nitrones is too high and therefore the nitrones reacted without any isomerization.[21,22] 4-*O*-Benzyl- substituted D-*xylo* nitrone **2c** reacted smoothly in vinyl acetate at reflux over 24 h to give an 83:10:7 mixture of the diastereoisomeric isoxazolidines **29a**, **29b** and **29d** in 85% yield (entry 3, Table 1).[35] The cycloaddition proceeded with very good diastereoselectivity for the *anti-trans* isoxazolidine **29b** and is completely regioselective, with only the sterically favored 5-substituted isoxazolidines being detected.



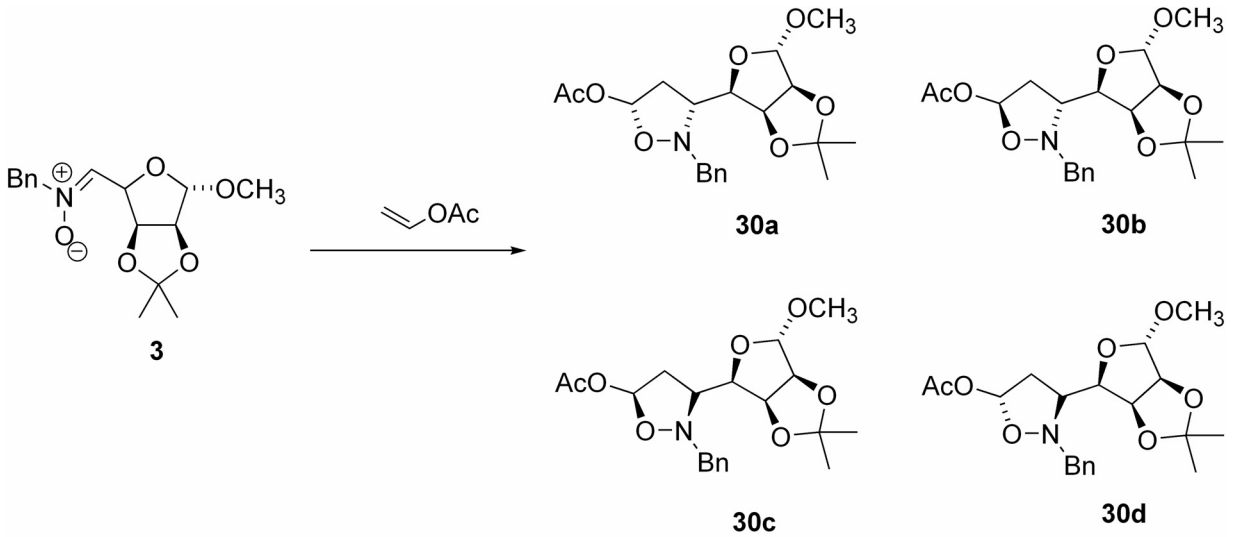
2a R^1,R^2 = R^3,R^4 = CMe_2
2b R^1,R^2 = CMe_2, R^3 = Bz, R^4 = TBDPS
2c R^1,R^2 = CMe_2, R^3 = Bn, R^4 = TBDPS
27 R^1,R^2 = R^3,R^4 = CMe_2
28 R^1,R^2 = CMe_2, R^3 = Bz, R^4 = TBDPS
29 R^1,R^2 = CMe_2, R^3 = Bn, R^4 = TBDPS

Scheme 7

Table 1. 1,3-Dipolar cycloaddition of nitrones **2**–**8** with vinyl acetate

Entry	Nitrone	Yield (%)	*anti-cis* **a**	*anti-trans* **b**	*syn-cis* **c**	*syn-trans* **d**
1	**2a**	90	9	70	8	13
2	**2b**	73	14	71	-	15
3	**2c**	74	10	83	-	7
4	**3**	86	47	21	18	14
5	**4**	78	28	56	16	-
6	**5**	68	84	16	-	-
7	**6**	66	56	16	15	13
8	**7**	73	51	18	17	14
9	**8**	88	78	9	7	6

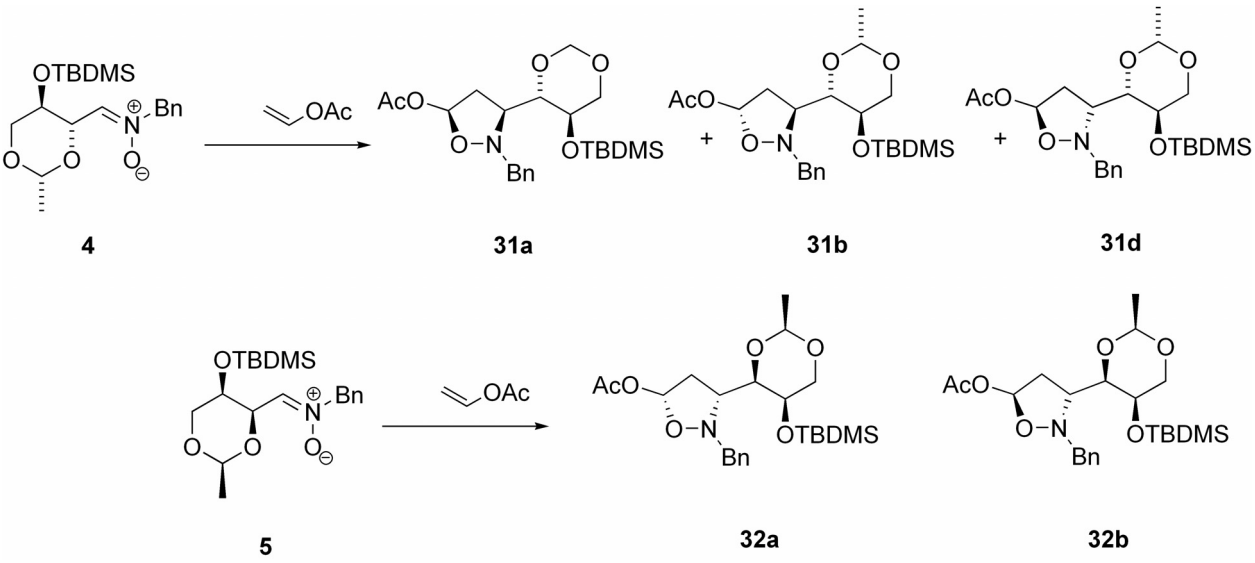
On the other hand, cycloaddition of nitrone **3** with vinyl acetate afforded a mixture of four diastereoisomers **30a**–**d** in 86% yield in favor of the major isomer **30a** possessing the *anti-cis* configuration (Scheme 8, entry 4, Table 1).[33]



Scheme 8

The D-*erythro* nitrone **4**, prepared starting from D-glucose, reacted smoothly in refluxing vinyl acetate over 20 h to give a 56:28:16 mixture of diastereoisomeric isoxazolidines **31a**, **31b** and **31d** in 78% yield (Scheme 9).[36] The cycloaddition proceeded with very good *anti*-facial (84:16) and *endo*-facial (72:28) diastereoselectivity (entry 5, Table 1). It is noteworthy that in this case the reaction — probably for steric reasons — proceeded with reversed diastereoselectivity as expected for an inverse-demand cycloaddition reaction where the corresponding 3,5-*cis*-adducts are the major products.[9,16] The structure of the major diastereomer as *anti-trans*-**31b** was established unambiguously by X-ray diffraction studies.[36]

On the other hand, the reaction of the D-*threo* nitrone **5**, prepared starting from D-galactose, with vinyl acetate proceeded diastereoselectively and gave only two diastereoisomers **32a** and **32b** in a 84:16 ratio, with *anti-cis* **32a** being predominant — although four diastereoisomers are possible — showing now a preference for *exo*- attack, as expected for an inverse-demand cycloaddition reaction (Scheme 3).[9,16] Moreover, in this case an excellent *anti*-diastereofacial induction was observed; the corresponding *syn*-adducts have not been detected in the reaction mixture (entry 5, Table 1). The structure of the minor *trans-anti* isoxazolidine **32b** was established unambiguously by X-ray diffraction studies.[36] Thus, the observed excellent facial diastereoselectivity for the D-galactose- derived nitrone **5** is in contrast with the afore- mentioned results obtained by the nitrone cycloadditions to vinyl acetate.

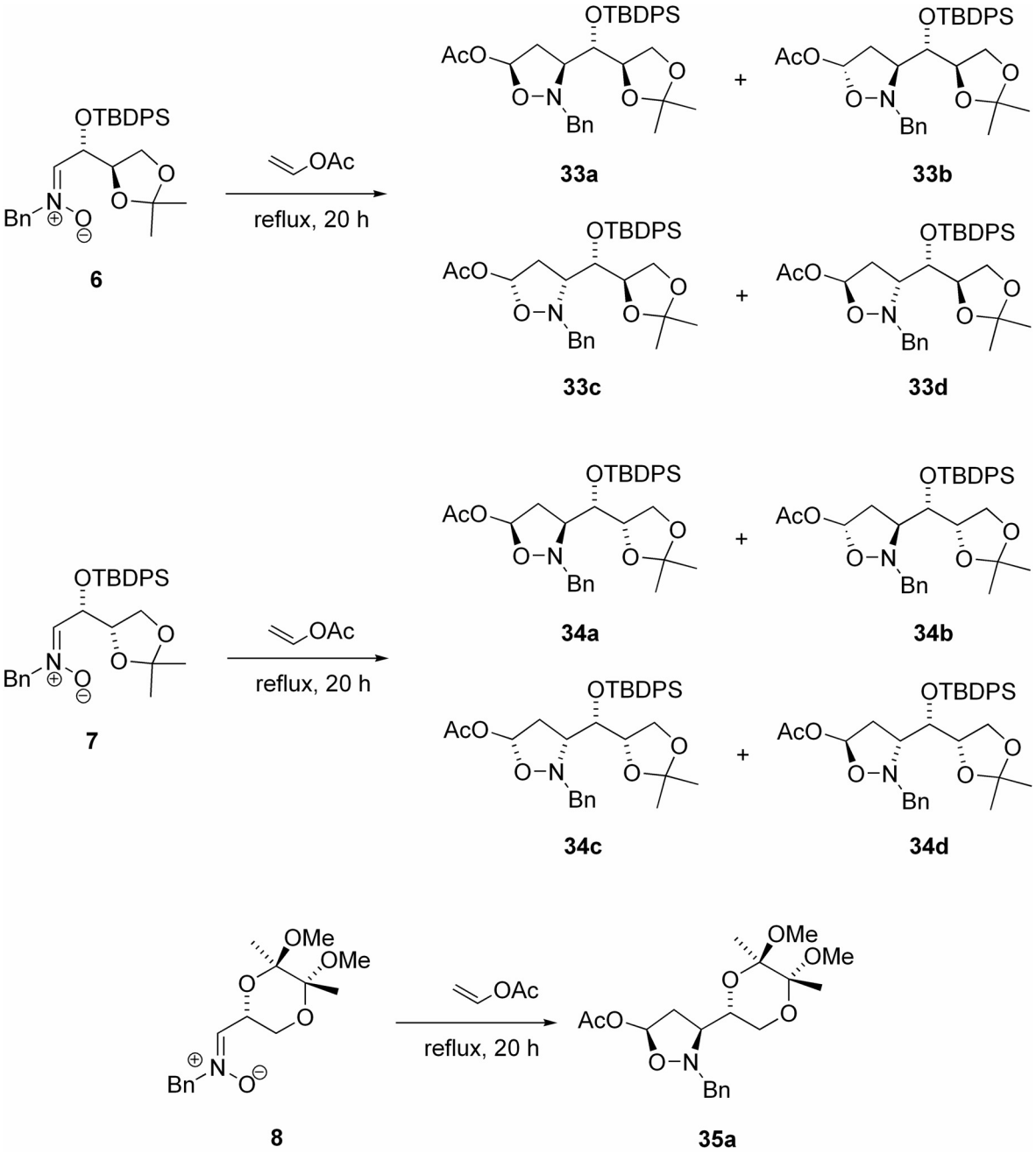


Scheme 9

The D-erythrose- derived nitrone **6**, prepared starting from D-iso-ascorbic acid and the diastereomeric L-threose- derived nitrone **7** synthesized from L-ascorbic acid, reacted smoothly in refluxing vinyl acetate over 20 h to give a mixture of all possible 3,5-disubstituted-diastereoisomeric isoxazolidines **33a–d** and **34a–d**, respectively (Scheme 10).[37] The major isomers **33a** and **34a**, possessing a C-1'/C-3 *anti*- relationship result from a dipolarophile attack from the sterically less hindered face of nitrone **6** and **7**, respectively (entry 7 and 8, Table 1). The cycloaddition of the D-glyceraldehyde- derived nitrone **8** (Scheme 10) to vinyl acetate proceeded analogously, with good diastereoselectivity in favor of *anti-cis* isoxazolidine **35a**, to give a mixture of diastereoisomers in the ratio 78:9:7:6 in 88% yield. (entry 9, Table 1).[37]

5. Isoxazolidinyl Nucleosides prepared by Vorbrüggen Nucleosidation

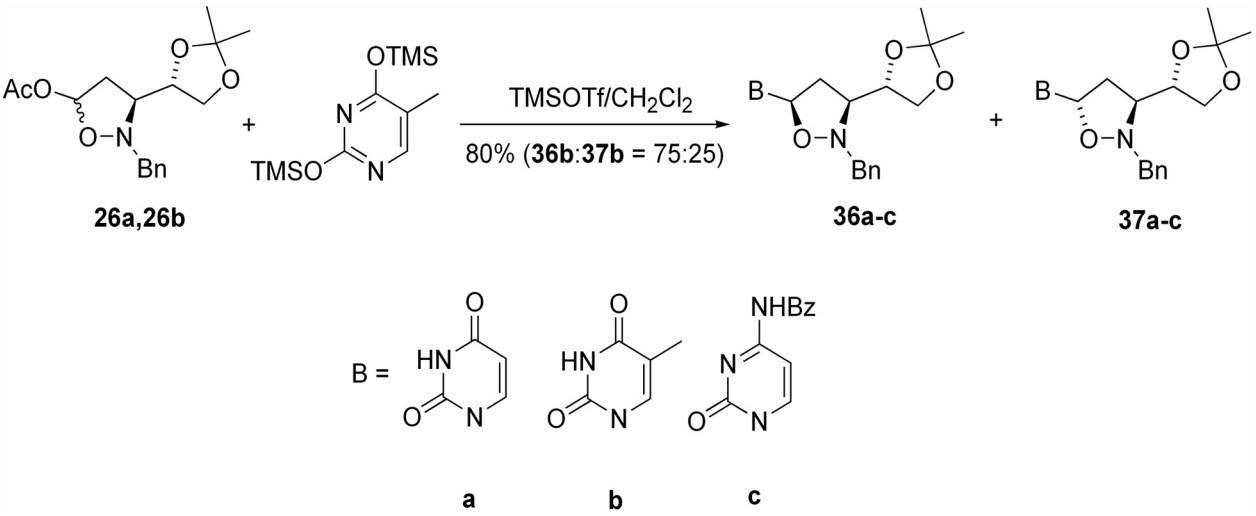
In this Section, we describe syntheses of the modified isoxazolidinyl nucleosides from acetoxyisoxazolidines by Vorbrüggen nucleosidation.[38,39] The condensation of the acetoxyisoxazolidines synthesized from D-*glycero*-, D-*lyxo*-, D-*xylo*-, D-*erythro*-, D-*threo*- and L-*threo*- derived nitrones with silylated -uracil, -thymine, -cytosine, -*N*-acetylcytosine, -*N*-acetylguanine and -purines proceeded with good yields and with moderate to good stereoselectivity with formation of the isoxazolidinyl β- and α-nucleosides. We have made the potentially useful observation that the anomeric distribution of the formed nucleosides may be dependent not just on the nature of the attacking nucleobase but also on the 3-substituent of the isoxazolidine.[35-37] This observation might be exploited in future to allow the generation of anomerically pure nucleosides via the Vorbrüggen method.



Scheme 10

5.1. Isoxazolidinyl nucleosides derived from D-glyceraldehyde

Merino and his colleagues have described the transformation of a mixture of *anti*- adducts **26a**/**26b** into isoxazolidinyl- nucleoside analogues as depicted in Scheme 11.[16] The condensation of a mixture of **26a** and **26b** with silylated thymine, using the glycosylation methodology developed by Vorbrüggen,[38,39] resulted in a nucleoside product consisting of *cis*-**36b** and *trans*-**37b** isomers (75:25) which were isolated in 80% combined yield.

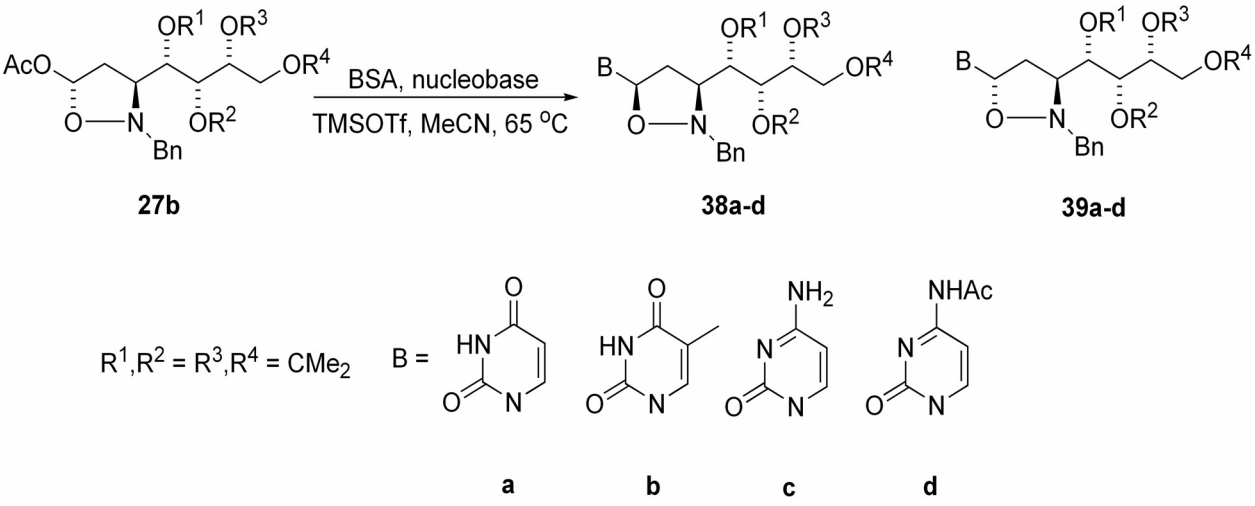


Scheme 11

Zhao and his coworkers have obtained *cis*- **36b** and *trans*- **37b** isomers in a 94:6 ratio in 83% combined yield.[40] Condensation of acetate **26a** with silylated uracil and *N*-benzoylcytosine in acetonitrile at room temperature, using TMSOTf as Lewis acid afforded the β-anomers **36a,c** with excellent stereoselectivity (95:5). The acetoxy-isoxazolidine **26a** was prepared in this case by Michael addition of *N*-methyl hydroxylamine to the α,β-unsaturated ester derived from 2,3-*O*-isopropylidene-D-glyceraldehyde, followed by reduction with DIBAL and subsequent acetylation.

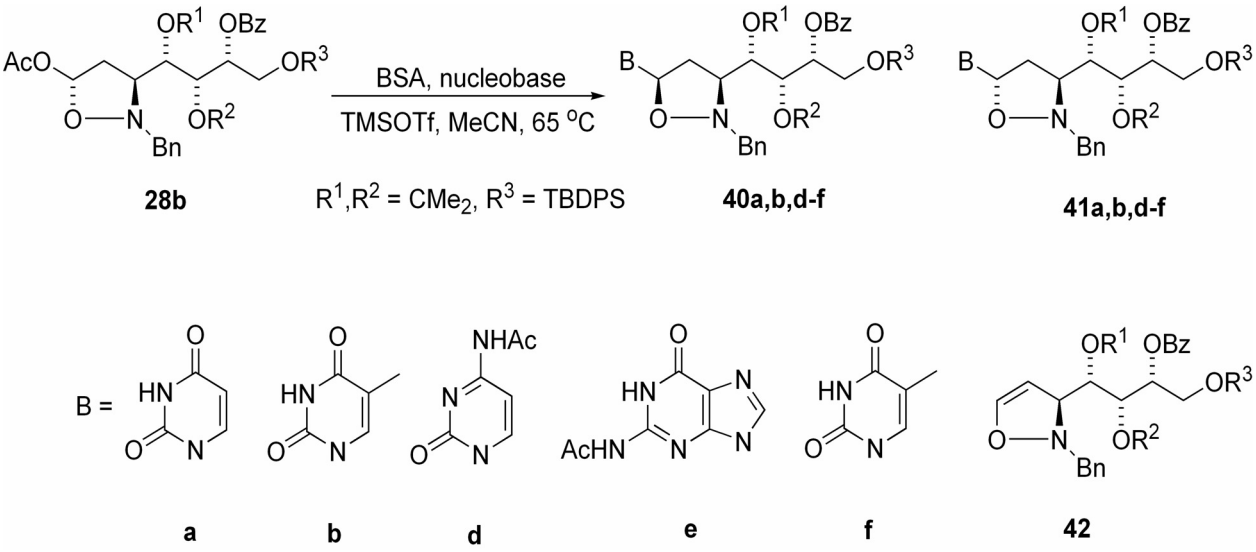
5.2. Isoxazolidinyl nucleosides derived from D-xylose

In contrast to other papers dealing with the condensation of a mixture of acetoxy- substituted isoxazolidines[16] with silylated nucleobases by the Vorbrüggen method, we have always used the major diastereomerically pure 5-acetoxy- substituted isoxazolidines.[33,35-37] The *anti-trans* isoxazolidine **27b** prepared by the 1,3-dipolar cycloaddition of nitrone **2a** with vinyl acetate was coupled with silylated nucleobases according to the Vorbrüggen methodology.[38,39] The condensation of **27b** with silylated uracil, thymine, cytosine or *N*-acetylcytosine at 70 °C, in the presence of trimethylsilyl triflate as catalyst, proceeded with low (uracil, thymine) - to good (cytosine or *N*-acetylcytosine) - yields and moderate stereoselectivity, with formation of the expected isoxazolidinyl β- and α-nucleosides (**38a**/**39a** ratio 63:37, **38b**/**39b** ratio 63:37, **38c**/**39c** ratio 55:45, **38d**/**39d** ratio 66:34, Scheme 12). The β-anomers **38a-d** predominate, but significant amounts of α-anomers **39a-d** were obtained. These results are fully in accord with the data obtained for related Vorbrüggen nucleosidations.[15-20]



Scheme 12

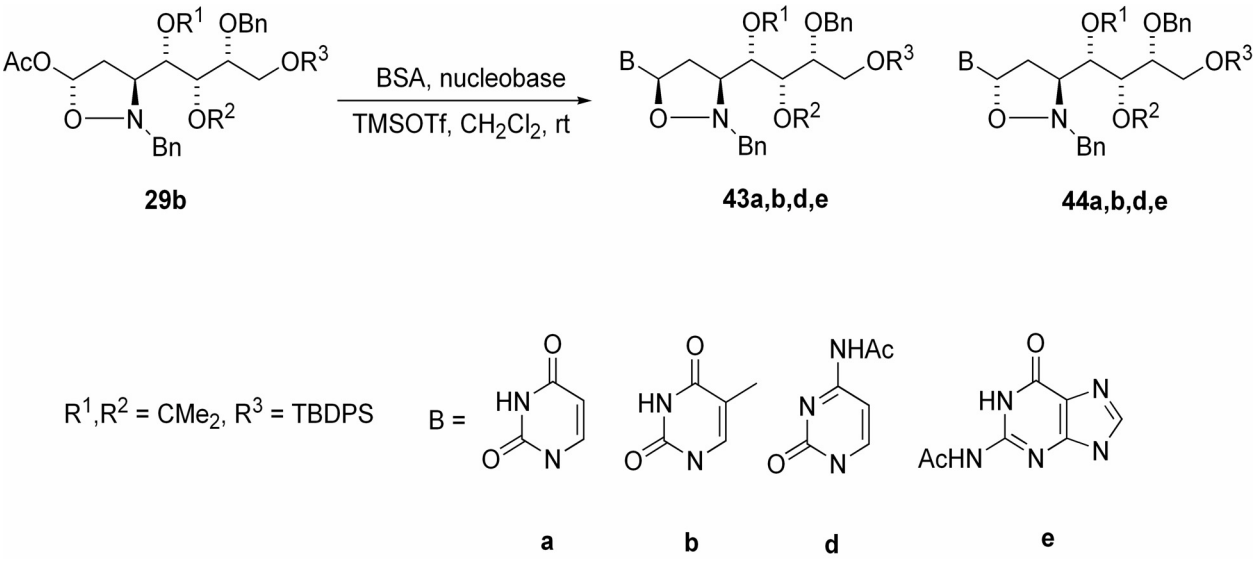
A surprising and unexpected fact is that, in the case of the *anti-trans*- 5-acetoxy- substituted isoxazolidine **28b**, prepared by the 1,3-dipolar cycloaddition of nitrone **2b** with vinyl acetate, the Vorbrüggen nucleosidations with silylated nucleobases proceeded at 65 °C with excellent stereoselectivity. The corresponding β-anomers **40a**,**b**,**d** are now the exclusive nucleosides for all of the used nucleobases (Scheme 13).[35] The research groups of P. Merino, U. Chiacchio and R. Romeo have reported that the anomeric distribution obtained by Vorbrüggen nucleosidation with chiral 5-acetoxyisoxazolidines depends on the attacking nucleobase.[28,41-43] The attack on the oxonium intermediate from either the α- or β-side is possible, and hence the product distribution is sensitive to structural changes of the reactants. In our case, the stereoselectivity of the addition of the silylated nucleobase is evidently more dependent on the structure of the substituent at C-3 originating from the starting chiral nitrone. Moreover, in this case the product of elimination, the corresponding isoxazoline derivative **42**, was also isolated (Scheme 13). It is noteworthy that in the case of silylated 5-fluorouracil, the isoxazoline **42** is formed as the major product (**40a**/**42** ratio 58:42, **40b**/**42** ratio 81:19, **40d**/**42** ratio 90:10, **40f**/**42** ratio 9:91). To the best of our knowledge, such a formation of 2,3-dihydro-isoxazoles by the Vorbrüggen nucleosidation has not been observed. 2,3-Dihydro-isoxazoles represent a class of heterocycles that may be employed as useful building blocks for synthesis.[44,45]



Scheme 13

We suppose that the isoxazoline **42** is formed by the elimination of the corresponding α-anomers **41a**,**b** and **41d**. Therefore, we next studied the Vorbrüggen nucleosidation in methylene chloride at room temperature. Indeed, the product of elimination **42** was not detected, and both β- and α-anomeric isoxazolidinyl nucleosides **40** and **41** were formed with high stereoselectivities in favor of the β-anomers **40** (**40a**/**41a** ratio 95:5, **40b**/**41b** ratio 80:20, **40d**/**41d** ratio 83:17, **40e**/**41e** ratio 70:30, Scheme 13). Also, the first successful isoxazolidinyl nucleosides **40e** and **41e** derived from *N*-acetylguanine were obtained.

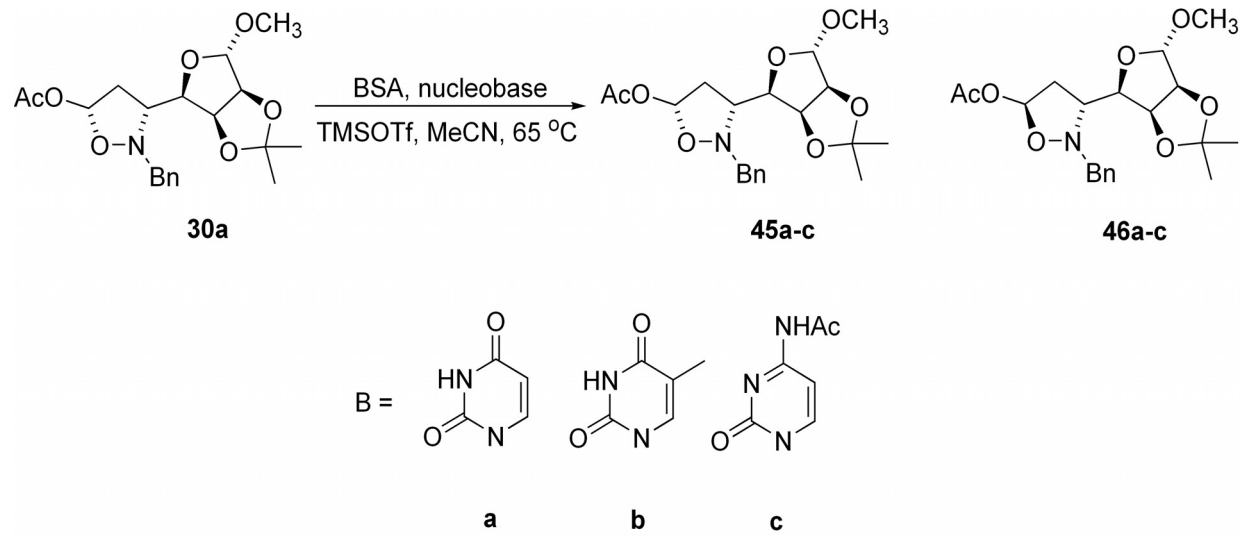
As has already been mentioned, the best stereoselectivity in the nucleosidation was achieved in the case of benzoyl substituted isoxazolidine **28b**. To exclude or to support the possibility of the participation of the neighboring benzoyl group, we have prepared the corresponding D-xylose- derived benzyl- substituted nitrone **2c**. The Vorbrüggen nucleosidation of *anti-trans* benzyloxy- substituted isoxazolidine **29b** with silylated uracil, thymine, *N*-acetylcytosine and guanine at RT in methylene chloride in the presence of trimethylsilyl triflate as catalyst, afforded the β-anomeric nucleosides **43** with the best diastereoselectivities in this series. Uracil and acetylated cytosine reacted with 90% diastereomeric excess (**43a**/**44a** ratio 95:5, **43b**/**44b** ratio 80:20, **43d**/**44d** ratio 94:6, **43e**/**44e** ratio 63:37, Scheme 14).



Scheme 14

5.3 Isoxazolidinyl nucleosides derived from D-lyxose

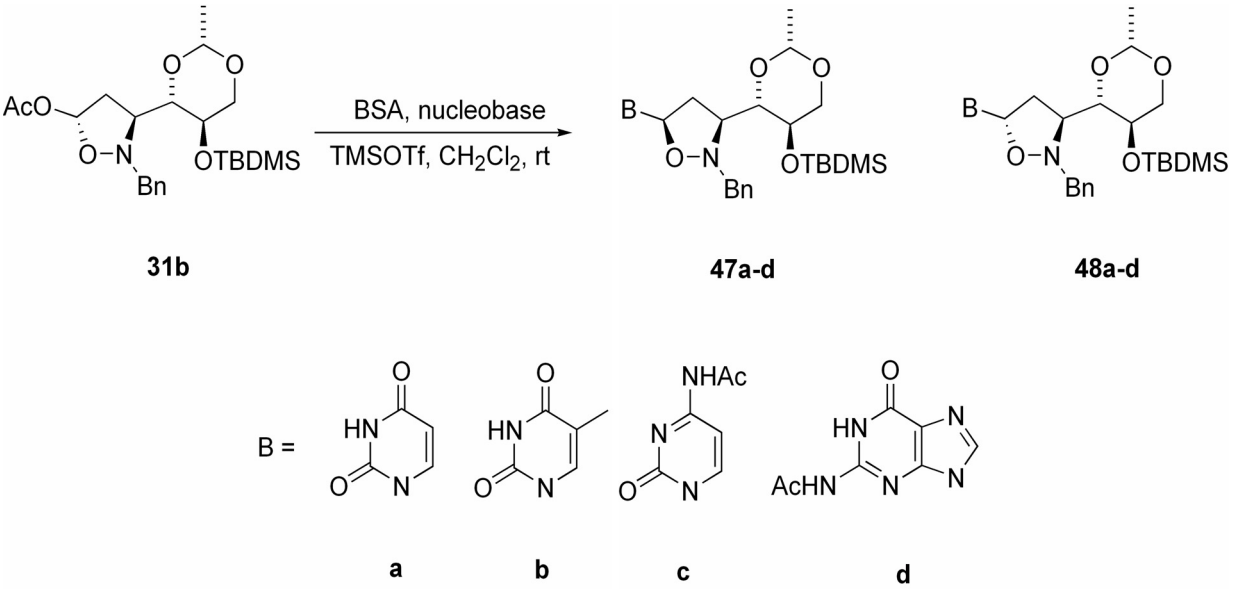
The condensation of the *anti-cis* isoxazolidine **30a** derived from D-lyxose with silylated uracil, thymine and *N*-acetylcytosine at 65 °C in the presence of 0.4 equiv. of trimethylsilyl triflate as catalyst, proceeded with good yields and from moderate- to good stereoselectivity under the formation of the expected isoxazolidinyl β- and α-nucleosides (**45a**/**46a** ratio 67:33, **45b**/**46b** ratio 88:12, **45c**/**46c** ratio 80:20, Scheme 15).[33] For *N*-acetylcytosine and thymine, the β-anomers clearly predominate, while in the case of uracil a significant amount of α-anomer has been obtained.



Scheme 15

5.4 Isoxazolidinyl nucleosides derived from D-erythrose

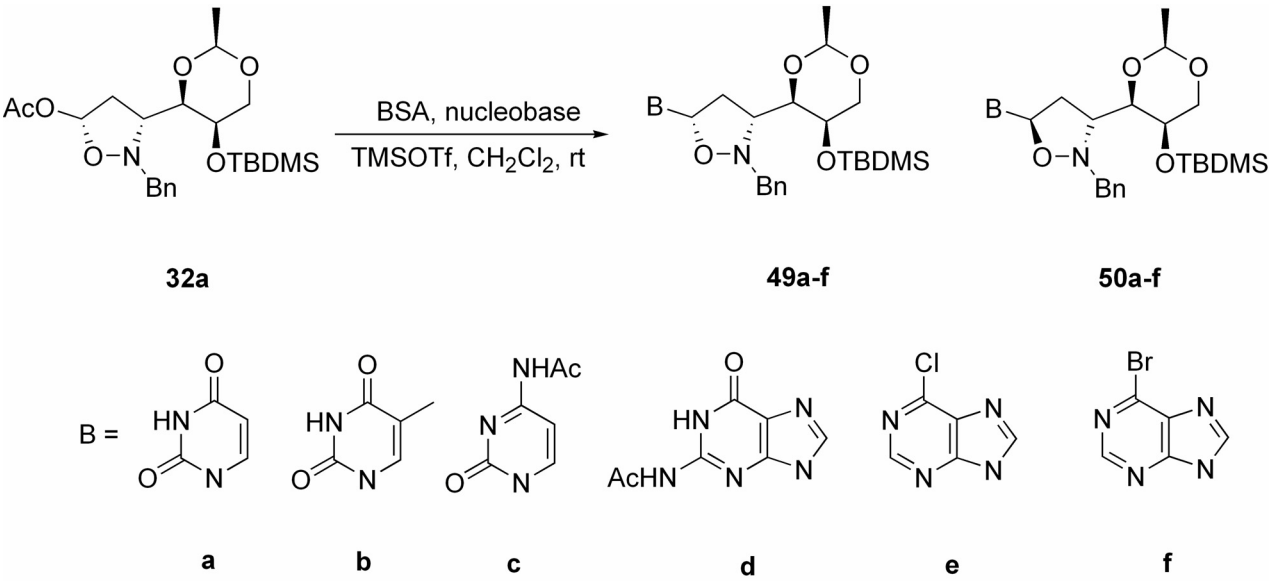
Following extensive screening, we found the best reaction conditions for the Vorbrüggen nucleosidation of acetoxy- substituted isoxazolidines prepared from sugar- derived nitrones to be at RT in methylene chloride.[35] The nucleosidation of the *anti-trans* isoxazolidine **31b** with silylated uracil, thymine and *N*-acetylcytosine at RT in methylene chloride in the presence of trimethylsilyl triflate as catalyst, afforded the mixture of anomeric nucleosides **47a-c** in moderate yields (65-66%), but with excellent diastereoselectivities (**47a**/**48a** ratio 92:8, **47b**/**48b** ratio 90:10, **47c**/**48c** ratio 94:6, Scheme 16).[36] However, the reaction with *N*-acetylguanine gave a lower yield (36%) and the diastereoselectivity was only moderate (**47d**/**48d** ratio 69:31).



Scheme 16

5.5 Isoxazolidinyl nucleosides derived from D-threose

The Vorbrüggen nucleosidation of the *anti-cis* isoxazolidine **32a** with silylated uracil, thymine, *N*-acetylcytosine, acetylguanine, 6-chloro- or 6-bromopurine at RT in methylene chloride in the presence of trimethylsilyl triflate as catalyst, proceeded with low (purines) to good (uracil, thymine and *N*-acetylcytosine) yields, and from moderate to good stereoselectivity with the formation of the expected isoxazolidinyl β- and α-nucleosides **49** and **50** (**49a**/**50a** ratio 91:9, **49b**/**50b** ratio 73:27, **49c**/**50c** ratio 87:13, **49d**/**50d** ratio 52:48, **49e**/**50e** ratio 70:30, **49f**/**50f** ratio 66:34, Scheme 17).[36] For uracil and *N*-acetylcytosine, the β-anomers **49** clearly predominate, while in the case of *N*-acetylguanine and purines a significant amount of α-anomer **50** has been obtained. This lower diastereoselectivity is in contrast with the excellent diastereoselectivity observed for *anti-trans* isoxazolidine **31b** derived from D-erythrose, but these results are fully in accord with the data obtained for the related Vorbrüggen nucleosidations.[15-20]



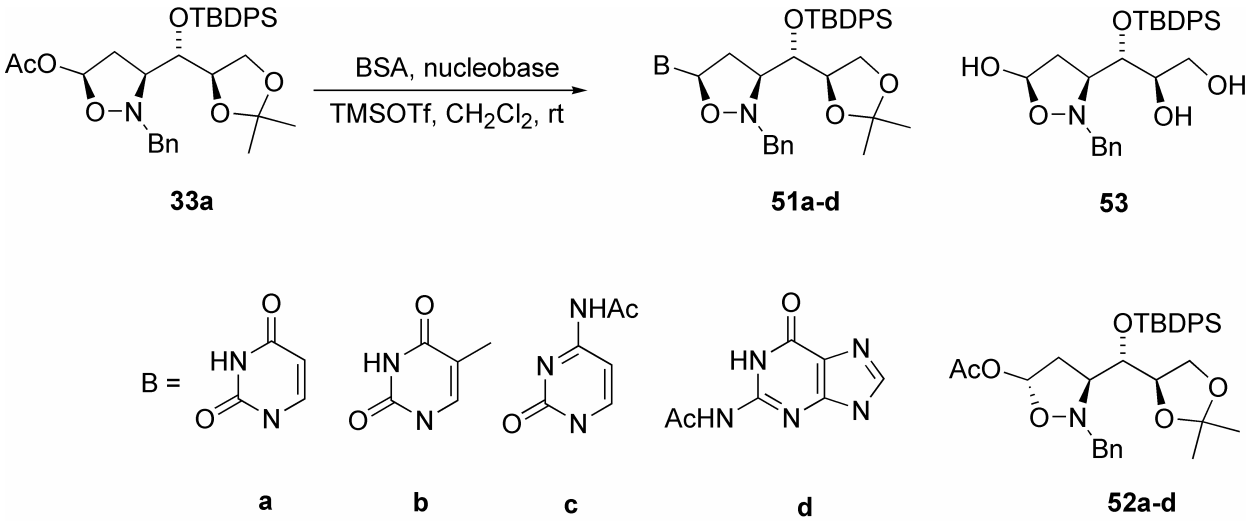
Scheme 17

5.6. Isoxazolidinyl nucleosides prepared from D-*iso*-ascorbic acid

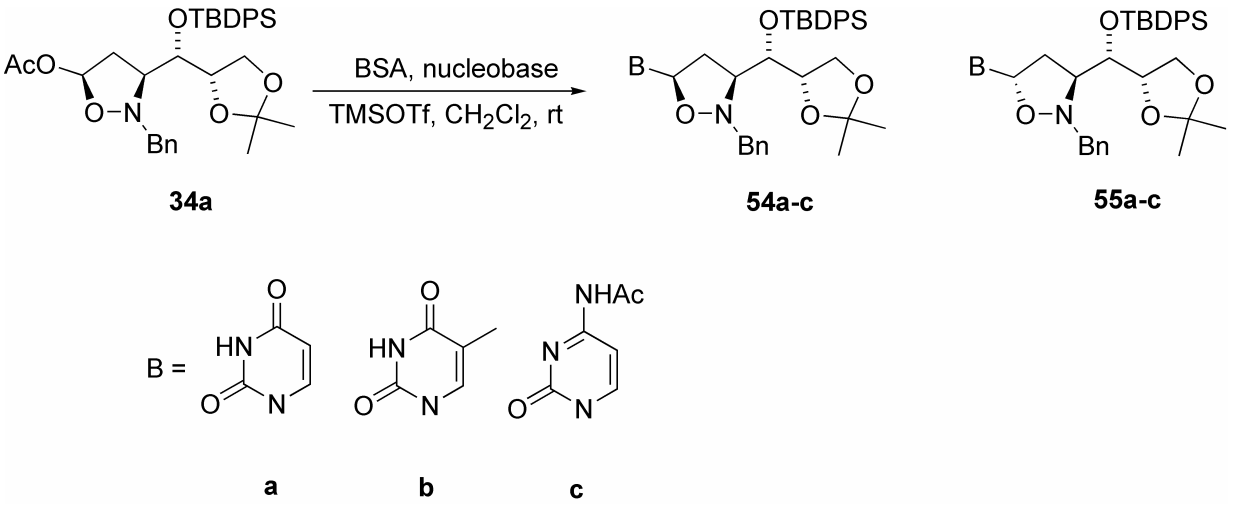
The nucleosidation of *anti-cis* isoxazolidine **33a** derived from D-erythrose with silylated uracil, thymine, *N*-acetylcytosine or *N*-acetylguanine in the presence of trimethylsilyl triflate as catalyst, afforded the expected β-anomeric nucleosides **51a-d** in low yields (20-48%) for all of the used nucleobases (Scheme 18).[37] The corresponding α-anomeric nucleosides **52a-d** were not detected in the reaction mixture. Moreover, and surprisingly, the major product — the 5-hydroxy-substituted isoxazolidine **53** (35-60 %) from all these reactions — does not contain the corresponding nucleobase. To the best of our knowledge, this kind of product of the TMSOTf-catalyzed hydrolysis of acetal moieties of the starting acetoxyisoxazolidine has not been observed in related Vorbrüggen nucleosidations.[15-20]

5.7 Isoxazolidinyl nucleosides derived from L-threose

Gratifyingly, the nucleosidation of the *anti-cis* isoxazolidine **34a**, derived from L-threose with silylated uracil, - thymine or *N*-acetylcytosine in the presence of trimethylsilyl triflate as catalyst, afforded only the β-anomeric nucleosides **54a-c** as single products in good yields (62-65%). The corresponding α-anomeric nucleosides **55a-c** have not been detected in the reaction mixture (Scheme 19).[37] This is the best observed diastereoselectivity for the nucleosidation of 5-acetoxy-substituted isoxazolidines achieved from sugar- derived nitrones.



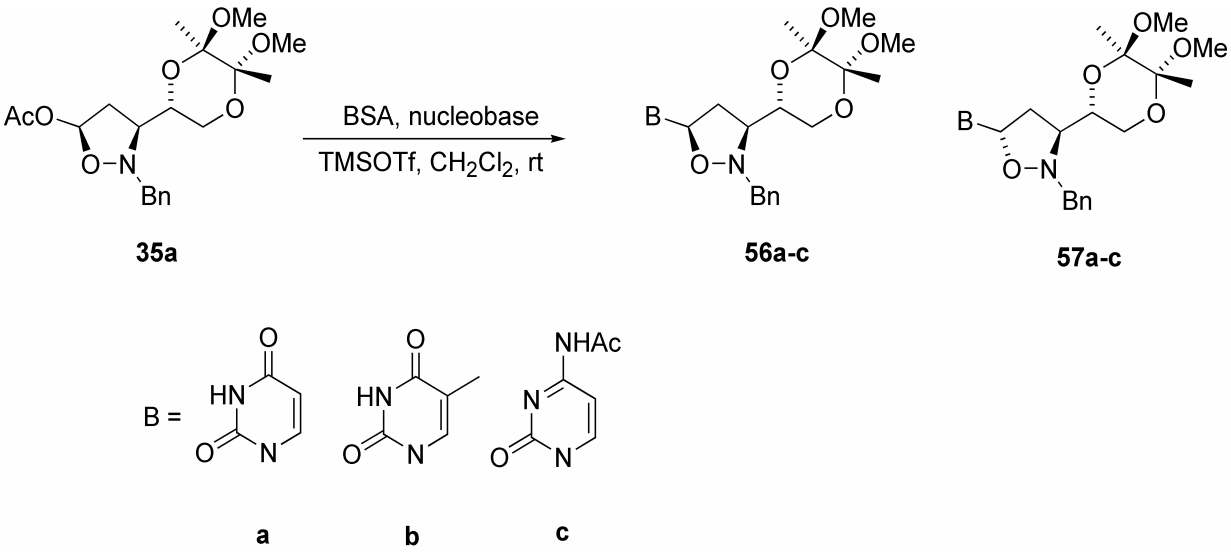
Scheme 18



Scheme 19

5.8 Isoxazolidinyl nucleosides prepared from D-mannitol

Finally, the nucleosidation of the *anti-cis* isoxazolidine **35a** derived from protected D-glyceraldehyde, prepared starting from D-mannitol with silylated uracil, -thymine or -*N*-acetylcytosine in the presence of trimethylsilyl triflate as catalyst afforded the β-anomeric nucleosides **56a-c** in good yields (62-87%) and with high diastereoselectivities (**56a**/**57a** ratio 85:15, **56b**/**57b** ratio 86:14, **56c**/**57c** ratio 90:10, Scheme 20).[37]



Scheme 20

6. Conclusions

From two strategies for the diastereoselective synthesis of isoxazolidinyl nucleosides a two-step methodology based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines proceeded more selectively than a one-step approach based on the 1,3-dipolar cycloaddition of *C*-glycosyl nitrones with vinyl nucleobases. We have made the potentially useful observation that the anomeric distribution of the formed nucleosides may be dependent not just on the nature of the attacking nucleobase but also on the 3-substituent of the isoxazolidine. This observation might be exploited in future to allow the generation of anomerically pure nucleosides via the Vorbrüggen method.

Acknowledgements

The authors are grateful to the Slovak Grant Agency (No. 13549/06), APVV (No. 20/000305) and the Deutsche Forschungsgemeinschaft. The NMR experimental work was facilitated by the support of Slovak National Research (No 2003SP200280203).

References and Footnotes

1. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
2. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863.

3. Merino, P.; Franco, S.; Merchan, F. L.; Romero, P.; Tejero, T.; Uriel, T. S. *Tetrahedron: Asymmetry* **2003**, *14*, 3731.
4. Merino, P. In: Sciences of Synthesis; Padwa, A. Ed.; Thieme: Stuttgart, 2004; Vol. 27, p 511.
5. Osborn, H. M. I.; Gemmel, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.
6. Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem*. **2003**, *7*, 585.
7. Fišera, L.; Ondruš, V.; Kubán, J.; Micúch, P.; Blanáriková, I.; Jäger, V. *J. Heterocyclic Chem.* **2000**, *37*, 551.
8. Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.
9. Fišera, L. In *Topics in Heterocyclic Chemistry. Heterocycles from Carbohydrate Precursors*, El Ashry, E. S. H., Ed.; Springer, 2007; p 287.
10. Merino, P. *Compt. Rend. Chim.* **2005**, *8*, 775.
11. De Clercq, E. *Biochim. Biophys. Acta* **2002**, *258*, 1587.
12. Merino, P. *Curr. Med. Chem. Anti Infective Agents* **2002**, *1*, 389.
13. Romeo, G.; Iannazzo, D.; Piperno, A.; Romeo, R.; Corsaro, A.; Rescifina, A.; Chiacchio, U. *Mini-Rev. Org. Chem.* **2005**, *2*, 59.
14. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Recent Research Development in Organic Chemistry* **2000**, *4*, 227.
15. Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321.
16. Merino, P.; Del Alamo, E. M.; Santiago, F.; Merchan, F. L.; Simon, A.; Tejero, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1543.
17. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Pieperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. *Eur. J. Org. Chem.* **2001**, 1893.
18. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R.; Siciliano, M. C. R.; Valveri, E. *ARKIVOC* **2002**, (*xi)*, 159.
19. Colacino, E.; Converso, A.; Ligueri, A.; Napoli, A.; Siciliano, C.; Sindona, G. *Tetrahedron* **2001**, *57*, 8551.
20. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2003**, *46*, 3696.
21. Kubán, J.; Blanáriková, I.; Fišera, L; Jarošková, L.; Fengler-Veith, M.; Jäger, V.; Kožíšek, J.; Humpa, O.; Prónayová, N.; Langer, V. *Tetrahedron* **1999**, *55*, 9501.
22. Kubán, J.; Kolarovič, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N.; Ertl, P. *Synlett* **2001**, 1862.
23. Kubán, J.; Kolarovič, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N. *Synlett* **2001**, 1862.
24. Blanáriková-Hlobilová, I.; Kopaničáková, Z.; Fišera, L.; Cyrański, M. K.; Salanski, P.; Jurczak, J.; Prónayová, N. *Tetrahedron* **2003**, *59*, 3333.
25. Dugovič, B.; Wiesenganger, T.; Fišera, L.; Hametner, C.; Prónayová, N. *Heterocycles* **2005**, *65*, 591.

26. Dugovič, B.; Fišera, L.; Cyranski, M. K.; Hametner, C.; Prónayová, N.; Obranec, M. *Helv. Chim. Acta* **2005**, *88*, 1432.
27. Rehák, J.; Fišera, L.; Kožíšek, J.; Perašínová, L.; Steiner, B.; Kóóš, M. *ARKIVOC* **2008**, *(viii)*, 18.
28. Chiacchio, U.; Rescifina, A.; Corsaro, A.; Pistara, V.; Romeo, G.; Romeo, R. *Tetrahedron Asymmetry* **2000**, *11*, 2045.
29. Legio, A.; Liguori, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Tetrahedron Lett*. **1996**, *37*, 1277.
30. Pan, S.; Amankulov, N. A.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587.
31. Colacino, E.; Converso, A.; De Nino, A.; Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Nucleoside and Nucleotides* **1999**, *18*, 581.
32. Fischer, R.; Drucková, A.; Fišera, L.; Rybár, A.; Hametner, C.; Cyrański, M. K. *Synlett* **2002**, 1113.
33. Hýrošová, E.; Fišera, L.; Jame, R. M.-A.; Prónayová, N.; Medvecký, M.; Kóóš, M. *Chem. Heterocycl. Comp*. **2007**, 14.
34. Fischer, R.; Drucková, A.; Fišera, L.; Hametner, C. *ARKIVOC* **2002**, *(viii)*, 80.
35. Hýrošová, E.; Medvecký, M.; Fišera, L.; Hametner, C.; Fröhlich, H.; Marchetti, M.; Allmaier, G. *Tetrahedron* **2008**, *64*, 3111.
36. Hýrošová, E.; Fišera, L.; Kožíšek, J.; Fronc, M. *Synthesis* **2008**, 1233.
37. Hýrošová, E.; Fišera, L.; Reissig, H.-U.; Al-Harrasi, A. *Tetrahedron Asymmetry* (submitted).
38. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
39. Vorbrüggen, H.; Ruh-Pohlenz, C. In *Organic Reactions, Synthesis of Nucleosides;* Paquette, L., Ed.; J. Wiley and Sons, Inc.: New York, 2000; Vol. 55, p 1.
40. Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 7430.
41. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **2000**, *65*, 5575.
42. Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Sindona, G.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2717.
43. Chiacchio, U.; Iannazzo, D.; Piperno, A.; Romeo, R.; Romeo, G.; Rescifina, A.; Saglimbeni, M. *Bioorg. Med. Chem.* **2006**, *14*, 955.
44. DeShong, P.; Li, W.; Kennington, J.; Ammon, H. L. *J. Org. Chem*. **1991**, *56*, 1364.
45. Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett*. **2000**, *2*, 2331.