Pergamon

Tetrahedron 54 (1998) 6587–6604

TETRAHEDRON

Tetrahedron report number 454

Syntheses of Isoxazolinyl and Isoxazolidinyl Nucleoside Analogues

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Received 8 January 1998

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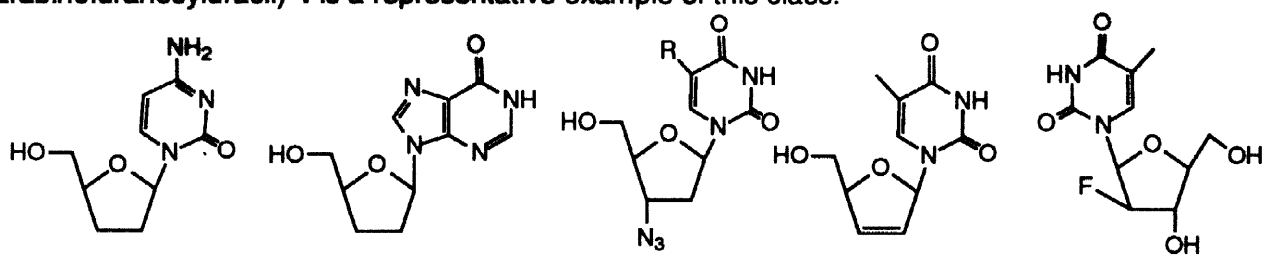
1. INTRODUCTION

Nucleosides have been parent structures in the rational design and development of novel antiviral drugs (Figure 1).[1] Modified nucleoside analogues inhibit viral polymerases by either as DNA/RNA chain terminators or as competitive inhibitors. The first generation of nucleoside antiviral analogues is derived from substituent manipulation of the ribose parent ring. The basic ability to inhibit viral polymerases is achieved (in the case of these first generation drugs) by the removal of the hydroxyl groups from 2',3'-positions of the ribose ring structure. Ribose derived nucleosides lacking the 2',3'-hydroxyl groups are generally known as dideoxynucleosides, hence the abbreviation (ddN). Since the derived chemical structures are useful for the inhibition of viral DNA or RNA synthesis, an enormous number of compounds with various substituents can be investigated as possible antiviral agents. Of these, some prominent first generation drugs include: ddC (**1a**),[1,2] ddI (**1b**),[1,2] AZT (**2a**) (R = Me),[1,3] AZddU (**2b**) (R = H),[1,3] and d4T (**3**).[1,4] Recently, promising results

PII: S0040-4020(98)00186-0

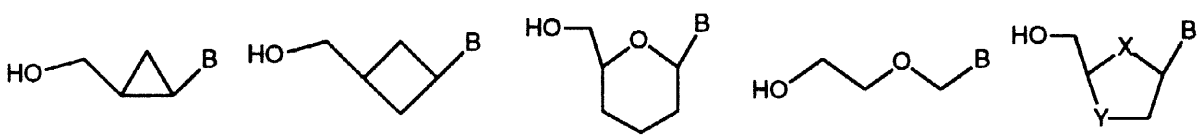
have also been observed for the corresponding L-isomers and L-FMAU (2'-fluoro-5-methyl-β-L-arabinofuranosyluracil) **4** is a representative example of this class.[1,5]



1a: ddC **1b**: ddI **2**: AZT, AZddU **3**: d4T **4**

Figure 1: Ribose derivatives as first-generation anti-viral agents.

A related strategy used in the design of nucleoside analogues, has involved manipulation of the ribose ring size (Figure 2), as well as subsequent manipulation of some substituents on the corresponding rings. In addition to the above-mentioned ribose (five-membered) ring structure, 3-, 4-, and 6-membered rings have been constructed and examined for possible antiviral activities. Interesting antiviral and anticancer compounds have been reported from those structures **5-7**.[6-8] Needless to say, much current work in the discovery of antiviral agents is targeted on manipulations of nucleoside backbones **5-7**. A very interesting variation on the theme of nucleosides is the acyclic structure **8**, which, aside from the exclusion of a ring structure, includes other important structural components of nucleosides and their analogues.[1g-h,9] In fact, some of these compounds have proved quite successful as antiviral agents. Several representative acyclic antiviral agents such as acyclovir, ganciclovir, and famciclovir are essentially derived from **8**.[10]



5 **6** **7** **8** **9-10**

Figure 2: Cyclic, acyclic, and heteroatom-containing nucleoside analogues.

Another notable class of compounds includes analogues with diheteroatom-containing sugar moieties **9-10** (Figure 2). Remarkable levels of anti-HIV and anti-HBV potency have been observed in 1,3-dioxolane **9** (X = Y = O)[11] and 1,3-oxathiolane nucleosides **10** (X = O, Y = S).[12,13] Furthermore, some *L*-(-)- enantiomers of **10**, of which 3TC [(-)-2'-deoxy-3'-thiacytidine] might well be the most prominent, exhibit remarkable antiviral capabilities.[12] Some extensive reports have detailed the synthesis of diheteroatom-containing oxathiolane and dioxolane moieties.[11-13]

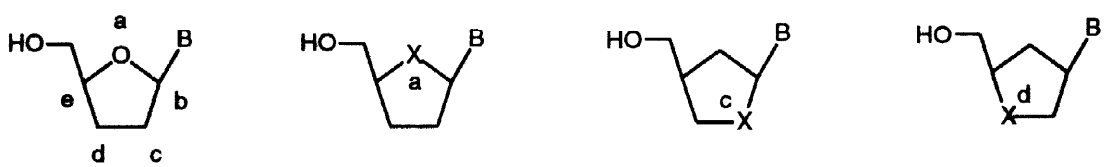
Since some success in the synthesis of antiviral agents has resulted from the manipulation of oxathiolane and dioxolane nucleoside systems, it is of interest to find similar nucleoside systems in which the heteroatoms are nitrogen and oxygen. In this regard, this review attempts to cover reports of nitrogen-containing nucleoside analogues, with particular emphasis on the synthesis of

isoxazolidinyl and isoxazolinyl nucleosides. We include all pertinent reports published before January 1998.

2. NOTATION METHOD

Here, we propose a notation method for the structural description of nucleoside analogues. This simple and efficient method will cover all the nucleoside ring structures and the use of this system should facilitate the discussion of structural features. Although this notation method enable adequate visualization of these nucleoside analogues without further reference to figures, it shall be combined with the traditional nomenclature for the flavor of nucleoside chemistry.

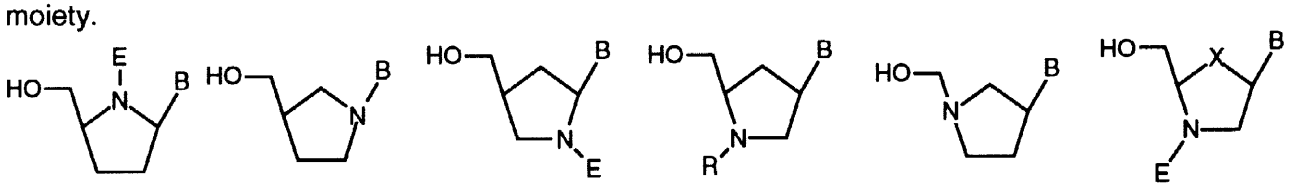
In our method, the structure of 2',3'-dideoxyribose nucleoside analogue **2** will be abbreviated into C_4O^a (Figure 3). The notation C_4O indicates a five-membered ring compound with one heteroatom (in this case, oxygen) and four carbons in the ring. Superscripts (a-e) will be used to further differentiate the position of the heteroatom. As such, superscript (a) indicates a heteroatom between the hydroxymethyl and the base, (b) would theoretically represent a heteroatom connected to the base, and so on. Compounds **11-13** will, therefore, be written as C_4X^a, C_4X^c, and C_4X^d, respectively.



2 (C_4O^a) **11** (C_4X^a) **12** (C_4X^c) **13** (C_4X^d)

Figure 3: Notations for the naming of cyclic nucleoside analogues.

This notation has several advantages: (1) Structures can be understood without structural formulas. For example, structure C_4O^a or even "O^a" means furan compound **2**. Class C_5 may be used as a point of reference, and refers to the corresponding cyclopentane derivatives. (2) All cyclic nucleoside analogues can be divided into classes and subclasses. For example, class **11** (C_4X^a) can be further divided into the subclasses C_4O^a, C_4S^a, and C_4N^a. (3) This notation can be used to group compounds together for prediction of structural stabilities. This last point is validated by the fact that nitrogen containing compounds **14-20** exhibit drastically different levels of stability (Figure 4). For example, compound **18** is unlikely to be stable due to the presence of a carbinolamine moiety.



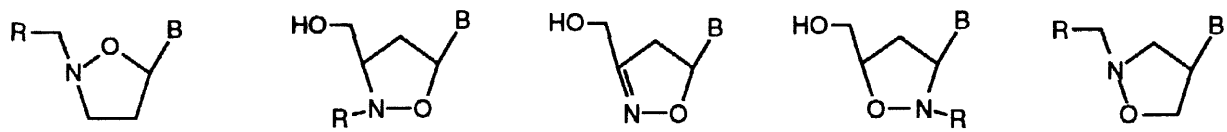
14 (C_4N^a) **15** (C_4N^b) **16** (C_4N^c) **17** (C_4N^d) **18** (C_4N^e) **19** ($C_3O^aN^d$) **20** ($C_3S^aN^d$)

Figure 4: Nitrogen-containing nucleoside analogues (E = electron withdrawing groups; R = alkyl groups).

The introduction of only one nitrogen atom into the 5-membered ring (Figure 4) can result in the generation of groups of compounds such as **14-18** with backbones C_4N^a, C_4N^b, C_4N^c, C_4N^d, and C_4N^e. Several groups have focused on the construction of derivatives of compound **14**, and some of these derivatives show interesting antiviral activities.[14] A few papers have been reported on the synthesis of **15** and some of its derivatives earlier in this decade.[15] Literature searches reveal that nothing is known about classes **16** (C_4N^c) and **18** (C_4N^e), and very little is reported about compounds of class **17** (C_4N^d).[16] A few structural manipulations result in ring systems **19-20** ($C_3O^aN^d$ and $C_3S^aN^d$).[17] Paying particular attention to compounds such as**19-20**, it would seem quite probable that the instability of these compounds results from the unstable carbinolamine like structures O-C-N or S-C-N. Consequently, the addition of nitrogen as a second heteroatom has proven particularly difficult for these ring systems. Since synthesis of **14-20** is a problem, attempts to determine the anti-viral activity of this class of compounds have been curtailed by a shortage of molecules for testing purposes.

3. ISOXAZOLINYL AND ISOXAZOLIDINYL NUCLEOSIDES

Unlike compounds **19** ($C_3O^aN^d$) and **20** ($C_3S^aN^d$), N-O containing compounds feature relatively stable hydroxylamine-type bond structures. Generally, these N-O containing five-membered ring derivatives are known as isoxazolidines (**21-22**, **24-25**) and isoxazolines (**23**). These compounds, which can be prepared by taking advantage of the unique properties of hydroxylamine moieties, can be divided into five categories such as in Figure 5. In spite of the wealth of information that exists on



21 ($C_3O^aN^e$) **22** ($C_3O^cN^d$) **23** ($C_3O^cN^d$-2H) **24** ($C_3O^dN^c$) **25** ($C_3O^dN^e$)

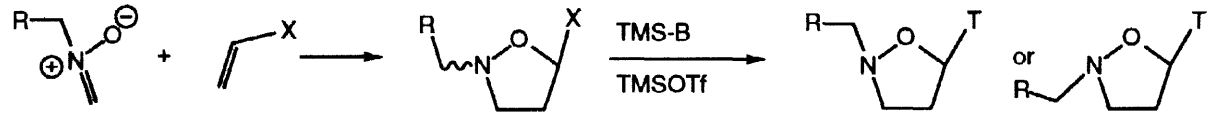
Figure 5: Isoxazolinyl and isoxazolidinyl backbones **21-25**.

the construction of N-O bond structures in chemical syntheses, the area of isoxazolinyl and isoxazolidinyl nucleosides remains poorly investigated. However, it should be noted that a variety of nucleoside structures containing N-O bonds have been constructed for exploratory studies to provide strategies for potential drug development. Comprehensive literature searches reveal that compounds belonging to classes **21-23** have been prepared through a limited number of methods. Furthermore, virtually nothing in the way of syntheses is known about compounds of classes **24-25**. Consequently, the information known about the ability of isoxazolidines to function as antiviral agents is by no means comprehensive. Compounds of class **21** ($C_3O^aN^e$) represent isoxazolidine nucleosides, and have been synthesized by Tronchet et. al[18] and Sindona et. al.[19] Isoxazolidines of class **22** ($C_3O^cN^d$) have been synthesized by Zhao et. al,[20] and also by Romeo et. al.[21] Finally, isoxazolines belonging to class **23** ($C_3O^cN^d$-2H) have been synthesized by Zhao and his co-workers with good enantioselectivity.[22] Below, we summarize some synthetic pathways utilized in the

preparation of these three classes of nucleoside analogues. In addition, we attempt to point out some chemically interesting components which are unique to each of these syntheses.

3.1 Preparation of Class $C_3O^aN^e$.

In 1992, Tronchet's group reported the first synthesis of nucleoside analogues of class **21** (Scheme 1).[18a] Specifically, the featured reaction in their synthesis involved the 1,3-dipolar cycloaddition of simple nitrones **26a-b** with vinyl acetate **27a** and imidazole **27b**. Subsequent base condensation of products **28a-d** with silylated thymine in the presence of trimethylsilyl triflate results in the formation of isoxazolidines **21a** and **21b**. In general, they found that the cycloaddition proceeded with relatively good regioselectivity, forming $C_3O^aN^e$ nucleoside ring structures. A pair of *tran* and *cis* isomers **21a-b** were observed. The structural analyses regarding the stabilities of the formed isomers are interesting. Tronchet found that the *cis* isomers are more stable than the *trans*. Since free rotation about the nitrogen atom is expected, these results seem a bit unexpected. Tronchet and co-worker's were, in fact, able to show the stability of the *cis*-derived isomers by calculating the relative stabilities of the *cis* and *trans* isomers using AM1 Hamiltonian precise mode calculations. In the case of **21b**, an energy difference of 2.6 kcal/mol was calculated in favor of the *cis* isomers . Tronchet et. al argue that this barrier sufficiently explains the predominance of the *cis* isomer observed in the case of **21b**. The replacement of a carbon atom by nitrogen is particularly interesting in these compounds. Since the nitrogen atom allows for relatively facile inversions (about nitrogen) precluded by carbon atoms, it will be interesting to see the structural impact of this feature in seeking out biologically active compounds of this class.



26a, R=H
26b, R=Ph
26a-b

27a, X=OAc
27a, X=OAc
27b, X=imidazole

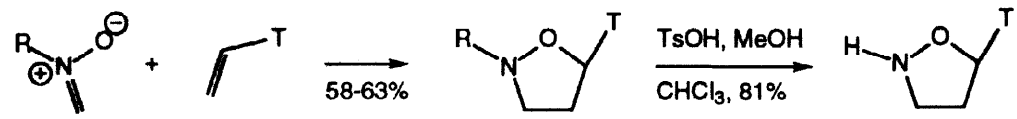
28a
28b
28c-d

21a-*trans*,
21b-*trans*,

21a-*cis*
21b-*cis*

Scheme 1: Tronchet's 1,3 dipolar cycloaddition approach to isoxazolidines.

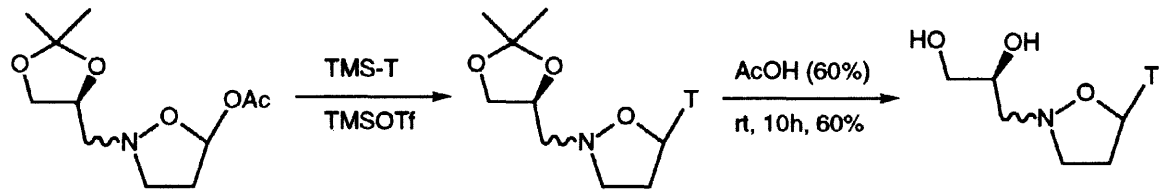
The method employed by Tronchet and co-workers, as outlined above, has been reinvestigated by Sindona's group and reported in 1996.[19] Their synthesis of other non-hydroxylated derivatives of compound **21** takes advantage of direct 1,3-dipolar cycloadditions of nitrones **26b-c** with vinylthymine **27c** (Scheme 2). Again, good regioselectivity is observed here. This step is then followed by hydrolysis of **21c** to afford **21d**. Essentially, their effort constitutes a one-pot synthesis of $C_3O^aN^e$ derivatives. Two points are in order here. First, in the case of Sindona's synthesis, the glycosidic bond survives acidic hydrolysis of a THP moiety. Sindona and co-workers suggest that the glycone might be protonated under acidic conditions, thereby enhancing the stability of the glycosidic bond. Secondly, compound **21d** is water soluble, a fact that might prove useful in future drug design. If derivatives of these compounds are to be synthesized, the first point should prove indispensable.



26b, R=Bn
26c, R=THP
27c, T=thymine
21b
21c
21d

Scheme 2: A one-pot synthesis of isoxazolidines.

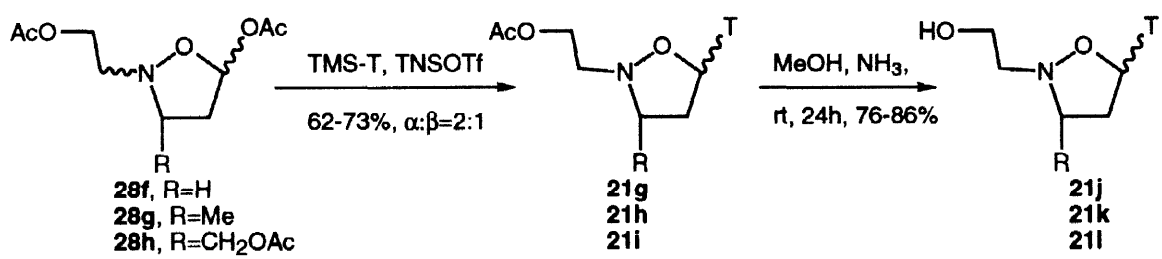
The synthesis of *N*-hydroxymethyl derivatives of isoxazolidines **21** (R = OH) have not been reported using the 1,3-dipolar cycloaddition methodologies, perhaps due to the unstable aminal structural elements which were pointed out earlier. This point is crucial. Since the tri-phosphorylation of the hydroxymethyl group is required for incorporation into elongating DNA chains, the need for a hydroxymethyl mimic is warranted. Tronchet et. al have synthesized compounds such as **21f**, where a hydroxyl group is one carbon atom added from its usual position (Scheme 3).[18a] Briefly, the synthetic steps utilized here are as follows: base condensation of **28e** followed by deprotection yields **21f**.



28e **21e** **21f**

Scheme 3: Synthesis of $C_3O^aN^e$ derivatives with potential tri-phosphorylation sites.

Scheme 4 shows the synthesis of substituted isoxazolidinyl thymine derivatives as explained above. Elaborated nitrones can be used as starting materials to prepare substituted isoxazolidines such as **21g-i**. The α:β ratio of compounds **21g-i** is 2:1 after base condensation with silylated thymine. Although compounds **21j-l** exhibit no antiviral activity, they represent the first attempt to substitute hydroxyl groups onto the isoxazolidine ring. If antiviral biological activity is to be observed with these compounds, these hydroxyl groups will almost certainly be needed.[18b]



28f, R=H
28g, R=Me
28h, R=CH_2OAc
21g
21h
21i
21j
21k
21l

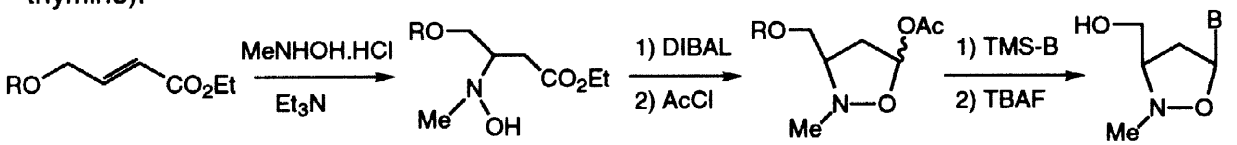
Scheme 4: Synthesis of substituted $C_3O^aN^e$ derivatives.

To conclude, several $C_3O^aN^e$ derivatives have been synthesized by 1,3-dipolar cycloaddition methods. Some noteworthy points regarding these derivatives include their stability under mild acidic and basic conditions. However, the poor levels of stereoselectivity observed upon base

condensation with **21g-i** may call for alternative pathways during future syntheses of the above compounds.

3.2 Preparation of Class $C_3O^cN^d$.

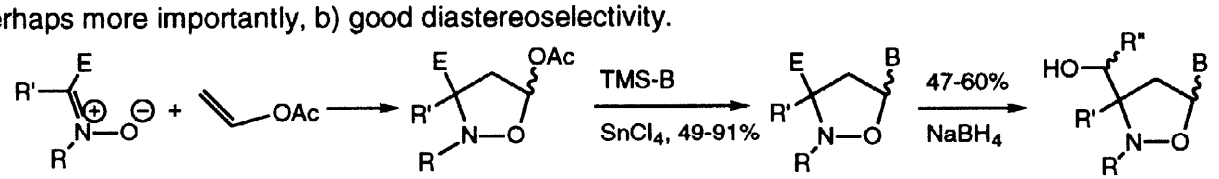
In 1995, Zhao and co-workers reported the synthesis of class $C_3O^cN^d$ (Scheme 5).[20a] These compounds, unlike the existing derivatives of **21**, contain hydroxymethyl groups which are closely analogous to those found on ribose. In short, they were the first isoxazolidines whose hydroxymethyl group was directly analogous to the ribose parent-structure of nucleosides. The synthetic pathway here involves the key Michael addition of *N*-methylhydroxylamine onto α,β-unsaturated ester **29** to form **30**. Subsequent DIBAL reduction and acetyl protection gives the intermediate **31a**. Condensation with silylated-thymine in the presence of TMSOTf as a catalyst afforded the TPS-protected intermediate which was directly converted to the desired product **22a** (B = thymine).



29 R = *t*-BuPh$_2$Si **30** **31a** **22a**

Scheme 5: A diastereoselective synthesis of the $C_3O^cN^d$ class of isoxazolidines.

It is appropriate to point out that the Lewis acid-promoted coupling ($Et_2O.BF_3$ or TMSOTf) of acetate **31a** and TMS-protected nucleoside bases gives rise to the *cis* compounds **22a** primarily. However, much higher levels of diastereoselectivity is observed when TMSOTf is used as a Lewis acid. Remarkably, the high levels of stereoselectivity observed here proceed in the absence of metal chelation. These theoretically intriguing results set the stage for preparation of various isoxazolidine nucleosides. The isoxazolidine derivatives can be prepared in a) good yield, and perhaps more importantly, b) good diastereoselectivity.



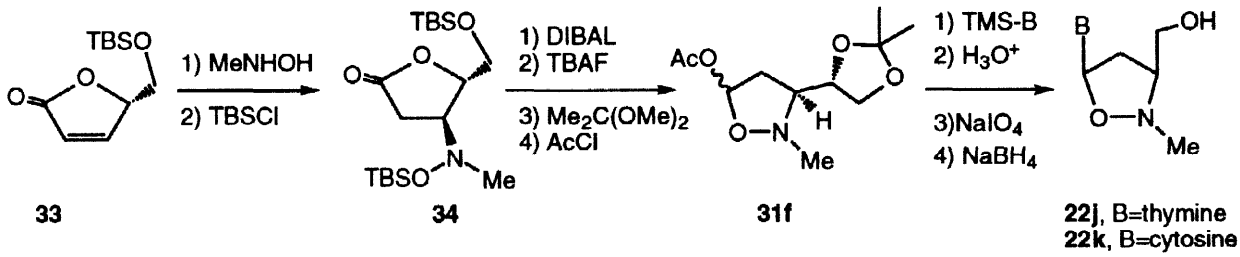
32a, R=Me, R'=Me, E=COOEt	**31b**	**22b**	**22f**, B=thymine
32b, R=Bn, R'=n-C_5H_{11}, E=COOEt	**31c**	**22c**	**22g**, B=5-F-uracil
32c, R=Bn, R'=H E=COOEt	**31d**	**22d**	**22h**, B=5-F-uracil
32d, R=Bn, R'=H, E=COPh	**31e**	**22e**	**22i**, B=thymine

Scheme 6: A [3+2] cycloaddition approach to isoxazolines of class $C_3O^cN^d$.

Romeo et. al have used dipolar addition reactions to prepare thymine and fluorouracil isoxazolidines **22f-i** (Scheme 6).[21] Nitrones containing electron withdrawing groups, as in **32a-d**, can be utilized in [3+2] cycloadditions with vinyl acetate to give a mixture of diastereomeric products **31**. Subsequent base condensation yields isoxazolidines **22b-e**. The synthetic sequence is completed by reduction of **22b-e** with sodium borohydride, producing target isoxazolidines **22f-i**. Since ketones can be used as the starting materials for the nitrone preparation, R' can be either

hydrogen or alkyl groups. While this reaction is facile and gives rise to multi-substituted $C_3O^cN^d$, base condensation here is not very diastereoselective. Unlike compound **31a** (Scheme 5), which produced primarily *cis* products upon condensation, compounds **31b-e** (Scheme 6) gave a mixture of *cis:trans* products **22b-e**. The regioselectivity of the cycloaddition, however, is quite good.

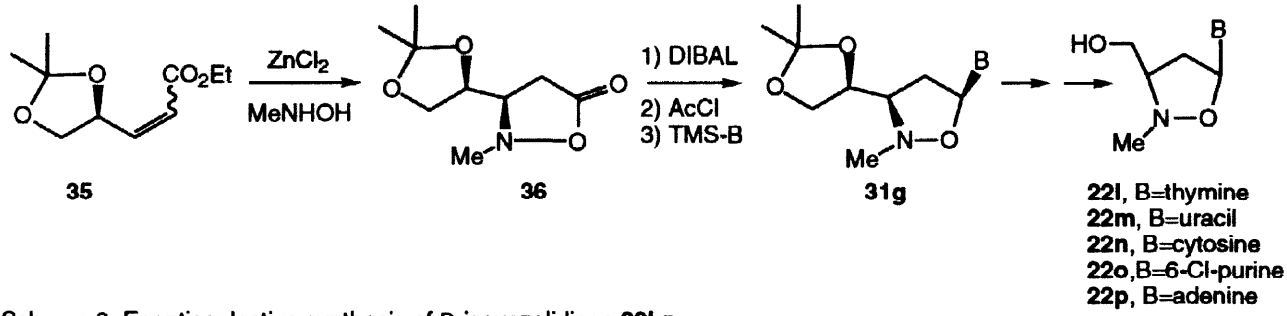
Following their early success with Michael additions unto unsaturated esters, Zhao and co-workers embarked upon a diastereoselective and enantioselective synthesis of pure isoxazolidine *L*-enantiomers **22j-k** (Scheme 7).[20b] The enantioselectivity of this process stems from the enantiomerically pure synthon **33**. This lactone undergoes a *trans* Michael reaction with *N*-methylhydroxylamine to give the corresponding Michael adduct. This adduct is then protected, yielding **34**. Following this protection, a set of synthetic transformations, namely, DIBAL reduction, TBAF deprotection, acetal formation, acetate protection, and base condensation, results in the synthesis of intermediate **31f**. Notably, the base condensation step (Scheme 7) yields *cis* products exclusively and, as observed earlier, the remarkably high levels of stereoselectivity present here proceeds in the absence of metal chelation. The conversion of **31f** to the desired L-compound **22j-k** is effected by hydrolysis, oxidation with $NaIO_4$, and reduction with $NaBH_4$. The synthetic utility of this method is particularly obvious when three points are considered. Regarding the transformation of intermediate **31f** to final product **22k-j**, it should be noted that a) the anomeric position is stable under the acidic conditions used to hydrolyze the acetal; b) the N-O bond in **31f** survives oxidation with sodium periodate; and c) the aldehyde formed upon oxidation (not shown) can be captured with a variety of Grignard reagents, leading to the production of isoxazolidines which contain alkyl groups as opposed to hydrogen. The introduction of alkyl groups will result in the formation of a new stereogenic center which provides an additional opportunity to obtain two possible isomers for the evaluation of antiviral activity.



Scheme 7: Enantioselective synthesis of L-isoxazolidines **22j-k**.

With the synthesis of L-isoxazolidines **22j-k** complete, D-enantiomers could theoretically be prepared from the alternative isomer of **33**, which would require a long synthetic sequence. Instead, the readily available unsaturated ester **35** was recruited in the scheme for the purpose of Michael addition (Scheme 8).[20c] The *syn*-adduct **36** was produced after metal-catalyzed cyclization with zinc chloride. The dimethyl dioxolane moiety was presumably responsible for the *syn* Michael addition of *N*-methylhydroxylamine to **35**. Interestingly, the olefin geometry of **35** did not affect the predominance of the *syn* isomer **36**, and it was reported that both the *Z*- and *E*- olefins give the

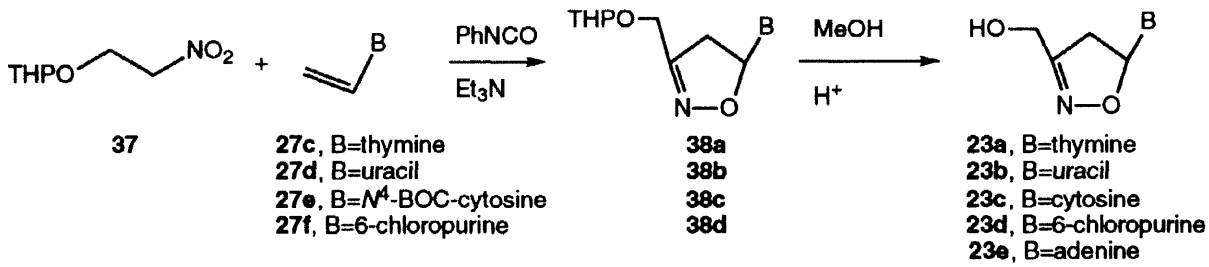
same product **36**.[20c] Formation of a variety of D-isoxazolidines **22l-p** from **36** utilizes reactions which have been described above (Scheme 7).



Scheme 8: Enantioselective synthesis of D-isoxazolidines **22l-p**.

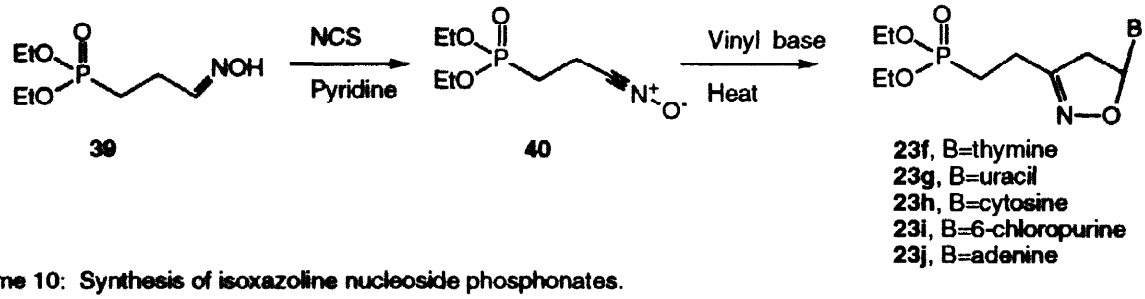
3.3 Preparation of $C_3O^cN^d$-2H (Isoxazolines).

The racemic isoxazoline compounds **23a-e** were successfully prepared by employing a [3+2] dipolar cycloaddition of *N*-vinyl-bases with appropriately protected nitrile oxides (Scheme 9).[22a-b] For example, the synthetic sequence begins with the use of *N*-vinyl-6-chloropurine **27f**, which was readily prepared after minor modifications of the Ts'o procedure. Compound **27f** readily undergoes a regioselective [2+3] cycloaddition with the $THPO(CH_2)_2NO_2$-derived nitrile oxide to form **38d**. Treatment of **38d** with Dowex 50 (H^+) in methanol affords the desired product **23d**. It should be noted that the glycosidic bond was surprisingly stable under this acidic condition. Conversion of **23d** to compound **23e** was achieved using sodium azide in ethanol at 80°C, followed by triphenylphosphine reduction. The hydrolysis of azide reduction intermediate requires its treatment with aqueous acetic acid at 100 °C and the final product **23e** can be obtained in 51% yield.



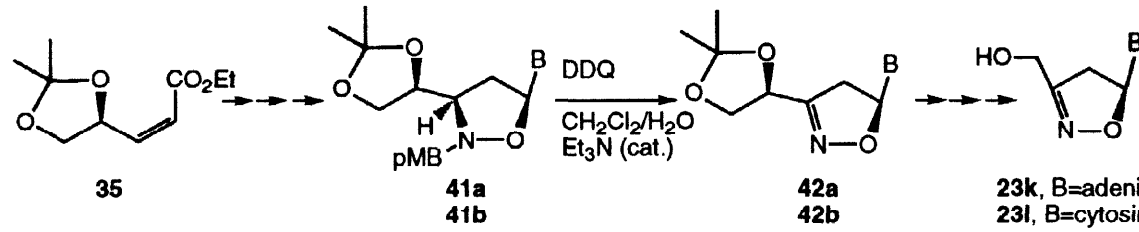
Scheme 9: The 1,3-dipolar cycloaddition approach to racemic isoxazolines.

These investigations have essentially laid the groundwork for preparation of the corresponding phosphonate analogues **23f-j** (Scheme 10).[22b] The synthesis of **23f-j** commences with NCS oxidation of oxime **39** in pyridine, yielding **40**. The phosphonate moiety survives the steps of oxime formation and oxidation. Cycloaddition with vinyl bases under heat affords the nucleoside phosphonates **23f-j**. The cycloaddition methods are very convenient for the preparation of isoxazolines since the nitrile oxide starting materials can be prepared by either the dehydration of nitro compounds, or oxidation of oximes. The regiochemistry of additions is generally controlled. However, the cycloaddition step lacks enantioselectivity. This fact may hamper the use of cycloaddition methods in the preparation of **23** (class $C_3O^cN^d$-2H).



Scheme 10: Synthesis of isoxazoline nucleoside phosphonates.

A route to the enantioselective syntheses of these isoxazolines **23** has been reported (Scheme 11).[22c] Nucleoside analogues **41**, in which the nitrogen atom is substituted with a *p*-methoxybenzyl group (pMB), were prepared for the development of oxidative methods to selectively remove the alkyl group on the nitrogen atom. While oxidative removal of the pMB group from *nitrogen* atoms is, for the most part, uncommon, it is well documented that the pMB group can be used as a protecting group for alcohols and removed by oxidative cleavage with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). It is found that compounds **41a** (B = purine derivatives) reacted with DDQ/CH_2Cl_2/H_2O in the presence of a catalytic amount of triethylamine to afford products **42a**, which was converted to the desired adenine product. In addition, the cytidine derivative **41b** (B = cytosine) can be similarly obtained. This approach offers the only effective method that can be used to allow access to a variety of optically active isoxazolines **23**, including the corresponding L-isomers, which are otherwise difficult to obtain. The use of this synthetic scheme for the preparation of **23k-l** allows for potentially divergent syntheses in which previously prepared isoxazolidines can be transformed to isoxazolines, circumventing the cycloaddition methods which were described previously.

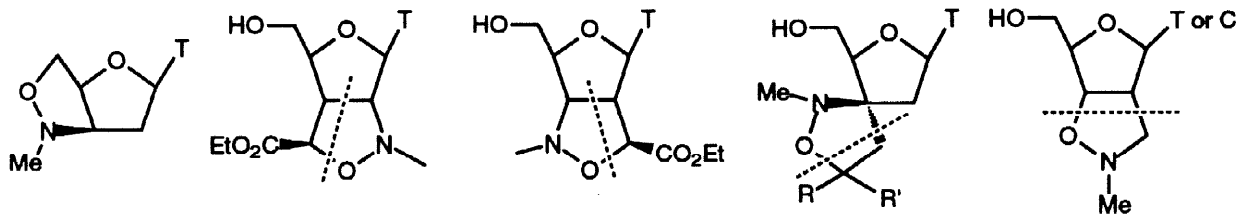


Scheme 11: Enantioselective synthesis of isoxazolines **23**.

4. POLYCYCLIC ISOXAZOLIDINE NUCLEOSIDES

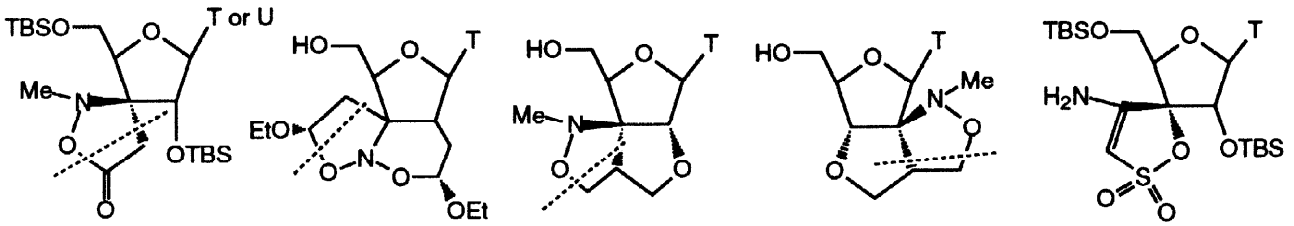
In addition to the above-mentioned syntheses, some recent reports document the preparation of polycyclic nucleoside derivatives **43-51** (Figures 6-7). Compound **43** is the product of a hydroxylamine-substituted C_4O^a compound,[23a] which was prepared by the Mitsunobu reaction.[23b] Generally, other compounds are approached by using [3+2] cycloaddition methods.[23-25] The sites of coupling are indicated by dashes. These structures are interesting since, unlike the nucleoside analogues described above, these polycylic analogues may resemble TSAO {[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide)]-β-D-pentofuranosyl} analogs

52.[26] With the exception of few examples, only thymine-containing derivatives **43-51** have been prepared.[23-25] Since this is the case, it is not yet clear whether any of these polycyclic compounds can act as anti-viral agents. Certainly, one should expect to see the synthesis of more polycyclic derivatives in the future.



43[23a,b] **44**[24a] **45**[24a] **46**[24b] **47**[25]

Figure 6: Bicyclic isoxazolidine nucleosides.



48[23c] **49**[24c] **50**[24d] **51**[24d] **52**[26]

Figure 7: Other selected cyclic nucleosides.

5. CONCLUSION

5.1 Chemistry.

A number of *N-O* containing nucleosides have been synthesized. Two major methods have been utilized in these syntheses. Generally, these methods are: a) [3+2] dipolar cycloaddition and b) Michael addition. Investigations have predominantly focused on the preparation of isoxazolidinyl and isoxazolinyl nucleosides utilizing a [3+2]-dipolar cycloaddition of various nitrones or nitrile oxides as a cornerstone reaction. Cycloadditions offer an efficient route for the synthesis of a variety of nucleoside analogues for the screening of their antiviral activities. The disadvantage of this method is that the synthetic efficacy in the preparation of isoxazolines and isoxazolidines is hampered by the poor enantio- or diastereoselectivities observed during cycloaddition.

On the other hand, Michael-addition methods which couple simple hydroxylamines to unsaturated lactones and esters effect highly stereoselective syntheses of isoxazolidines and even isoxazolines. In short, the Michael addition method can be used for the *enantioselective* preparation of *N-O* nucleosides. These preliminary results have indicated that these derivatives are quite stable under a variety of reaction conditions, including acid hydrolysis, oxidation, and reduction. It will require some effort to develop other methods which may result in alternative approaches to facile preparation of new derivatives **21-25**.

5.2 Biological Evaluation.

Since isoxazolidine nucleosides such as **22** can be *N*-alkyl substituted, it is believed that the underlying properties of these nucleosides will present the unique opportunity for structural modification of lead compounds of class $C_3O^cN^d$. It would be interesting to see what sort of structural requirements are needed for high affinity to viral polymerases. Although it has not been reported that this class of compounds show antiviral activity, it is certainly expected that more isoxazoline derivatives will be prepared for biological studies. Alternatively, compounds **22** may also provide leads in the discovery of anticancer agents which function in similar ways as some of the compounds described in this report.

Regarding the class of isoxazoline nucleosides **23**, biological tests have revealed moderate anti-HIV potency for a mixture of D- and L-isomers. It would be interesting to see whether isoxazoline derivatives can be utilized as potent anti-viral agents in the future. So far, modification of the bases, and inclusion of both phosphonate and hydroxymethyl derivatives have not proven highly effective. Strictly speaking, structural modifications at the nitrogen atom in the nucleoside ring of isoxazolines are ostensibly less numerous than modifications of isoxazolidines. However, the modifications that have been made so far do not exhaust the possible changes that can be made to improve the potency of isoxazolines.

Finally, regarding isoxazolidines **24-25** of classes $C_3O^dN^c$ and $C_3O^dN^e$, it is too premature to make judgments regarding the potential use of these derivatives as antiviral agents since preparations of these compounds are not reported.

Acknowledgments: We acknowledge financial support from the NSF Faculty Early Career Development Program, the American Cancer Society, the New York University Technology Transfer Fund, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. SP acknowledges the New York University MacCracken Fellowship.

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Shifeng Pan received his BS. degree from Fudan University, Shanghai, P R of China, in 1993. After three years graduate study with Professor Tingwei Dong, he received his MS. degree in organic chemistry from the same university in 1996. He is currently a Ph.D. candidate under the direction of Professor Kang Zhao at New York University, working on synthesis of novel nucleoside analogues. He is now a recipient of MacCracken Fellowship from New York University. To date, he co-authored 10 publications.

Nduka Amankulor was born in Los Angeles, CA, in 1977. He is currently completing his final year of undergraduate studies at New York University with a focus on Neuroscience and Chemistry. His current research, under the supervision of Dr. Kang Zhao, involves the synthesis of protein tyrosine phosphatase (PTPase) inhibitors. His previous work on PTPase κ, under the supervision of Dr. Jan Sap (Sackler Institute, NYU Medical School) resulted in the elucidation of PTPκ's mode of binding with E-Cadherin. In general, he is interested in the design and synthesis of artificial, biologically relevant molecules. Specifically, he is interested in the use of organic molecules as tools in investigating signal transduction pathways. His research activities have led to presentations at several venues, including the 37st Annual Meeting of the American Society for Cell Biology.

Kang Zhao received his undergraduate degree from Shandong University, P R of China, in 1982. He attended graduate school at Columbia University in 1983, where he received his Ph.D. (with Professor Gilbert Stork) in 1988. After two years as a postdoctoral fellow with Professor Gilbert Stork at Columbia University and two years as a Cystic Fibrosis Foundation Fellow with Professor Donald Landry at Columbia Medical School, he was appointed Assistant Professor at New York University. He is co-author of over 40 refereed journal publications that are related to the development of synthetic methods, with particular emphasis on *N-O* bond chemistry and glycosidation chemistry. He is the recipient of a Goddard Fellowship, an American Cancer Society Junior Faculty Research Award, and a NSF Faculty Early Career Development Award. He currently holds the positions of Visiting Professor of Medicine at Hunan Medical University and Columbia Medical School, Chair of the Chemical Sciences of the New York Academy of Sciences, and W. M. Keck Foundation Early Career Professor at New York University.