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Polyalkoxy Nitrones as Chiral Building Blocks in Asymmetric Synthesis

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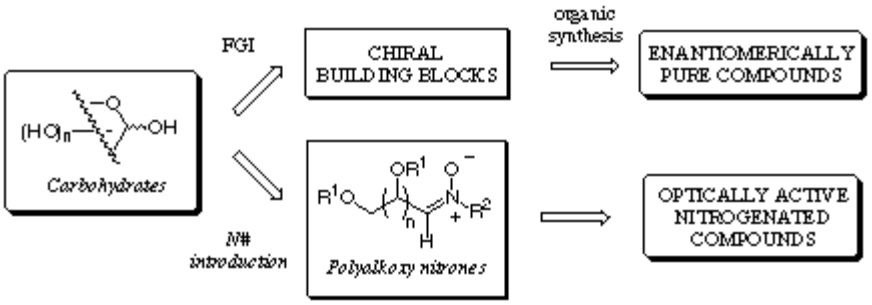
Introduction

The growing demand for enantiomerically pure compounds has led chemists to investigate a variety of approaches to such a sort of molecules. One method that has been widely recognized lies in the use of carbohydrates for preparing suitable chiral building blocks bearing, in most cases, several oxygenated functions in different oxidation states.[1]

A considerable part of the synthetic applications of carbohydrate-derived chiral building blocks is connected with their use as precursors of nitrogenated compounds such as amino sugars, alkaloids or amino acids.[2] Unfortunately, the development of nitrogenated building blocks prepared from carbohydrates has proceeded at a lower space and has not reached the degree of complexity of its oxygenated counterparts. However, for the preparation of a variety of optically active nitrogenated compounds it is possible to introduce a nitrogen functionality at an earlier stage in order to prepare nitrogenated chiral building blocks of wide applicability. In this context the spectrum of application of carbohydrate-derived nitrones (polyalkoxy nitrones) is very broad and the synthetic importance of these compounds is still rapidly developing.



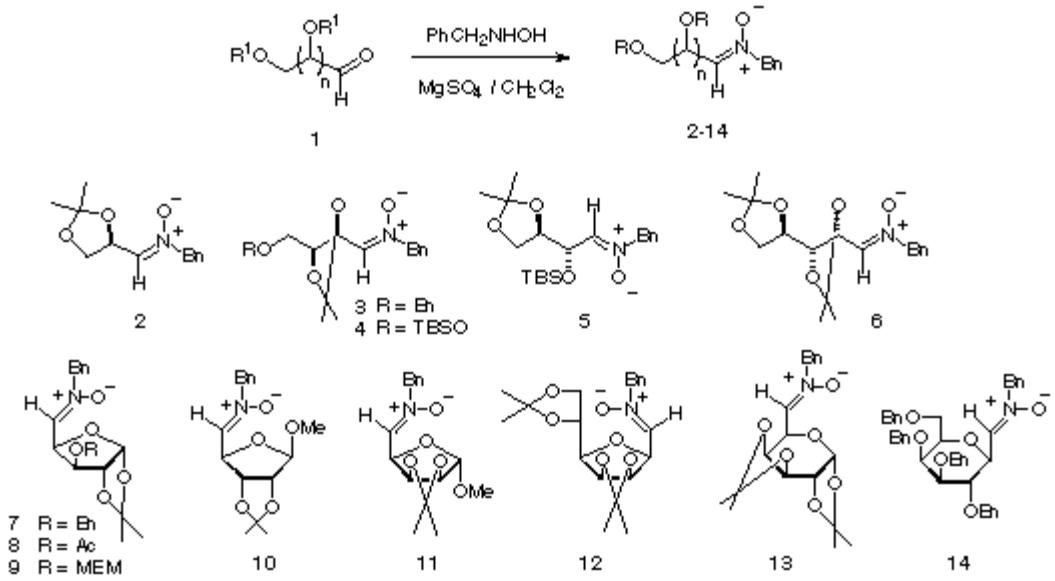
Polyalkoxy nitrones have been used as 1,3-dipoles in cycloaddition reactions during the synthesis of

optically active nitrogenated compounds.
[3] Since the 1,3-dipolar chemistry of nitrones has been widely reviewed,[4] the main focus of this review will be limited to recent studies carried out in our laboratories at the University of Zaragoza on the reactivity of the title compounds as electrophiles in nucleophilic additions and application of the resulting hydroxylamines in organic synthesis.

Synthesis

Several methods for preparing nitrones have been developed. These include oxidation of hydroxylamines,[5] imines[6] and amines,[7] alkylation of oximes[8] and condensation between a carbonyl compound and a N-substituted hydroxylamine[9]. Among these methods the later is more appropriate for preparing polyalkoxy nitrones since a variety of polyalkoxy aldehydes are easily accessible from the carbohydrate-based chiral pool. Thus, the reaction of polyalkoxy aldehydes with N-benzyl hydroxylamine, in the presence of magnesium sulfate as a drying agent led to the polyalkoxy nitrones illustrated in Scheme 1, as the result of a dehydrocondensation process[10].

Scheme 1

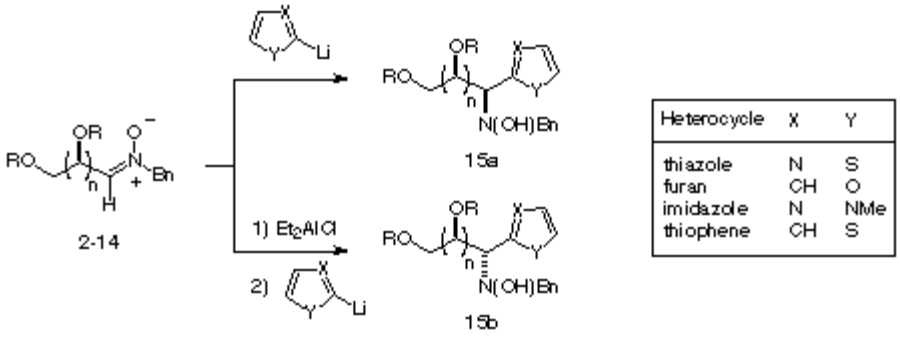


The yields are good and in all cases only the Z-isomers were obtained as could be demonstrated by NMR spectroscopy (NOE experiments).

Reactivity

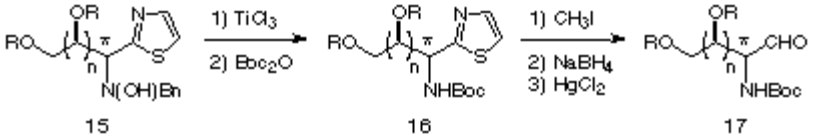
Polyalkoxy nitrones show a rich variety of nucleophilic additions, as might be expected for the electrophilic character of the nitrone functionality. For instance, asymmetric nucleophilic additions of metalated heterocycles provided the corresponding hydroxylamines with high syn diastereoselectivity. Alternatively, the reaction with nitrones previously treated with 1.0 equiv of Et_2AlCl led preferentially to the anti isomers. In consequence a complete stereocontrol could be achieved as it has been demonstrated for thiazole[11], furan[12], imidazole[12], thiophene[13] and their benzoderivatives (Scheme 2).

Scheme 2



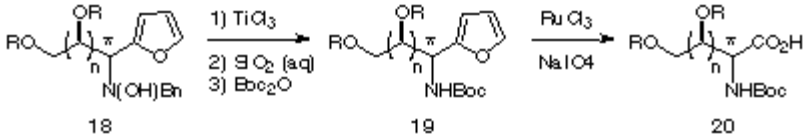
In the case of thiazole and furan, the synthetic equivalences of these heterocyclic rings with the formyl and carboxyl groups, respectively, were exploited for developing new synthetic methodologies. The conversion of (hydroxyaminoalkyl)thiazoles **15** to the protected (aminoalkyl)thiazoles **16** could be done by a two-step process consisting of concomitant deoxygenation and debenzylation with titanium (III) chloride and further reaction with di-tert-butyl dicarbonate in dioxane[14] (Scheme 3). Finally, transformation of the thiazole ring into a formyl group according to the described protocol[15] furnished a-amino aldehydes **17**.

Scheme 3



Similarly, (hydroxyaminoalkyl)furans **18** were transformed into protected (aminoalkylfurans) **19**. Oxidation of the furan ring with ruthenium (III) chloride (or ruthenium (II) oxide) in the presence of sodium periodate, according to the literature[16], afforded b-hydroxy-a-amino acids **20** (Scheme 4)[17].

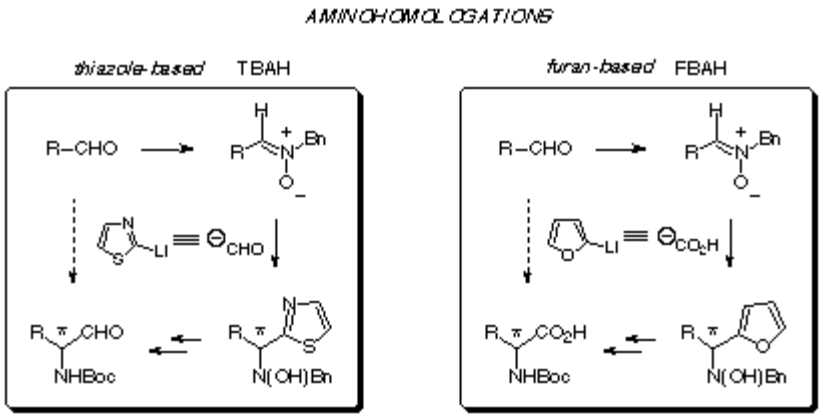
Scheme 4



These reaction sequences allowed the preparation of novel chiral (aminoalkyl)- and (hydroxyaminoalkyl) heterocycles, whose absolute configuration could be assigned by circular dichroism on the basis of new sector rules developed in our laboratory for both thiazole[18] and furan[19] derivatives. In other cases, X-ray crystallography of those products, or some other derivative, was used as a definitive corroboration[20].

Since the starting nitrones (precursors of hydroxylamines **15** and **18**) were prepared from the corresponding aldehydes, the overall processes outlined in Schemes 3 and 4 can be considered as stereoselective homologations with incorporation of an amino functionality into the newly generated asymmetric center. We referred to these transformations as thiazole-based aminohomologation (TBAH)[14] and furan-based aminohomologation (FBAH)[17], respectively (Scheme 5).

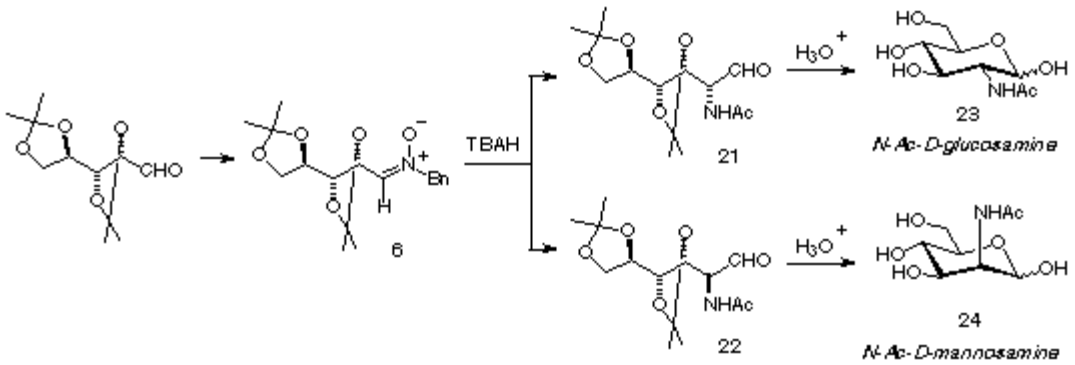
Scheme 5



The reactivity of polyalkoxy nitrones with hetaryl nucleophiles of synthetic utility[21] (such as furan and thiazole) made possible the total syntheses of several natural products of interest. Both chemical transformations prior to the cleavage of the heterocyclic system and further elaborations of the prepared key intermediates (a-amino aldehydes and a-amino acids) allowed the total synthesis of amino sugars, aza sugars or complex nucleosides.

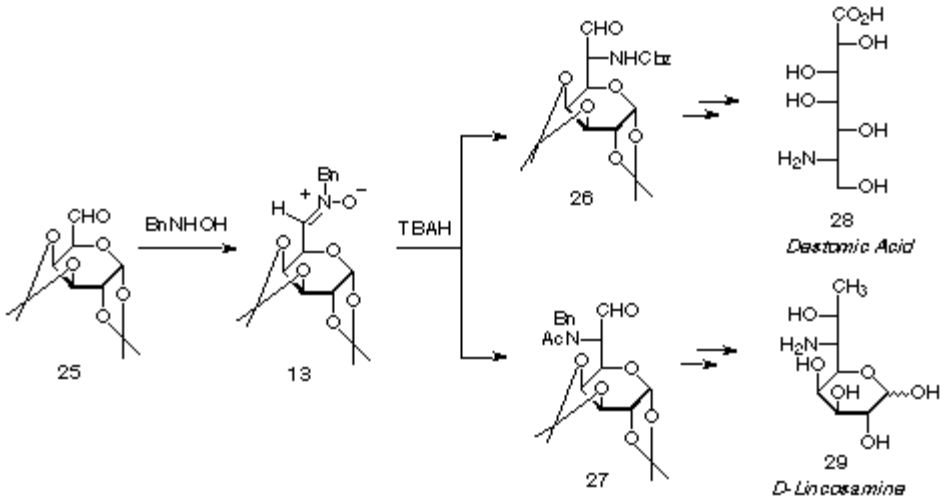
The arabinose-derived nitrone **6**, obtained from the corresponding aldehyde, was made to react with 2-lithiothiazole to furnish the corresponding hydroxylamines which were converted into a-amino aldehydes **21** and **22** following the thiazole-base aminohomologation protocol, TBAH, described above (Scheme 6). Deprotection of the acetonide moiety afforded the aminosugars N-acetyl-D-glucosamine **23** and N-acetyl-D-mannosamine **24**, respectively.[14],[22]

Scheme 6



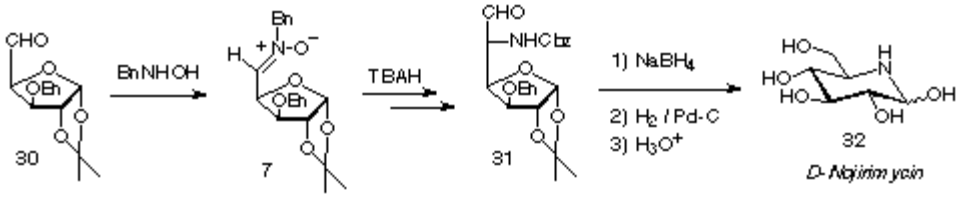
The stereocontrolled aminohomologation of aldehyde **25** led to epimeric a-amino aldehydes **26** and **27**, advanced intermediates in synthesis of destomic acid and lincosamine, respectively (Scheme 7)[23].

Scheme 7



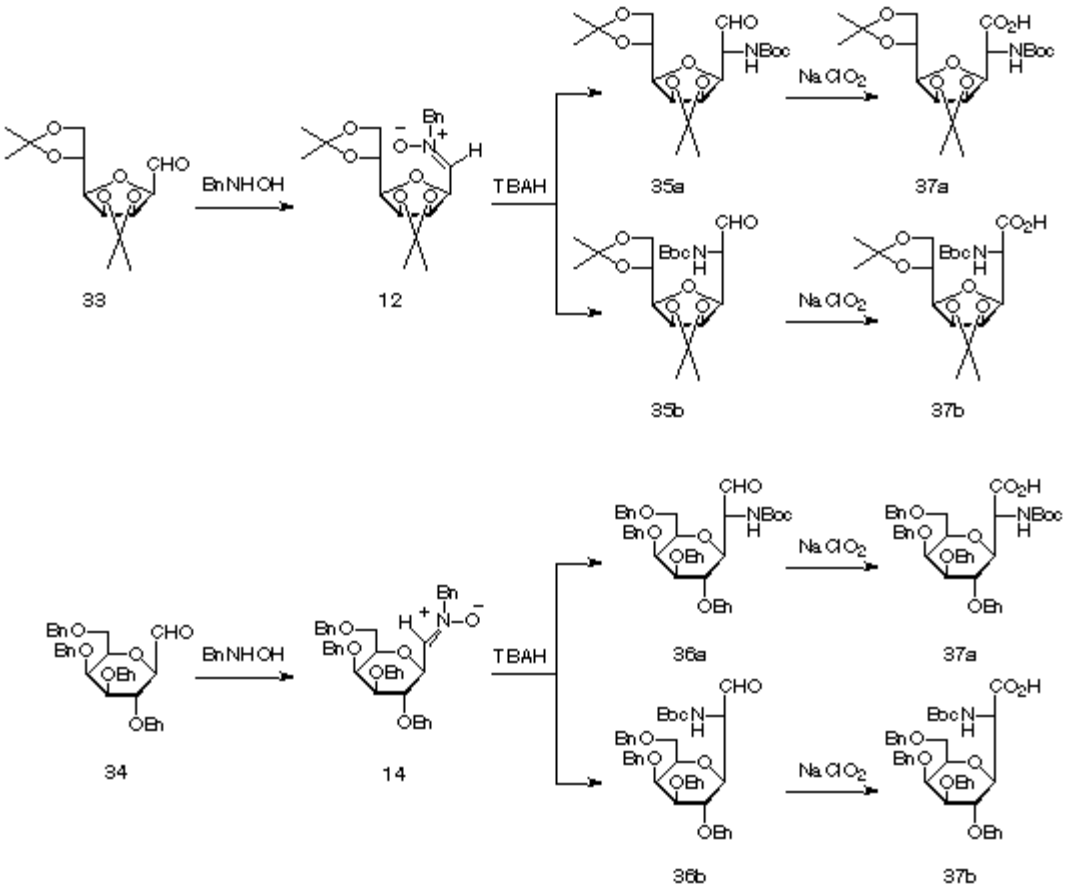
Similarly, aldehyde **30** was subjected to the same methodology to furnish a-aminoaldehyde **31** which was further transformed into the aza sugar D-nojirimycin (Scheme 8)[14].

Scheme 8



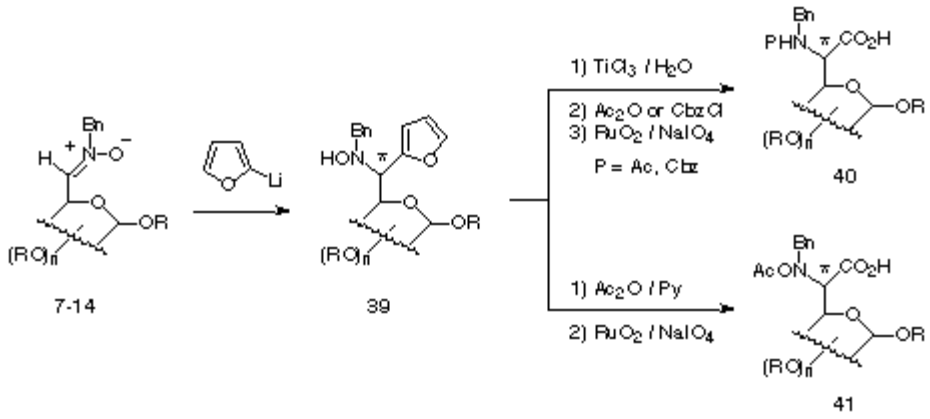
The above nitrone-thiazole methodology was also applied for the synthesis of novel anomeric C-glycosyl a-amino acids. Aminohomologation of both **33** and **34** led to a-amino aldehydes **35** and **36**. Oxidation of these compounds using $NaClO_2$ in aqueous NaH_2PO_4 afforded a-amino acids **37** and **38**, respectively[24]. As outlined in Scheme 9 all possible stereoisomers were synthesized.

Scheme 9



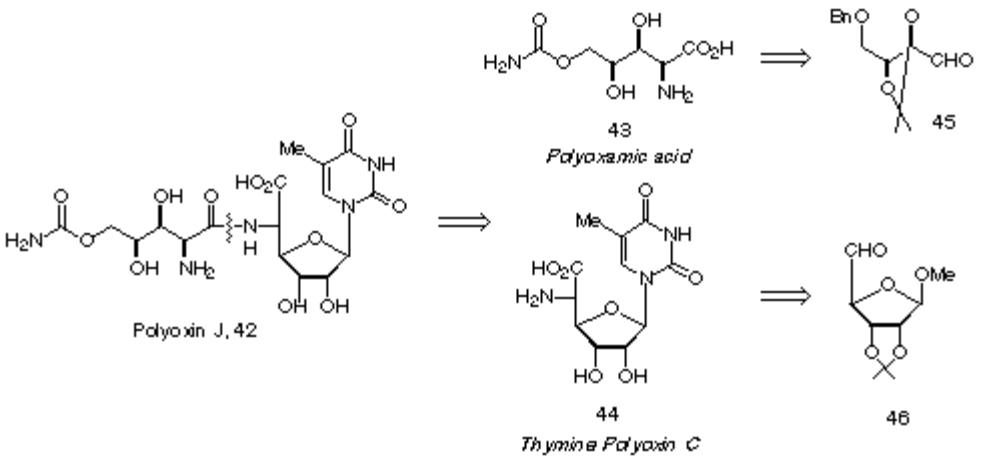
In addition to the above mentioned synthesis of b-hydroxy-a-amino acids through the reaction of 2-furyllithium with aldose-derived nitrones, the furan-based methodology was also utilized for preparing both glycosyl a-amino acids and their N-hydroxy derivatives (Scheme 10)[24].

Scheme 10



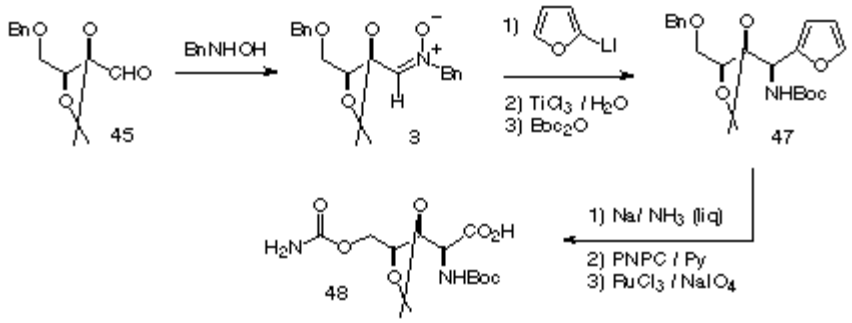
This approach was used for the total synthesis of Polyoxin J **42**, a peptidyl nucleoside antibiotic of interest as an inhibitor of chitin biosynthesis. The two constituent fragments of Polyoxin J (polyoxamic acid **43** and thymine Polyoxin C **44**) were synthesized in our laboratory by aminohomologation of the corresponding polyalkoxy aldehydes **45** and **46** (Scheme 11)[25].

Scheme 11



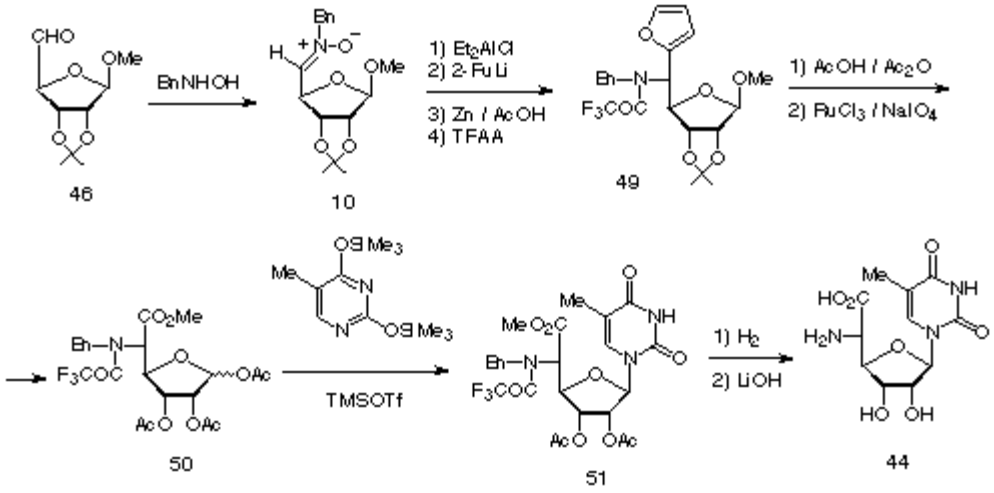
Application of our method to the L-threose-derived aldehyde **45** afforded the protected furfurylamine **48** (Scheme 12). The necessary functional group transformations were carried out prior to the unmasking of the carboxyl group. Thus, after replacement of the benzyl group by the carbamate unit the furan ring was oxidized by using the system $RuCl_3$ - $NaIO_4$ to give suitable protected polyoxamic acid derivative **49** in a 25.8% overall yield from aldehyde **45** (7 steps)[26].

Scheme 12



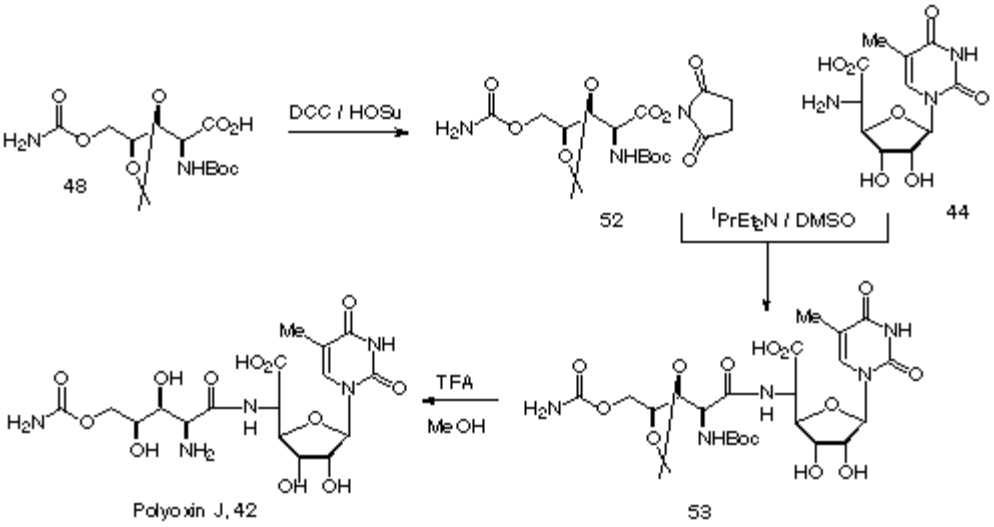
Several synthetic approaches to the thymine polyoxin C **44** were envisioned,[27] the best of them being that illustrated in Scheme 13. In this case, the addition of the metalated heterocycle was carried out in the presence of 1.0 equivalent of Et_2AlCl in order to obtain the hydroxylamine with the required stereochemistry. Further deoxygenation and trifluoroacetylation gave intermediate **49**. Concomitant acid hydrolysis and acetylation of this compound followed by oxidation of the furan ring and glycosylation with 2,4-bis(trimethylsilyl)thymine gave the nucleoside amino acid **50**. Complete deprotection of this derivative by reductive and hydrolytic methods furnished natural thymine polyoxin C in a 9.6% overall yield from aldehyde **46** (10 steps)[26] .

Scheme 13



The final coupling between **48** and **44** was performed by the N,N-dicyclohexylcarbodiimide N-hydroxysuccinimide (DCC / HOSu) active ester method. Thus protected polyoxamic acid **48** was converted into active ester **52** (Scheme 14) which was then treated with thymine polyoxin C **44** to afford the dipeptide **53**. Finally, deprotection of **52** by treatment with aqueous trifluoroacetic acid gave, after purification by column chromatography, Polyoxin J in 46% yield[25],[26] .

Scheme 14



Conclusions

As discussed, our heterocycle-nitrone methodologies were appropriate for the development of highly efficient stereoselective synthetic routes to a variety of nitrogenated compounds of interest. For further application of polyalkoxy nitrones our attention is now focused in the use of different nucleophiles which allow access to more elaborated compounds. Thus there is still great room for development of effective synthetic methodologies based on nucleophilic addition to polyalkoxy nitrones.

Acknowledgements

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