Application of the Asymmetric Hetero Diels-Alder Reaction for Synthesising Carbohydrate Derivatives and Glycosidase Inhibitors

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Abstract: This review provides a discussion of recent developments in the asymmetric hetero Diels-Alder reaction (AHDAR), with particular emphasis on the synthesis of carbohydrates, their derivatives, and inhibitors of carbohydrate processing enzymes.

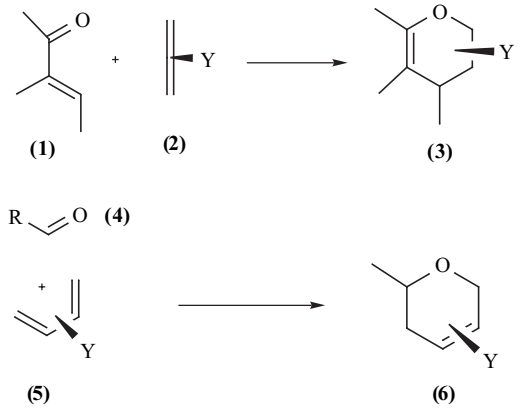
Keywords: Heterodiene, Heterodienophile, stereocontrol, enantiocontrol, diastereocontrol.

1. INTRODUCTION

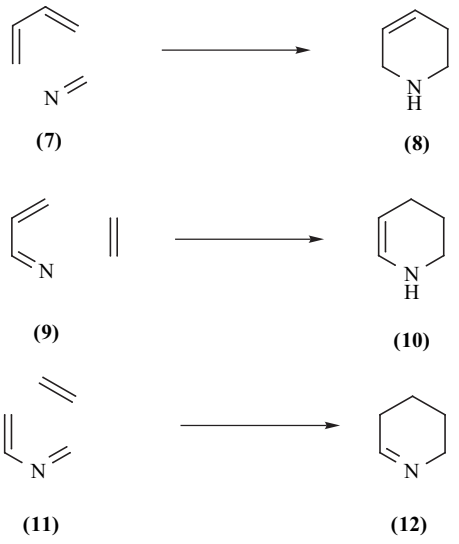
The extensive synthetic utility of the traditional 'diene plus dienophile' Diels Alder reaction for accessing functionalised cyclohexene skeletons with excellent regio- and stereoselectivity is well recognised within organic chemistry [1] and biological systems [2]. The analogous cycloaddition reactions between heterosubstituted dienes and dienophiles have also demonstrated their worth for the regio- and stereoselective synthesis of a wide range of heterocycles [3]. This review aims to summarise the impact that the Asymmetric Hetero Diels-Alder Reaction (AHDAR) has had on the preparation of carbohydrates and their derivatives, as well as on the preparation of pyrrolidine derivatives of use within glycobiology programmes. Thus syntheses of carbohydrates, their derivatives, and inhibitors of carbohydrate processing enzymes that use an AHDAR as a key step will be described. Although a wide range of natural products and their derivatives have been prepared by the AHDAR, carbohydrates have been selected as the subject matter for this review due to the recent appreciation of their many and varied roles within biological systems [4]. Thus it is now recognised that cell surface carbohydrates are involved in cell differentiation, interaction and recognition events, and that many disease pathways rely upon the interaction of carbohydrates with lectins for their progression. Many methods have therefore, been developed to prepare both natural and unnatural carbohydrates of use for glycobiology programmes, and the AHDAR has played a pivotal part in the progress of such research.

Two approaches can be considered for entry to dihydropyrans, of use for entry to carbohydrate analogues that utilise an AHDAR. For example, α,β-unsaturated carbonyl compounds **(1)** can be utilized in an inverse-electron demand Diels-Alder reaction as an electron-poor diene component, with suitably substituted alkenes **(2)**, to yield 3,4-dihydro-2*H*-pyrans **(3)**. Alternative entry to the pyran products **(6)** can be achieved *via* reaction of an aldehyde or a ketone **(4)** with a diene **(5)** (Scheme 1).

Three variants of the imino DAR are commonly used for entry to the tetrahydropyridines **(8)**, **(10)** and **(12)**, of use for accessing inhibitors of the carbohydrate processing enzymes (*vide infra*). Thus the nitrogen functionality can be introduced *via* an imine dienophile **(7)**, a 1-azadiene **(9)** or a 2-azadiene **(11)** (Scheme 2).



Scheme 1. Synthesis of dihydropyran products.



Scheme 2. Synthesis of tetrahydropyridine products.

Stereocontrol to allow asymmetric entry into the targets is normally effected by use of chiral dienes or dienophiles, incorporation of chiral auxiliaries within the substrates, or usage of chiral Lewis acids - the benefits and success of the latter approach, together with mechanistic rationales for explaining the stereocontrol observed in such reactions, have recently been reviewed by Jørgensen [3d]. Since it is often

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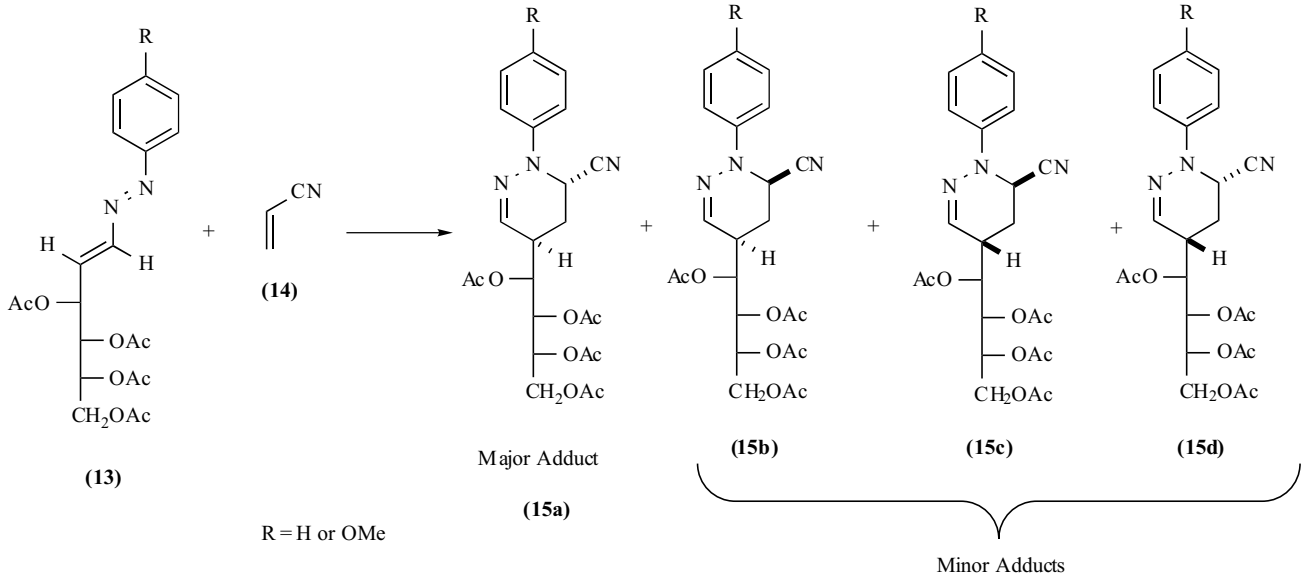


Scheme 3. Synthesis of carbohydrate-based tetrahydropyridazines.

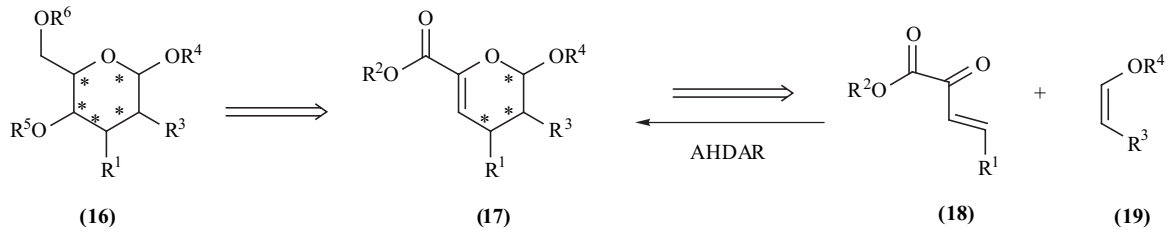
possible to predict the regio- and stereochemical outcome of the AHDAR, this impacts on its synthetic utility. Studies continue to be reported that analyse and compare experimental and theoretical data in order to allow an improved understanding of factors that control the regio- and stereoselectivities of hetero-DA cycloaddition reactions [5]. For example, in one particular study [6] a series of carbohydrate-based tetrahydropyridazines were prepared by the AHDAR between chiral 1,2-diaza-1,3-butadienes **(13)** and acrylonitrile **(14)** and the regio- and diastereoselectivities were theoretically predicted and then rationalised from experimental observations (Scheme 3).

The reactions were found to be regiospecific and the observed diastereoselectivities were consistent with a preferred attack to the *Re* face of the heterodiene unit. This is a result of the chiral sugar located at C4 largely protecting the opposite *Si* face.

a) Application of the AHDAR for the Synthesis of Carbohydrates and Their Derivatives

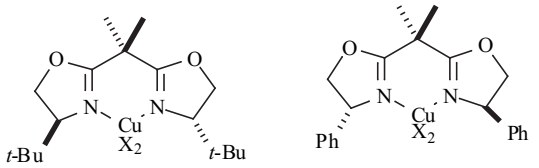
The use of the AHDAR for preparing optically active carbohydrate derivatives offers many advantages compared with the strategic manipulation of naturally occurring carbohydrates. Firstly, the AHDAR allows entry to either enantiomer of the target derivative, by careful choice of starting materials, whereas the D-series of carbohydrates are more accessible from natural sources than L-monosaccharides. Second, well designed AHDARs require fewer steps to access the desired target than manipulation of monosaccharides, due to the need for extensive protection / deprotection steps within traditional carbohydrate synthesis strategies. Third, the availability of many substrates suitable for incorporation within the AHDAR means that a vast array of targets can be accessed *via* this route – far more than *via* manipulation of carbohydrates themselves. The success of the HDAR for accessing achiral carbohydrate derivatives has been well exemplified [7] and this has been expanded to allow asymmetric entry to enantiomerically pure derivatives [3]. The scope of the AHDAR for accessing optically active carbohydrate derivatives is evident from retrosynthetic analysis of the target carbohydrates, as indicated in Scheme 4.

Thus use of optically active α,β-unsaturated carbonyl compounds **(18)** and/or optically active alkenes **(19)** has allowed the development of diastereoselective HDARs that allow formation of functionalised derivatives **(17)** with up to three controlled stereocentres in a single step [8]. Such reaction processes have met with excellent success but can suffer from slight limitations if chiral auxiliaries are incorporated in order to render the diene or dienophile asymmetric – removal of the chiral auxiliary adds an extra synthetic step to the process and in some cases this can lower the overall yield of the process. Recent efforts have therefore been expended to develop catalytic enantioselective HDARs that use chiral Lewis acids to invoke enantiocontrol [3d, 9]. Most reports in this area have detailed the reactions of dicarbonyl dienophiles with dienes in the presence of



Scheme 4. Utilisation of the AHDAR for accessing optically active carbohydrates.

chiral bisoxazoline copper(II) catalysts, such as (*S*)-**(20)** or (*R*)-**(21)** (Figure **1**) [9].

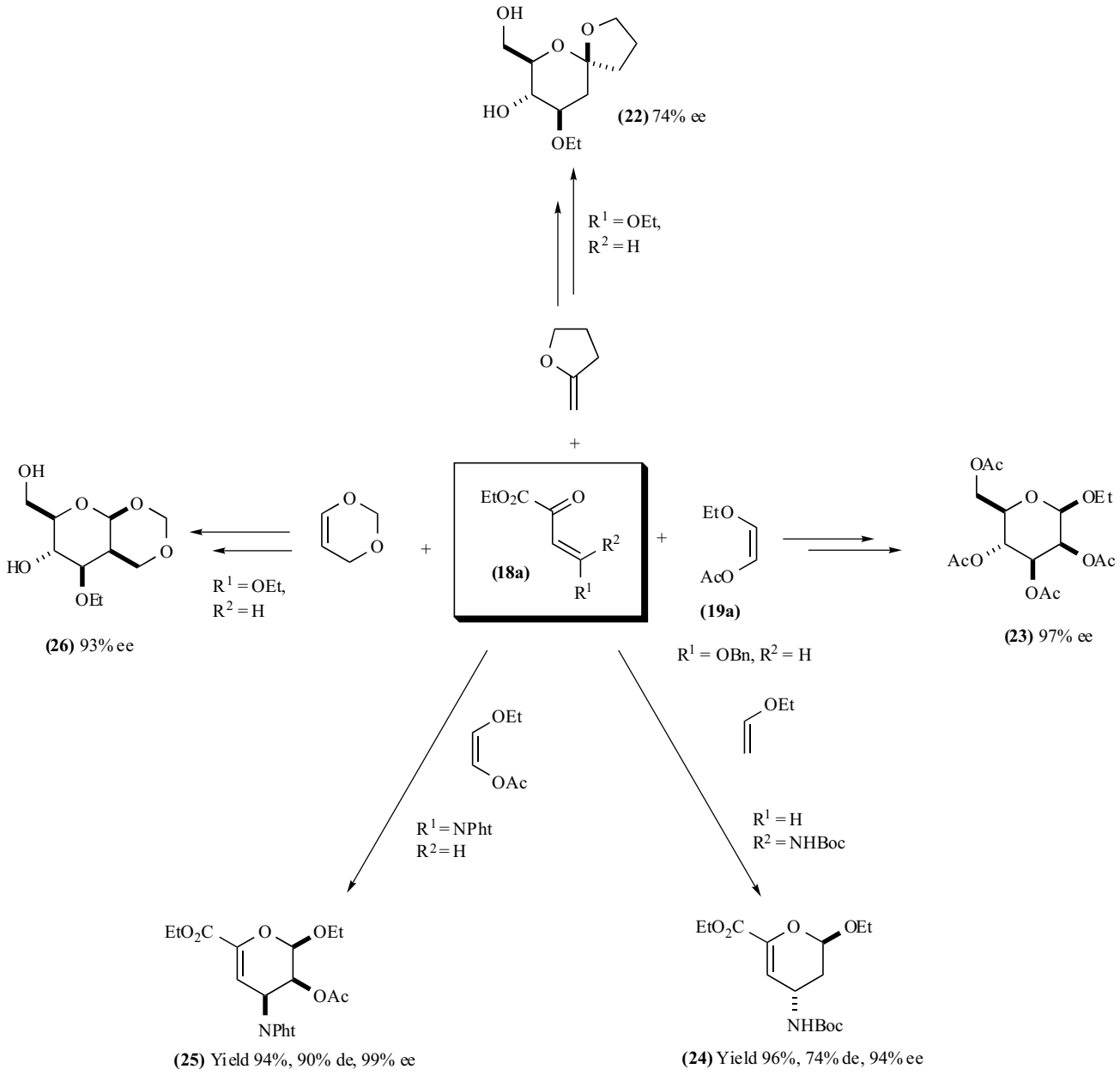


(*S*)-**(20)** (*R*)-**(21)**

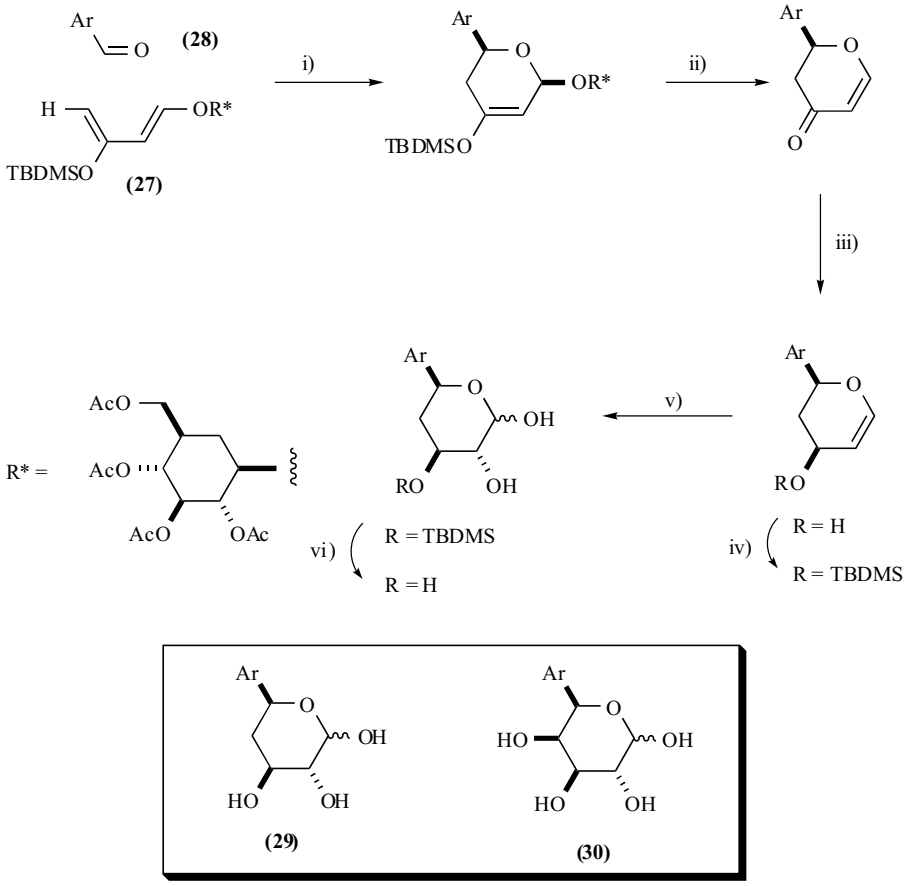
Fig. (1). Chiral bisoxazoline copper(II) catalysts.

In these cases the reactions are considered to be normal electron-demand HDARs, that is, the dienophile, activated by the chiral Lewis acid, interacts through its LUMO with the HOMO of the diene. Thus, it has been demonstrated that several chiral bisoxazoline Lewis acids can catalyse the enantioselective inverse-electron demand HDAR of α,β-unsaturated carbonyl compounds with electron rich alkenes with reactions proceeding with good yield, high diastereoselectivity and excellent enantioselectivity [9]. Such routes, using 20 mol% of (*S*)-**(20)** have allowed entry to a wide range of carbohydrate derivatives **(22)**-**(26)** including spiro-carbohydrates **(22)** (Scheme 5).

The absolute configurations of the compounds have been assigned *via* X-ray crystallographic data and it is proposed that the alkene approaches the *Si*-face of the reacting α,β-unsaturated carbonyl functionality when coordinated to the catalyst *via* a square planar intermediate. This work has recently been further extended to effect efficient catalytic double asymmetric induction during a tandem transetherification – intramolecular HDAR and this has allowed entry to optically active polyheterocyclic skeleta with up to 92% de and 97% ee [10].



Scheme 5. Use of the AHDAR for accessing carbohydrate derivatives.



i) $Eu(fod)_3$, CCl_4, 80%; ii) CF_3CO_2H, CH_2Cl_2, 0.5 h, 81%; iii) $NaBH_4$, $CeCl_3$, MeOH-EtOH, -78°C, 80%, > 99% ee; iv) TBDMSOTf, Et_3N, CH_2Cl_2, 2 h, 93%; v) OsO_4, $Ba(ClO_3)_2.H_2O$, THF, H_2O, 6 h, 62%; vi) Amberlite IR-120 (H^+), dioxan-H_2O, 70°C, 4 h, 64%

Scheme 6. Synthesis of aryl glycosides.

The AHDAR between carbohydrate derived dienes **(27)** and aromatic hetero dienophiles **(28)**, using $Eu(fod)_3$ as a chiral catalyst has been reported to allow asymmetric synthesis of a number of systems including (5*S*)-4-deoxy-5-*C*-(4-nitrophenyl)-L-*threo*-pentose **(29)** and (5*R*)-5-*C*-(4-nitrophenyl)-L-arabinose **(30)** [11]. For example, (1*E*)-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-diene and the (3*Z*)-4-*O*-acetyl derivative underwent *Re*-face and *endo* selective HDA reactions with 4-nitrobenzaldehyde, 5-nitrofuran-2-carbaldehyde and 5-nitrothiophene-2-carbaldehyde. Functionalisation in a similar manner to that reported by Danishefsky [12] then afforded the required derivatives (Scheme 6).

The results of these studies illustrated that the dienes displayed comparable *Re*-face selectivities in their $Eu(fod)_3$ catalysed cycloadditions with aromatic aldehydes and that the stereodirecting role of the sugar auxiliary was not compromised by the introduction of the terminal acetoxy group. This route offers the advantage that it permits extensive aryl-group variation coupled with multiple but controllable stereochemical options.

The mechanism of the catalytic enantioselective HDAR of carbonyl compounds catalysed by chiral aluminium complexes has been probed from a theoretical point of view using semi-empirical and ab initio calculations [13]. This has suggested that although the uncatalysed reaction is likely to proceed in a concerted fashion with an unsymmetrical transition state, the catalysed variant is more likely to proceed in a two step manner, whereby nucleophilic attack of the activated diene onto the electrophilic carbon of the carbonyl group occurs. This leads to an aldol like local energy minimised intermediate. Ring closure is then postulated to occur in a second step.

The synthesis of 2-deoxy glycosides has attracted great attention due to the occurrence of this linkage within antibiotics [14] and a number of approaches to these targets based on the AHDAR have been developed. Both variants of the oxo-Diels Alder reaction have been utilised for entry to these systems i.e. α,β-unsaturated carbonyl compounds have been utilized within an inverse-type Diels-Alder reaction as electron-poor heterodienes, to yield 3,4-dihydro-2*H*-pyrans, and aldehydes have been utilised for reaction with dienes. It has been illustrated that incorporation of electron donating substituents within the dienophile and/or electron withdrawing groups within the heterodiene can improve the endo-selectivity of the reaction [15]. Examples of some deoxysaccharides formed in this way, **31**-**38**, are illustrated in Figure **2** [16] and one synthetic route that utilises an AHDAR for the synthesis of targets **43** and **44**, from **39** and ethanal, is illustrated in Scheme 7 [17].

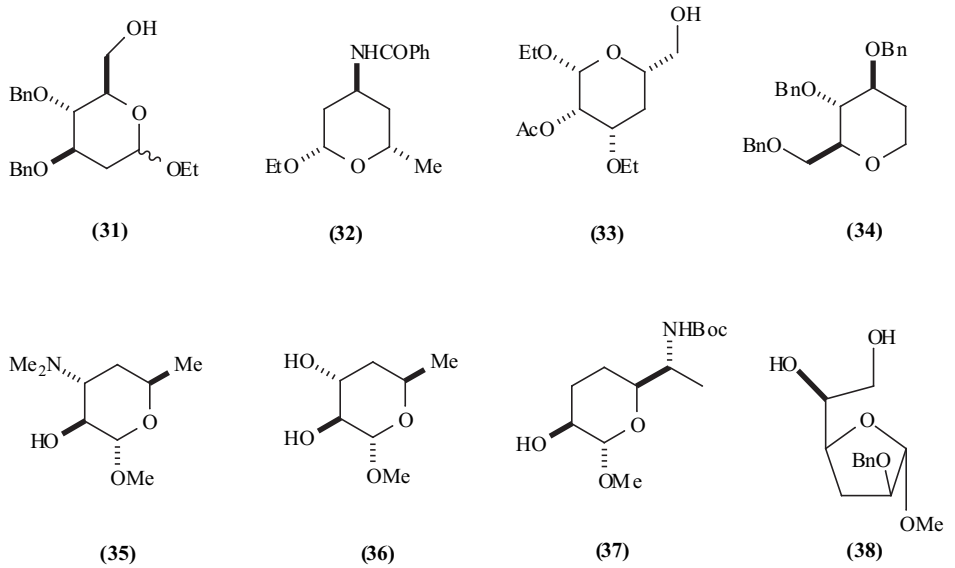
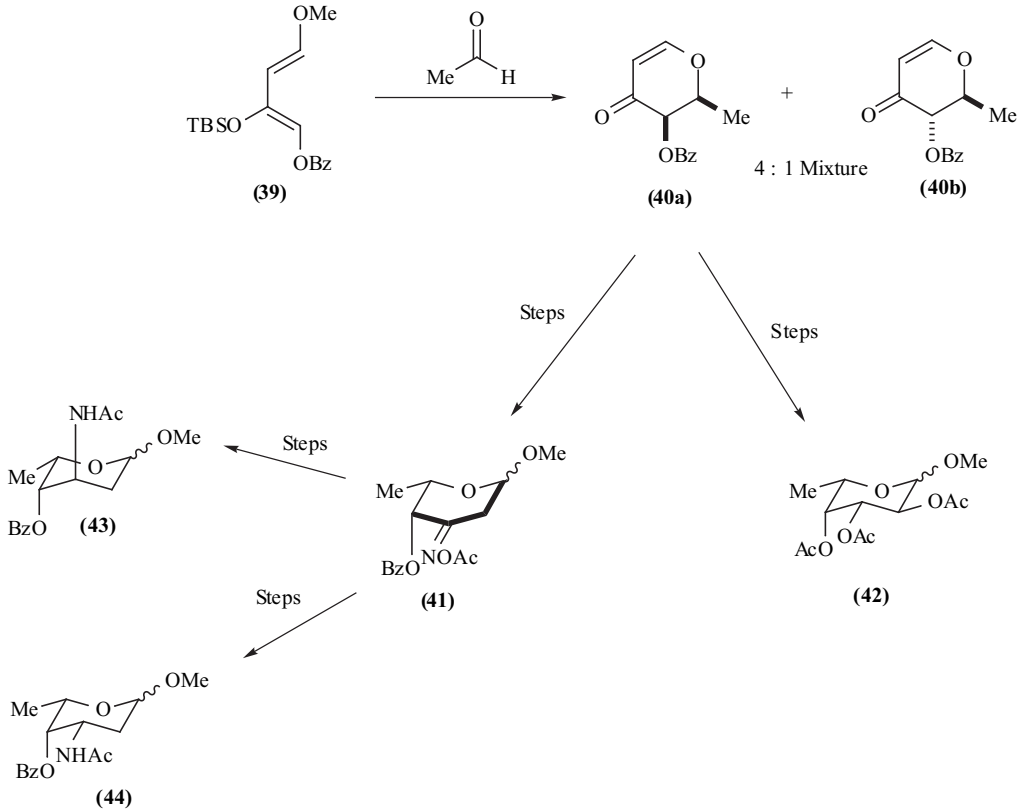


Fig. (2). Deoxysaccharides.



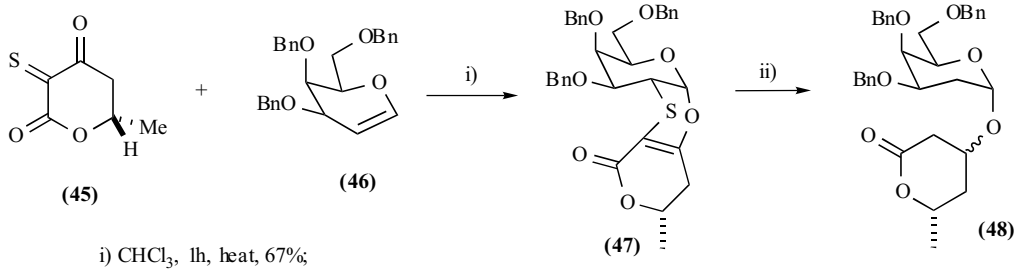
Scheme 7. Synthesis of 2-deoxysaccharides.

Glycosidic materials that are precursors to models for 2-deoxy disaccharides have also been prepared *via* an inverse electron-demand cycloaddition reaction between carbohydrate derived glycals **(46)** and a sulfur / oxygen / nitrogen diene **(45)** [18] (Scheme 8).

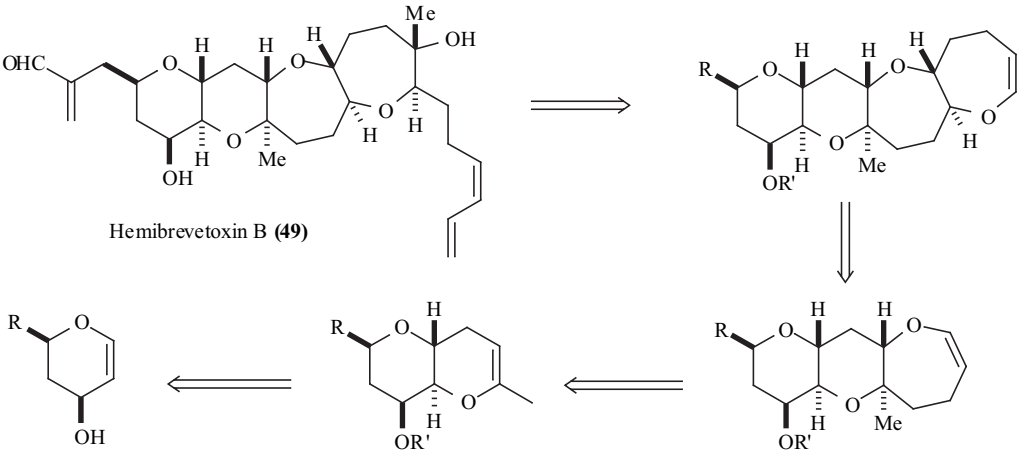
The cycloadditions occurred with excellent regio- and stereocontrol with additions usually occurring to the bottom face of the glycal double bond for glucals and galactals and to the top face for allals. Extrusion of sulfur from the thioether containing derivatives **(47)** could only be achieved using Raney Nickel. In all cases a competing elimination reaction occurred to re-produce the glycal starting materials. Hence modest to good yields were obtained for this last step that afforded the model disaccharide analogues **(48)**.

This approach is complementary to that of Capozzi, which utilises a carbohydrate heterodiene [19]. The reader is referred to the excellent review [14] on the synthesis of 2-deoxy glycosides for further examples of recent interest.

C-Glycosides are also attracting interest as carbohydrate analogues that offer the advantage of enhanced stability in biological systems compared with natural glycosides [20].



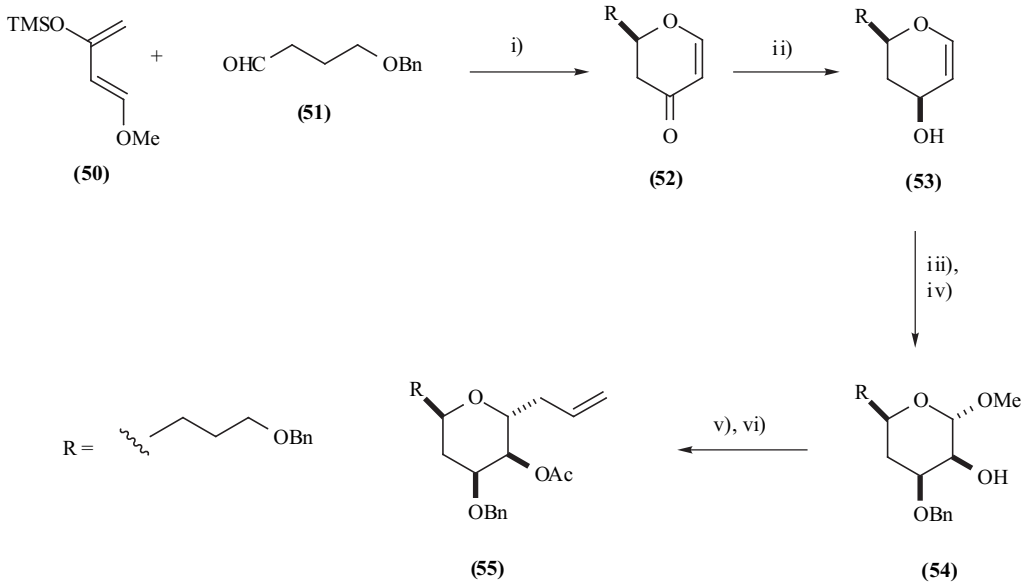
Scheme 8. Synthesis of 2- deoxysaccharides



Scheme 9. Retrosynthetic analysis of hemibrevetoxin B (**49**).

Due to the occurrence of many *C*-glycoside moieties within natural product systems they are also current synthetic targets of intense interest. Not surprisingly, efforts have been invoked to synthesise a range of *C*-glycosides using the AHDR [21]. One notable example has been described by Rainer *et al.* in their formal synthesis of Hemibrevetoxin B **(49)** (Scheme 9) [22].

The intermediate **(54)** required for *C*-allylation was prepared using the HDAR between Danishefsky's Diene **(50)** [23] and an aldehyde **(51)** (Scheme 10). This provided the required dihydropyrone **(52)** in 92% yield. Reductions under Luche conditions, epoxidation followed by epoxide opening with methanol, regioselective benzyl ether formation, acetylation and Lewis acid mediated *C*-allylation then afforded the required *C*-glycoside **(55)**.

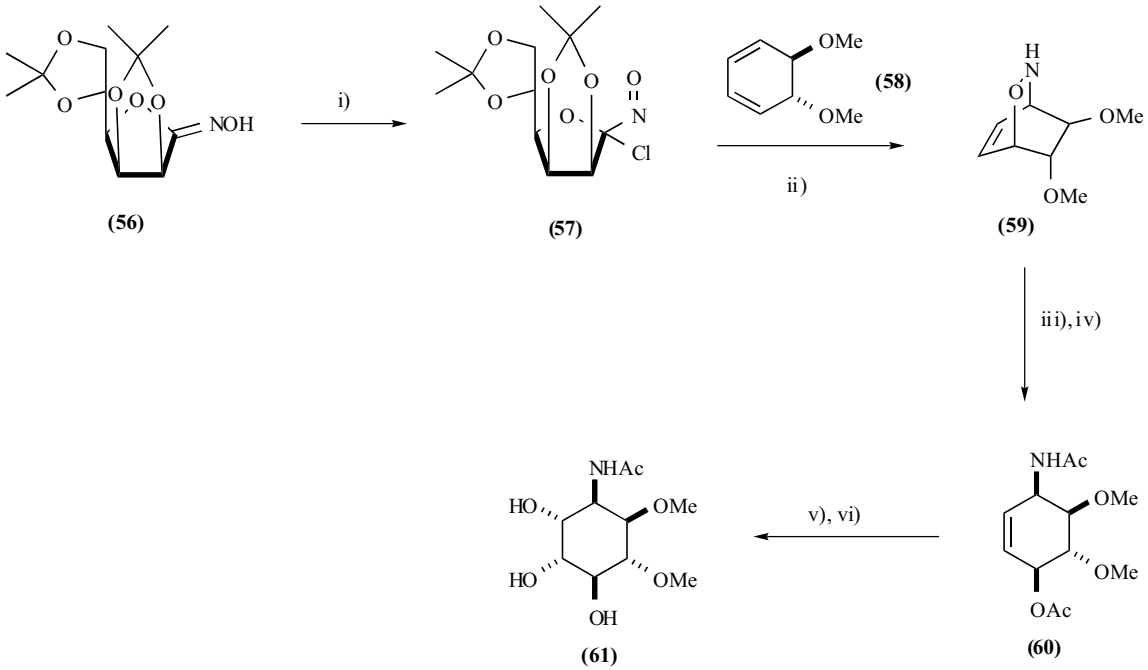


Scheme 10. Synthesis of *C*-glycoside (**55**).

b) Application of the AHDAR for Synthesising Inhibitors of the Carbohydrate Processing Enzymes

All carbohydrates within the body are biosynthesised *via* a series of enzyme processing reactions with glycosyl transferase enzymes allowing assembly of carbohydrates and glycosidase enzymes allowing selective hydrolytic removal of specific carbohydrate residues [24]. In certain disease states the trimming action of these glycosidase enzymes is altered and unusual disease associated carbohydrates are formed. Recent work has concentrated on designing and synthesising carbohydrate analogues that mimic the shape and charge of the transition state involved in carbohydrate processing, and assessing the ability of these targets to inhibit glycosidase enzymes. Areas for therapeutic application include the treatment of AIDS, diabetes and tumour metastasis [24]. The application of the AHDAR for accessing pyrrolidine derivatives, which can be selectively functionalised to afford carbohydrate processing inhibitors, has found much application. As mentioned above, use of chiral dienes and / or dienophiles, or chiral Lewis acids can allow entry to enantiomerically pure targets. Chiral nitrosodienophiles have proved particularly useful for gaining asymmetric entry to pyrrolidine derivatives [25], indeed their use within AHDARs has been reviewed, with particular attention focussing on the synthesis of natural products [3c]. The reaction is synthetically useful for a number of reasons. Firstly, in most instances the reaction occurs with complete stereoselection, due to the concerted nature of the [4π supra + 2π] cycloaddition reaction. Second, high regioselectivity can normally be achieved if the diene is sufficiently dissymmetric in terms of π-electron density. Third, reductive cleavage of the N-O bond of the cycloadduct allows entry to syn amino alcohols or pyrrolidine rings depending on the synthetic transformations utilised. Fourth, all four carbons of the primary cycloadduct bear a potential functionality. Chiral nitroso dienophiles have been prepared in a number of ways, including manipulations of carbohydrates. When the nitroso group is directly linked to an electron withdrawing group the dienophile is highly reactive and it is often prepared in-situ. For example, nitrosocarbonyl dienophiles are prepared *in-situ* as transient intermediates by oxidation of the corresponding hydroxamic acids with periodate [26] or with oxalyl dichloride and DMSO and then triethylamine in dichloromethane [27]. α-Chloronitroso ether derivatives of carbohydrates have proved of interest as they are easily prepared from carbohydrate lactone oximes. They have been used within AHDARs that have allowed entry to a number of natural products, and their analogues, including conduramines and inosamines [28]. For example, reaction of the C2-symmetric diene **(58)** with the chiral nitroso dienophile **(57)** in a 5:1 ratio, led to excellent kinetic resolution, whereby (-)-**(59)** was formed in good yield (approximately 80%) and excellent ee (>96%). Reductive cleavage of the N-O bond followed by acetylation gave chiral conduramine derivative **(61)** as a crystalline compound in 76% yield (Scheme 11).

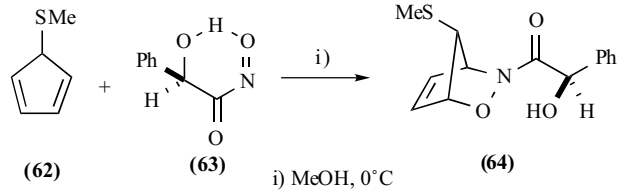
Mannostatin A and some derivatives have also been prepared using a synthetic strategy that features an AHDAR. Mannostatin A is a naturally occurring α-mannosidase inhibitor that displays five chiral centres and a wide array of functionality. A [4+2] cycloaddition strategy was considered ideal for generation of three of these five centres, whilst simultaneously installing two of the heteroatoms *via* an appropriate N=O dienophile [29]. The asymmetric cycloaddition reaction between 1-(methylthio)-cyclopenta-2,4-diene **(62)** and an acylnitroso compound **(63)** derived from (*R*)-mandelic acid was performed to afford adduct **(64)**



i) t-BuOCl; ii) CH_2Cl_2, -20 °C, 80%; iii) Zn/AcOH; iv) Ac_2O, pyr., 76% over 2 steps; v) $KMnO_4$ then Ac_2O, 82%; vi) HCl, 95%

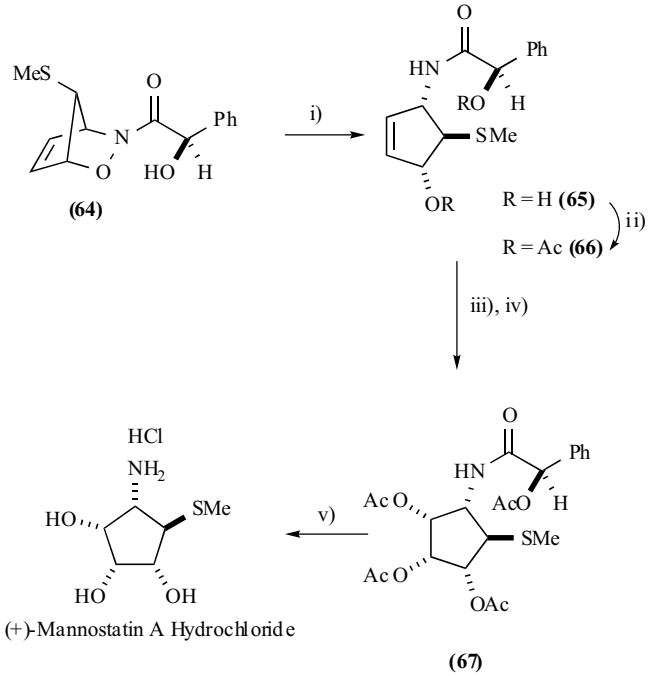
Scheme 11. Use of a chiral nitroso dienophile (**57**).

in 45-50% yield as a 3.3:1 diastereomeric mixture (Scheme 12).



(62) (63) (64)

Scheme 12. Towards mannostatin A.



i) Al(Hg), 78%; ii) Ac_2O, pyr-DMAP, 94%; iii) OsO_4-pyr; iv) Ac_2O, 43% over 2 steps; v) MeOH, HCl, 70˚C, 100%

Scheme 13. Synthesis of mannostatin A hydrochloride.

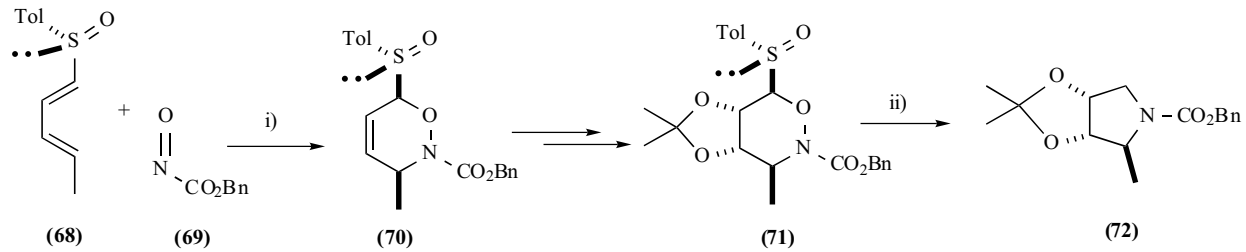
The relative and absolute stereocontrol in forming the three contiguous *O*-, *S*- and *N*-containing chiral centres were governed by the anti-orientation of the methylthio group in **62** as it approaches the heterodienophile and intramolecular hydrogen bonding in **63** that direct face selective *endo* cycloaddition anti to the bulky phenyl group in **63**. Although it was anticipated that *cis* hydroxylation of **63** would occur from the least hindered *endo* face of the bicyclic alkene to provide the required diastereoisomer, this proved more difficult to effect than expected due to competing oxidation processes. Therefore, reductive cleavage of the key intermediate **(64)** was realised using aluminium amalgam in THF-H_2O. The alcohol thus produced, was acetylated for characterisation purposes. Stoichiometric osmylation then proceeded with high facial selectivity to afford, after acetylation, acetate **(67)** in 43% yield. Subsequent exhaustive deacetylation by exposure to acid (0.4 M HCl : MeOH, 60 degrees) quantitatively afforded optically active mannostatin A hydrochloride (Scheme 13).

This material provided entry to further mannostatin derivatives through functional group derivatisations and interconversions. Thus a series of compounds were prepared to probe the structure-activity relationships within this family of *N*-linked glycoprotien biosynthesis inhibitors.

The first AHDAR between enantiomerically pure 1-sulfinyl dienes and nitroso derivatives has allowed novel entry to optically pure 1,4-imino-L-ribitol derivatives (Scheme 14) [30]. Thus, [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **(68)** was reacted with benzyl nitrosoformate **(69)** (prepared *in situ* by oxidation of *N*-benzyloxycarbonyl hydroxamic acid with tetrabutylammonium periodate) to afford 2*H*-1,2-oxazine **(70)** in 54% yield and as a single diastereoisomer. Standard manipulations of **70** (*cis*-dihydroxylation and acetonide formation) allowed entry to **71** for which the absolute configuration was unequivocally assigned as S_3,S_4,S_5,R_6 by X-ray analysis. The transformation of the 1,2-oxazine into a pyrrolidine was performed with H_2 in the presence of Pd/C as the catalyst. Hydrogenolysis of the N-O bond, removal of the sulfonyl moiety with formation of an unstable aminoaldehyde, cyclisation to the corresponding pyrroline derivative and reduction of the C=N bond took place to yield target **(72)** in excellent yield and in only one synthetic step (Scheme 14).

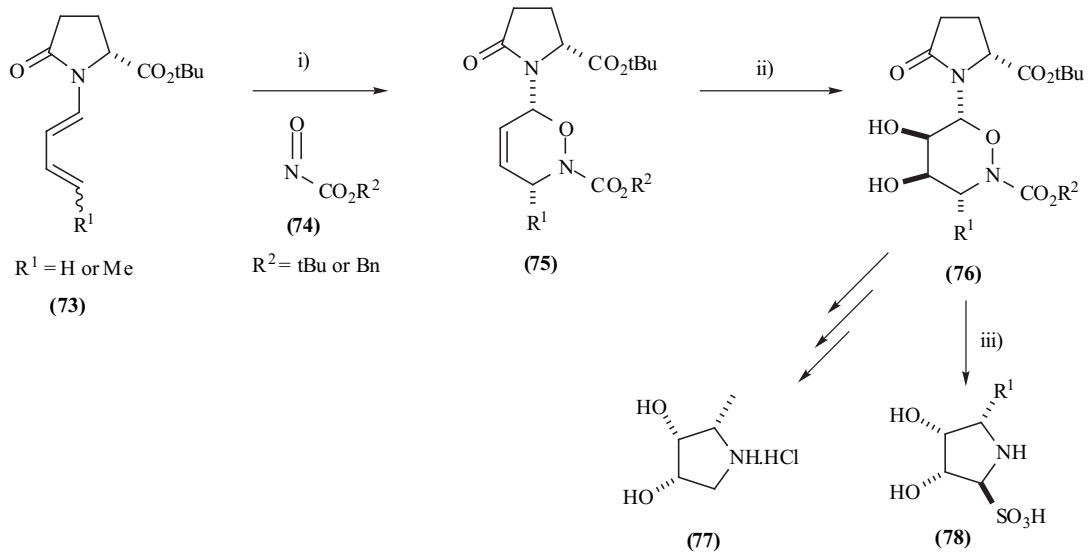
The stereochemical course of the reaction can be explained if the heterodienophile **(69)** approaches the less hindered face of the diene **(68)** with the sulfinyl group in a *s-trans* arrangement with respect to C(1)=C(2) – the less hindered face of the diene is the one that supports the lone electrons pair at sulfur.

AHDARs using D-pyroglutamic acid as a chiral auxiliary have also allowed entry to amino sugars that are analogues of L-fucose (Scheme 15) [31]. The required dienes **(73)** were prepared in enantiomerically pure form by condensation of t-butyl-D-pyroglutamate with crotonaldehyde or pentenal. The Diels Alder reactions with achiral alkyl acyl-nitroso dinenophiles **(74)**, prepared in-situ by oxidation of the corresponding hydroxamic acids, were performed at 0˚C and



i) CH_2Cl_2, -78˚C to 0˚C, 54%; ii) H_2, Pd / C, EtOH, r.t. 72%

Scheme 14. Use of enantiomerically pure 1-sulfinyl dienes.

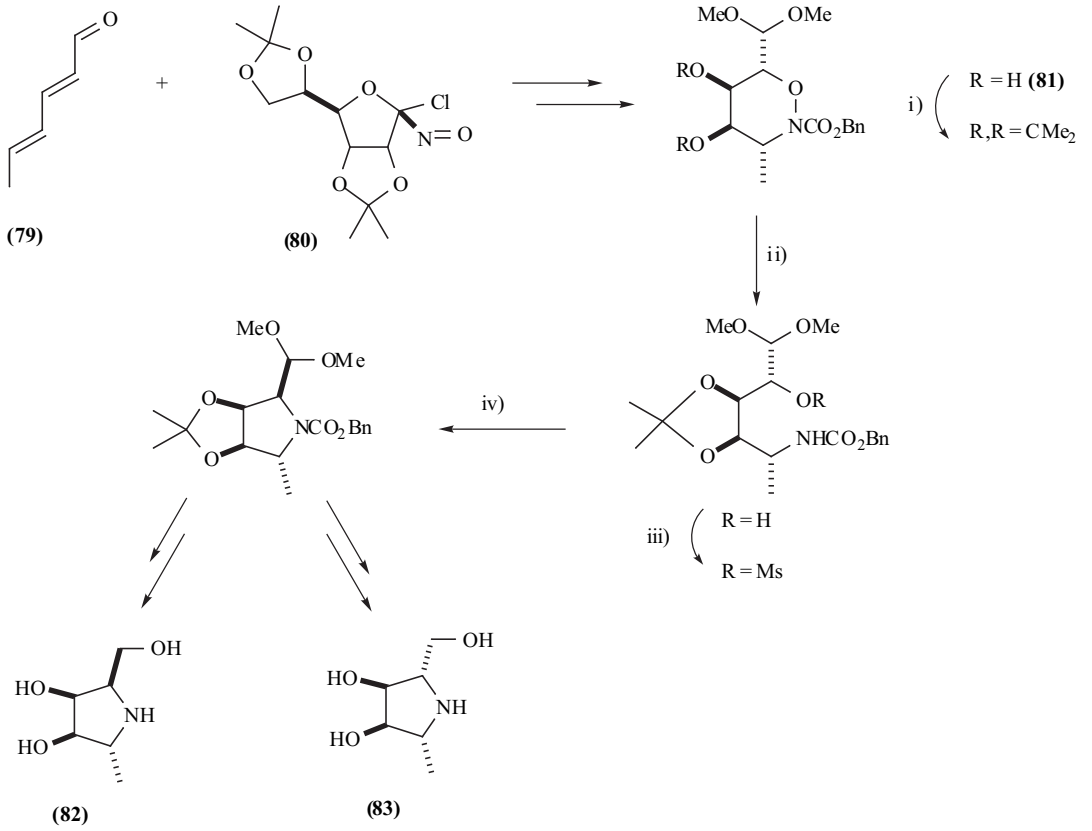


i) Hydroxamic acid, $BnMe_3NIO_4$, 1h, 0˚C; ii) OsO_4, NMO, acetone/H_2O, 1 d, 40˚C; iii) *p*-TsOH, SO_2, H_2O, 5 d, 60˚C

Scheme 15. Synthesis of amino sugars.

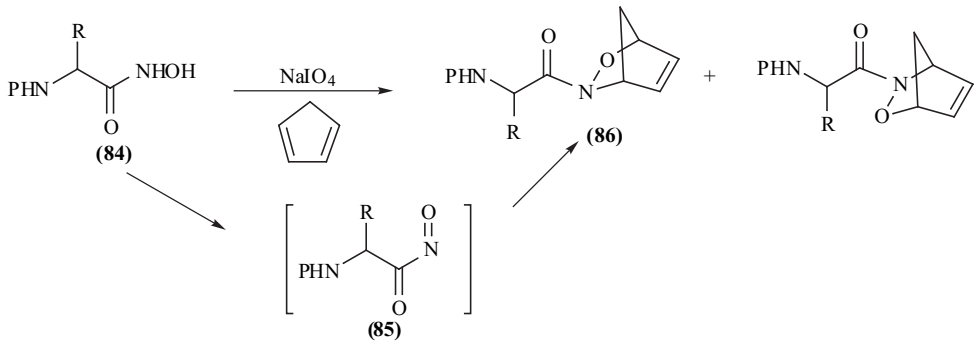
allowed entry to the (5'*R*, 6*R*) adducts **(75)** in approximately 60% yield with good diastereoselective excess (de = 70%). A number of synthetic transformations then ensued before the N-O bond was reduced and the chiral auxiliary removed by hydrogenolysis over Raney-Nickel at 40˚C.

This methodology is an extension of work performed in the non-chiral series, for access to racemic erythrose and 5-deoxy ribose [32], and it is also equally applicable for entry to the enantiomeric (5'*S*, 6*S*) adducts [33]. The inhibitory activities of pyrrolidines **(77)** and **(78)** on various glycosidases have been calculated. Inhibition of α-D-mannosidase and α-L-fucosidase showed the most interesting results with **77** and **78** showing good inhibitory activities (μM) as competitive inhibitors. Work by the same authors has allowed entry to 5-methyl-trihydroxypyrrolidines **(82)** and **(83)** from the enantiomerically pure oxazine diol



i) 2,2-Dimethoxypropane, H^+, 100%; ii) H_2, Pd/C, EtOH, 50˚C then $ClCO_2Bn$ / NaOH, 84%;
iii) MsCl, Et_3N; iv) aq. NaOH, 80˚C, 65% over 2 steps

Scheme 16. Synthesis of trihydroxypyrrolidines.



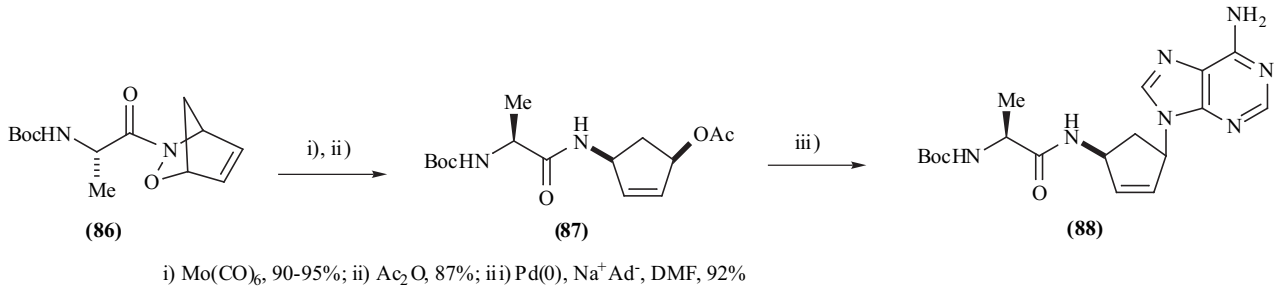
Scheme 17. Synthesis of enantiomerically pure 5'-aza noraristeromycin analogues.

(81) (Scheme 16) [34]. The former was accessed with excellent enantioselectivity (>98%) from sorbaldehyde **(79)** *via* an AHDAR using a chiral chloronitroso derivative **(80)** [35] that was itself prepared from D-mannose [36].

Enantiomerically pure 5'-aza noraristeromycin analogues have also been prepared from amino acid derived chiral acylnitroso dienophiles **(85)** [37]. Thus, periodate-mediated oxidation of hydroxamic acids **(84)** to acylnitroso dienophiles **(85)** in the presence of freshly distilled cyclopentadiene afforded a mixture of chromatographically separable optically pure diastereomers of **85** (Scheme 17).

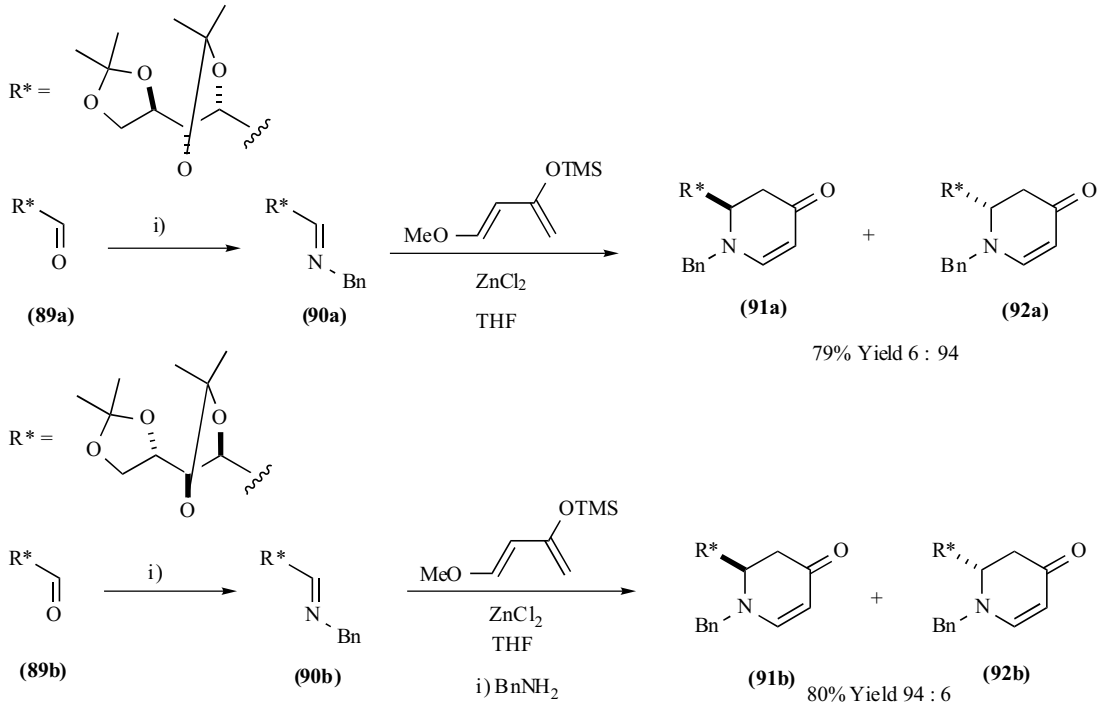
The hydroxamate N-O bond of **86** was then cleaved using molybdenum hexacarbonyl and acetylation of the resulting alcohol afforded an allylic acetate **(87)**. A palladium(0) catalysed addition of adenine to this allylic acetate then afforded the required carbocyclic nucleoside **(88)** (Scheme 18).

Derivatisation of the nucleoside has also been reported to yield a number of diastereomerically pure compounds of biological interest [38]. In cases where removal of the amino acid chiral auxiliary was required, this was achieved *via* the Edman degradation [39].



i) $Mo(CO)_6$, 90-95%; ii) Ac_2O, 87%; iii) Pd(0), Na^+Ad^-, DMF, 92%

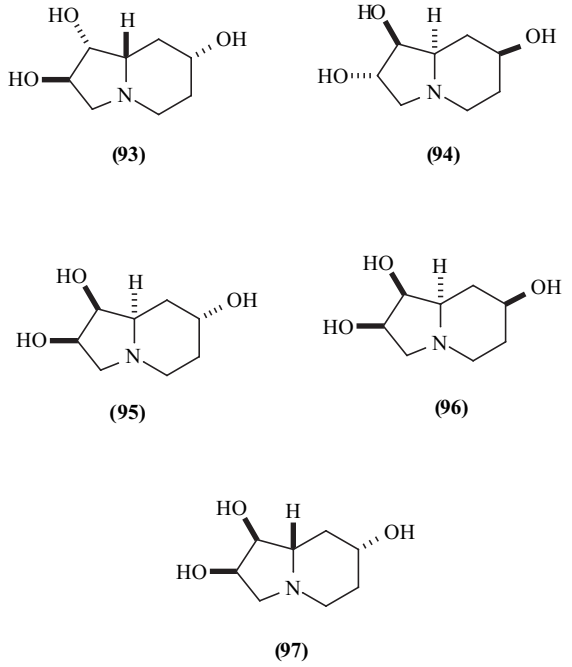
Scheme 18. Access to the carbocyclic nucleoside (**88**).



Scheme 19. Use of chiral azomethine dienophiles.

Enantiocontrol has also been achieved *via* utilisation of chiral azomethine dienophiles. Thus, chiral alkoxy aldehydes **(89)** have been converted to chiral azomethines **(90)** and allowed to react with Danishefsky's diene in the presence of zinc chloride to give diastereomeric pyridones **(91)** and **(92)** [40] (Scheme 19).

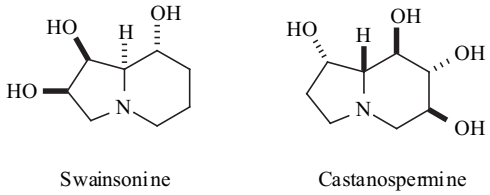
The reactions proceeded with high diastereoselectivity and the configuration of the newly formed chiral centre was determined as (*S)* using X-ray crystallography. This can be rationalised by assuming chelate stabilisation by the Lewis acid. The enone systems of **91** and **92** were then reduced diastereoselectively and subsequent intramolecular reductive amination reactions then allowed entry to the Swainsonine analogues **(93)-(97)** depicted in Figure **3**. A similar approach using an AHDAR of sugar-derived azomethines derived from D-glucose, L-arabinose and D-mannose also allowed entry to quinolizidine analogues of castanospermine (Figure **4**) [41].



(93) **(94)** **(95)** **(96)** **(97)**

Fig. (3). Swainsonine analogues.

Complimentary entry to azasugars, of use as inhibitors of glycoprocessing enzymes, which offers the advantage of allowing the reaction to be performed in aqueous solution has also been described [42]. Performing reactions in aqueous media offers particular advantage when carbohydrate derivatives are to be synthesised, since the starting material carbohydrates will themselves be soluble in aqueous media, reducing the need for extensive protecting group manipulations. The aqueous aza Diels-Alder reaction has proved of use for gaining entry to heterocyclic products **(101)** from three components – an aldehyde **(98)**, an amine salt **(99)** and a diene **(100)** (Scheme 20). Chiral amines have been employed when access to optically pure heterocyclic compounds is required.

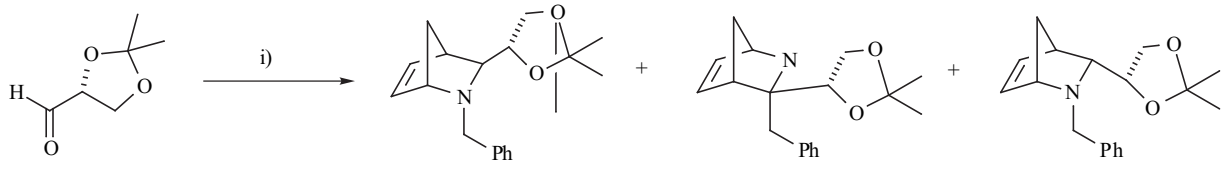


Swainsonine Castanospermine

Fig. (4). Swainsonine and castanospermine.

Lanthanide triflates have also been found to promote aqueous aza Diels-Alder reactions and this has increased the scope of the reaction [43]. For example, the lanthanide-promoted reactions of two chiral aldehydes, prepared from D-mannitol and D-glucosamine, with benzylamine hydrochloride and cyclopentadiene has allowed entry to intermediates that are central to the synthesis of aza-sugars [44]. Best results were obtained with the aldehyde **(102)**, itself obtained *via* the diazotisation of D-glucosamine hydrochloride followed by a ring contraction rearrangement. In this case the aza-DA reaction produced only one major product, which was acetylated to give **103** in a combined yield of 35% for the three steps. The absolute configuration of the azanorbornene systems were determined by CD spectroscopy and the assigned structures were further verified by X-ray crystallography and NOE studies of their derivatives. The explanation for the stereoselectivity of the aza DA reactions is based on the assumption that the lanthanide(III) coordinates the nitrogen of the Schiff base and the adjacent oxygen to form a 5-membered ring intermediate. *Si* attack would be unfavourable due to steric hindrance. Conversion of the products into azasugars **(104)** was achieved by standard dihydroxylation and hydrogenation procedures as illustrated in Scheme 21.

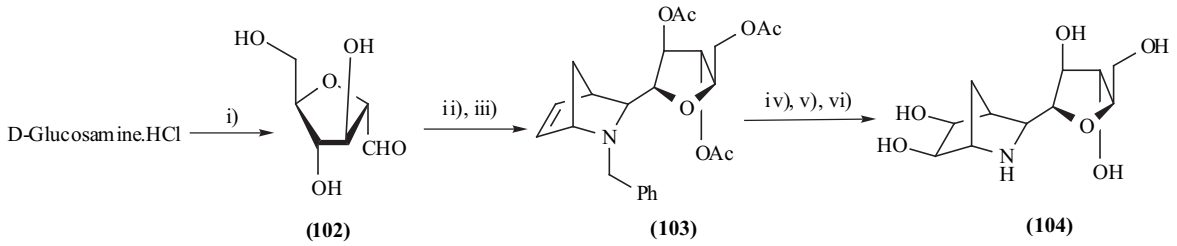
Finally, entry to hydroxylated pyrrolizidines of the alexine family, such as **105** has proved possible *via* an AHDAR between a heterodiene **(108)** prepared *in-situ* from the oxime of ethyl bromopyruvate and a carbohydrate derived alkene **(109)** [45]. Synthetic yields for the key AHDAR were excellent with a single diastereomer of the spirocyclic compound **(107)** being prepared in 64% yield (Scheme 22).



(98) **(101a)** **(101b)** **(101c)**

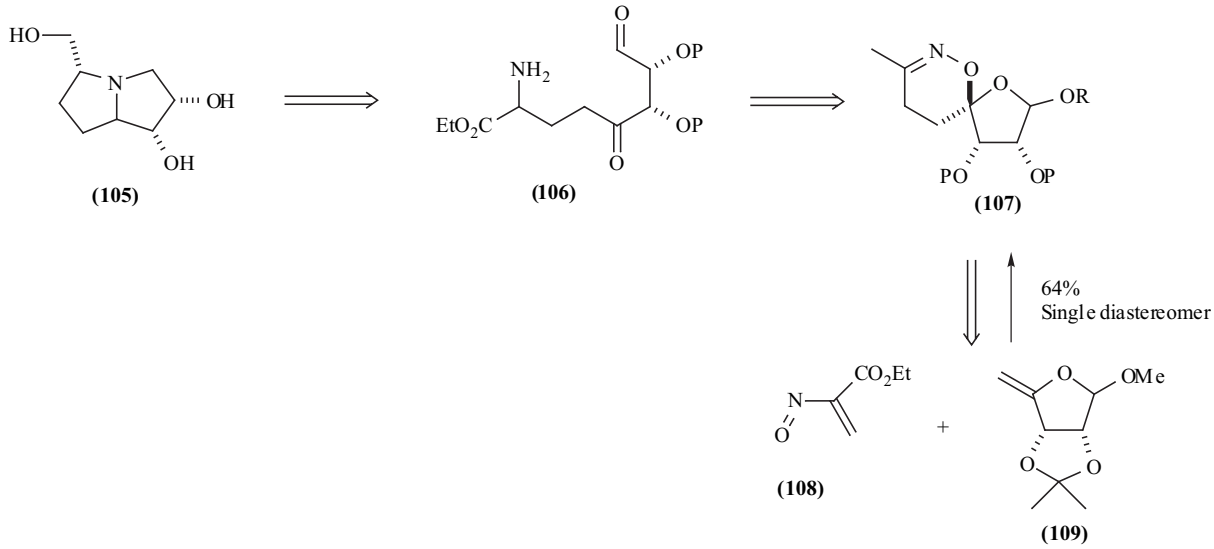
i) Benzylamine hydrochloride **(99)**, cyclopentadiene **(100)**, $Nd(OTf)_3$

Scheme 20. Entry to heterocyclic products (**101**).

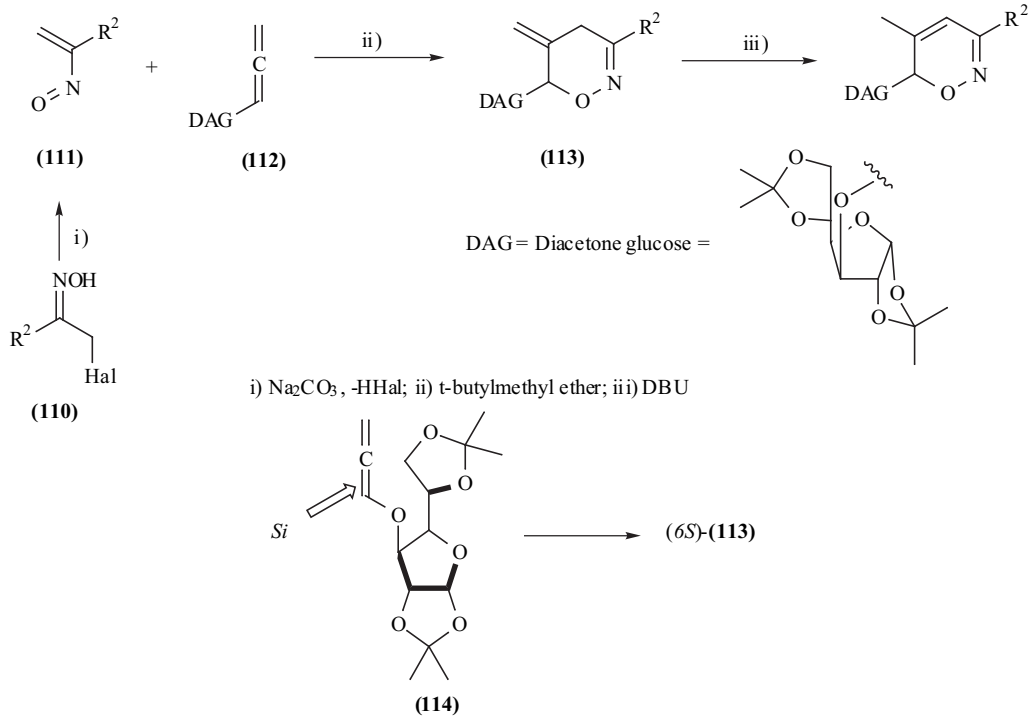


i) $NaNO_2$, AcOH; ii) cyclopentadiene, benzyl amine.HCl, $Nd(OTf)_3$;
iii) Ac_2O, pyr.; iv) OsO_4, Me_3NO; v) NaOMe, MeOH;
vi) H_2, Pd / C, MeOH

Scheme 21. Synthesis of azasugars (**104**).



Scheme 22. Entry to alexine pyrrolizidines.



Scheme 23. Synthetic utility of carbohydrate derived chiral auxiliaries.

Mention has been made of the use of chiral auxiliaries for effecting AHDARs. Since carbohydrates are well known as chiral auxiliaries [46], they have been incorporated within the synthesis of carbohydrates and their derivatives. For example, the AHDAR of nitroso alkenes **(111)** with alkoxyallene **(112)** derivatives bearing carbohydrate auxiliaries has been described, and this allows asymmetric entry to 6*H*-1,2-oxazines **(113)**. A diacetone glucose derived alkoxyallene **(114)** provided optimum results furnishing the cycloadducts with a diastereomeric ratio of approximately 90 : 10 (Scheme 23) [47].

2. CONCLUSIONS AND FUTURE PROSPECTS

The worth of the AHDAR for accessing carbohydrates, their derivatives, and inhibitors of carbohydrate processing enzymes has been extensively demonstrated within the literature. As the biological relevance of carbohydrates continues to be unravelled, entry to further carbohydrates will be required. It is without doubt that the AHDAR will continue to be developed and applied for accessing these targets. Future research may also extend the methods available for performing AHDARs on a solid support [48], since this area remains relatively under studied [49], particularly for accessing carbohydrates on a solid support, or for preparing combinatorial libraries of carbohydrates.

3. ABBREVIATIONS

AHDAR	=	Asymmetric Hetero Diels-Alder Reaction
CD	=	Circular dichroism
DAG	=	Diacetone glucose
DBU	=	1,8-Diazabycyclo[5.4.0]undec-7-ene
DMAP	=	4-Dimethyl aminopyridine
DMSO	=	Dimethyl sulfoxide
HDAR	=	Hetero Diels-Alder Reaction
HOMO	=	Highest occupied molecular orbital
LUMO	=	Lowest unoccupied molecular orbital
NMO	=	*N*-Methyl morpholine-*N*-oxide
p-TsOH	=	*para*-Toluene sulfonic acid
Pyr	=	Pyridine

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