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REVIEW

A Review of Methods to Synthesise 4'-Substituted Nucleosides

Mark Betson*[a], Nigel Allanson[a] and Philip Wainwright[a]

Abstract

Modified nucleosides have received a great deal of attention from the scientific community, either for use as therapeutic agents, diagnostic tools, or as molecular probes. Perhaps the most difficult position of a nucleoside to modify is the 4'-position. Chemists have developed innovative methods to achieve this in a stereoselective manner to allow incorporation of a variety of functional groups. This review provides a summary of the most commonly used or recently published methods for ribose, deoxy-ribose, 4'-thioribose, and carbocyclics.

1. Introduction

The synthesis of modified nucleosides is of great interest as a means to access compounds for use as antiviral and anti-cancer agents.[1] Modified nucleosides are designed to mimic their naturally occurring counterparts and incorporate themselves into RNA and DNA in order to inhibit cellular division or viral replication. Medicinal chemists have made many different types of modifications to nucleosides in order to find compounds that are biologically active, low in toxicity and have effective pharmacokinetic properties. An important subset of modified nucleosides is the 4'-substituted nucleosides. These have attracted much attention, particularly as antiviral compounds. Two such nucleosides which progressed to the later phases of development are Festinavir (**1**) which was developed for the treatment of HIV and Balapiravir (**2**), developed as a treatment for hepatitis C (Fig. 1). For the synthetic chemist 4'-substituted nucleosides provide a greater challenge than their 2'- and 3'-substituted counterparts and therefore creative synthetic strategies have been developed to synthesise them. When designing a synthetic route consideration needs to be given to the length of the synthesis as well as the method utilised to introduce the 4'-substituent in a stereoselective manner.

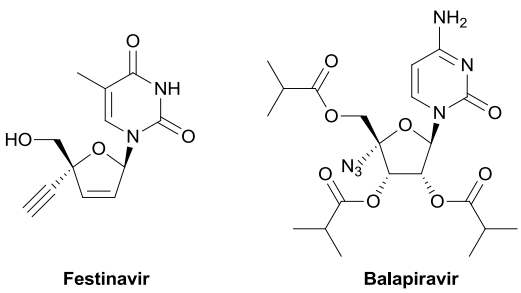

Fig 1

Other reviews have been published which summarised either the medicinal properties of these nucleosides[2-3] or provided a summary of the syntheses of ribose 4'-substituted nucleosides as of 2004.[3] Significant technological developments have been made in the last 10 years that have provided new routes to 4'-substituted ribose nucleosides and also to other related sugar mimics such as carbocycles and 4'-thionucleosides. This tutorial will provide an up-to-date summary designed to highlight the

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most frequently used and practical approaches for the synthesis of 4'-substituted nucleosides. The review will cover the following families of nucleosides and methods:

Ribose nucleosides

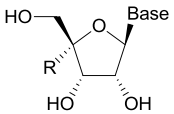

Fig 2

This article will summarise the following methods for modifying ribose nucleosides: a) Cannizzaro approach to 4'-hydroxymethyl nucleosides, b) synthesis and application of the 4',5'-methylene unit, and c) stereoselective introduction of Grignard reagents to ketones.

Deoxyribose nucleosides

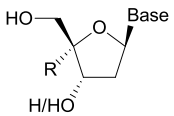

Fig 3

Both 2'-deoxy and dideoxy ribose nucleosides have also received considerable attention for modifications made at the 4'-position. The review will cover the following methods: a) deoxygenation of ribose nucleosides, b) Cannizzaro approach, c) activation of the 4' position with phenylselenium and phenylsulfur to access C-linked 4'-deoxy ribose nucleosides, d) regioselective opening of 4',5'-epoxides, e) synthesis from chiral starting materials, f) utilisation of chiral auxiliaries, g) enzymatic resolution methods, and h) asymmetric oxidation procedures.

Carbocyclic nucleosides

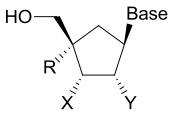

Fig 4

The review will cover synthesis of 4'-substituted carbocyclic nucleosides by a) modification of existing nucleosides, b) application of Grubbs metathesis catalyst, c) stereoselective addition of Grignard reagents to enone sugar precursors, and d) utilisation of chiral auxiliaries to induce stereochemistry at the 4' position.

4'-Thioribose nucleosides

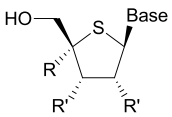

Fig 5

Finally the review will look at the synthesis of 4'-substituted-4'-thioribose nucleosides. This will include a) introduction and displacement of a 4'-O-acetyl group, and b) synthesis of the 4'-hydroxylmethyl unit *via* an aldol reaction and its subsequent manipulation to other functional groups.

Throughout the review reference will be made to the different positions on the sugar ring. For clarity Fig 6 shows how these positions are numbered.

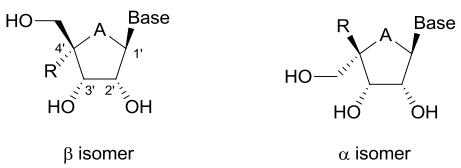

Fig 6

In Fig 6 two 4'-epimers are presented. If the anomeric substituent (base unit for a nucleoside or hydroxy for a sugar) is on the same face as the R group at the 4'-position it is known as the α-isomer,

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if it is on the opposite face it is known as the *β*-isomer. In the literature further labelling has been used on ribose and deoxyribose derived nucleosides. Fig 7 details these isomer designations.

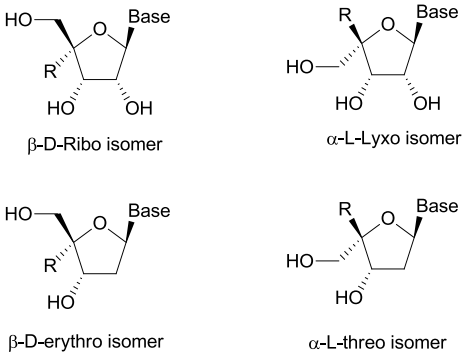

Fig 7

Finally some schemes will use the word 'base' on the nucleoside structure. This represents that one or more of the natural bases of adenine, guanine, cytosine, uracil, or thymine has been used at this position and the reader is encouraged to refer to the cited references for further details as to which specific bases were used.

2. Ribose nucleosides

The class of nucleosides which has had the most extensive modifications made at the 4'-position is the ribose nucleosides. This section covers the classic and most commonly used Cannizzaro approach as developed by Moffatt *et al*, and goes on to look at the same authors' work for the utilisation of a 4',5'methylene unit to access 4'-substituted fluoride, azide, and alkoxy derived nucleosides. The stereoselective additions of Grignards to ketone intermediates allowing access to a range of C-linked 4'-substituted ribose nucleosides are also discussed.

2.1 Synthesis and functionalisation of 4'-methanol unit

Perhaps the most important reaction for preparing 4'-substituted ribose and 2'-deoxy ribose nucleosides is the Cannizzaro reaction (scheme 1). Originally developed by Moffatt,[4] and then utilised further by others[5-6] the key steps are the formaldehyde alkylation and subsequent reduction of **2** to **3**. The reaction proceeds well but Moffatt found it was necessary to protect the 2'- and 3'-hydroxyls to avoid the formation of elimination side-products. Furthermore under standard Cannizzaro conditions the reduction step was slow, and any base labile protecting groups (for example benzoyl) were found to hydrolyse before the reduction was complete. However, by adding sodium borohydride the reduction step can be accelerated, allowing **3** to be isolated in 40-45% yields from **1**. Of the two primary hydroxyls of intermediate **3** it was found that the less hindered hydroxyl on the *α*-face reacts in preference to the *β*-hydroxyl. Therefore **3** was treated with the bulky 4,4'-dimethoxyltrityl chloride to give **4**, the *β*-hydroxyl is then silyl protected, and the *α*–hydroxyl deprotected with acid giving **6**. Compound **6** can be oxidised to **7** under Swern oxidation conditions. Both **6** and **7** are valuable synthons for the preparation of a wealth of 4'-substituted nucleosides.

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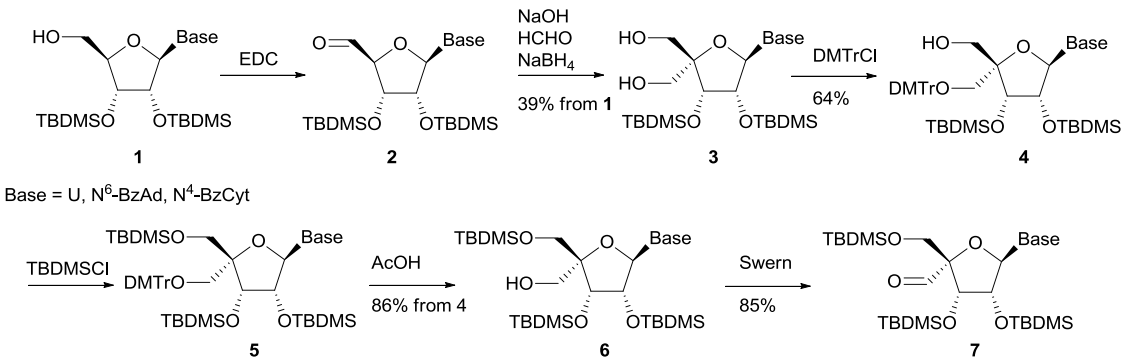
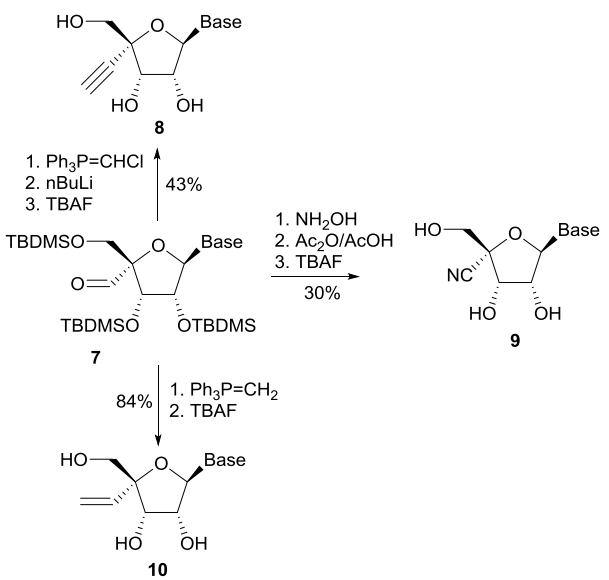


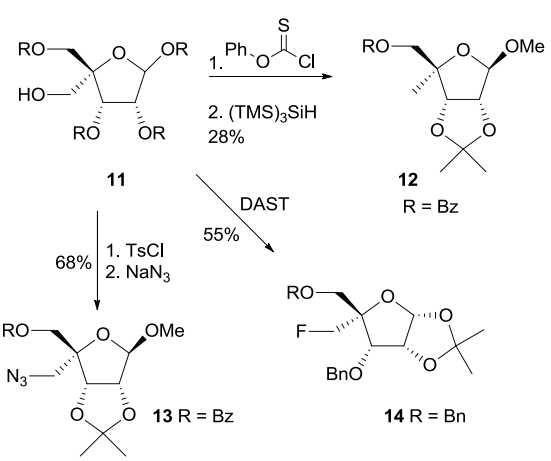
Scheme 1 Utilisation of the Cannizzaro reaction for the hydroxymethylation of nucleoside 5'-aldehydes

Matsuda *et al*[5] utilised Moffatt's work to access a range of 4'-substituted nucleosides as potential anti-viral candidates against HIV and HSV (scheme 2). The aldehyde **7** proved to be a good substrate for Wittig reactions allowing access to **8** and **10**, while the nitrile **9** was prepared *via* condensation of the aldehyde with hydroxylamine followed by subsequent dehydration with sodium acetate-acetic anhydride.



Scheme 2 Reactions of the 4'-α-aldehyde

The 4'-α-hydroxymethyl unit has also been used to access a variety of 4'-substituted ribose nucleosides (scheme 3). The hydroxyl can be removed either by radical means[7] or *via* conversion to the iodide and then hydrogenation[8] to provide methyl analogues such as **12**. Substitution of the hydroxyl by treatment with either DAST or TsCl/sodium azide can also be used to access the fluoride and azide analogues respectively.[8-9]



Scheme 3 Reactions of the 4'-α-hydroxymethyl unit

Both the 4'-α-aldehyde and alcohol functional groups have been used to excellent effect to access a wide range of conformationally constrained bicyclic nucleosides (scheme 4).

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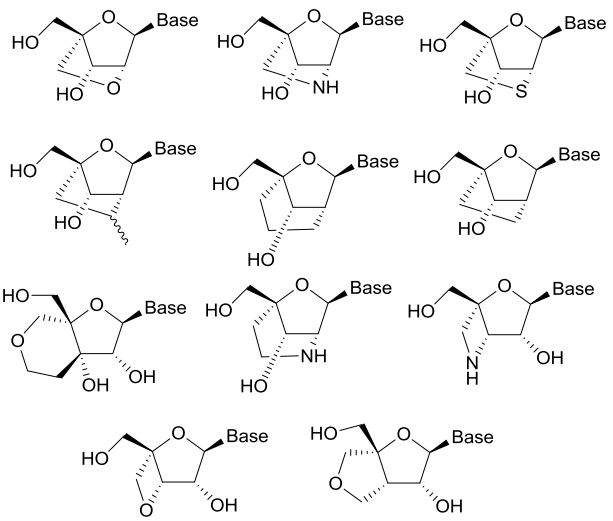
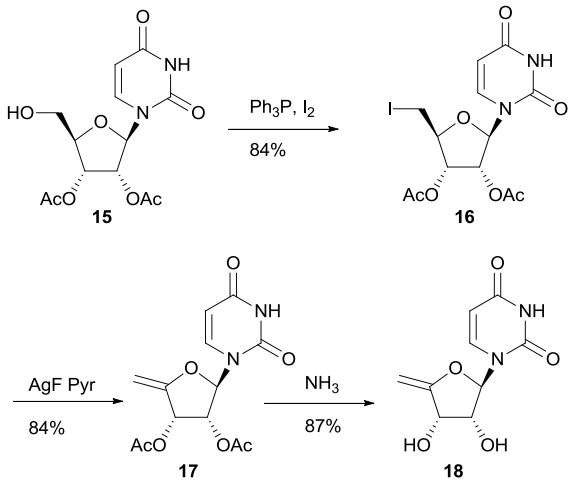
The reader is directed to the excellent review recently published on this topic for further details.[10]



Scheme 4 Bicyclics prepared from 4'-α-hydroxymethyl and aldehyde nucleosides

2.2 Synthesis and functionalisation of a 4'-methylene unit

Moffatt and Verheyden[11] developed a synthesis of 4',5'-unsaturated nucleosides (scheme 5) which have proved to be valuable intermediates in the synthesis of 4'-substituted nucleosides. Iodination of **15** and subsequent elimination to the alkene with silver fluoride in pyridine provided **17** in good yield. The authors went on to investigate this reaction further for a range of nucleosides bearing a variety of 2'- and 3'-hydroxyl protecting groups and base units.[12] Prisbe *et al*[13] later improved on this synthesis by omitting the need to protect the 2'- and 3'-hydroxyls and using sodium methoxide in methanol to eliminate the iodide (52% for thymidine).



Scheme 5 Synthesis of 4',5'-methylene substituted nucleosides

Moffatt and Verheyden also utilised the 4',5'-methylene unit for the synthesis of 4'-fluoride substituted nucleosides (scheme 6).[14] Treatment of alkene **19a** with iodine and silver fluoride provided **20a** as a 3:2 mixture of epimers at the 4'-position. The isomers could be separated by chromatography, conditions could not be found to provide exclusively the desired β-D-Ribo isomer. Furthermore attempts to react **20a** with lithium benzoate in order to reintroduce the alcohol failed. The authors speculated this was due to adverse dipole interactions in the transition state. It has also been reported that removal of the acetonide protecting group with acid can lead to low yields due to the enhanced instability of the glycosidic linkage caused by the presence of the 4'-fluoride group.[14] Both of these issues were later resolved by Guillerm *et al* who switched the protecting groups at the 2'- and 3'-hydroxyls to benzoyl (**19b**).[15] This change allowed protecting group cleavage to be achieved under basic conditions, and used the method developed by Prisbe *et al*[13] (see scheme 8) to access the benzoate **21** by treatment of the iodide **20** with *m*-CPBA.

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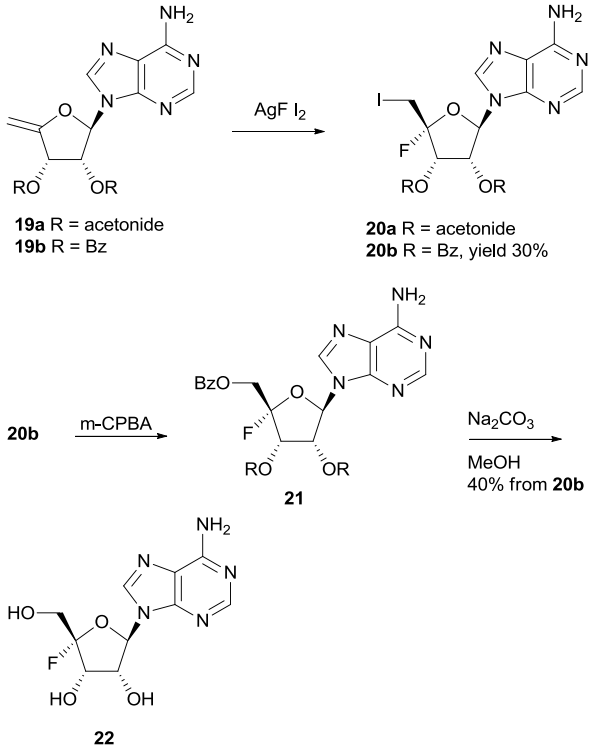
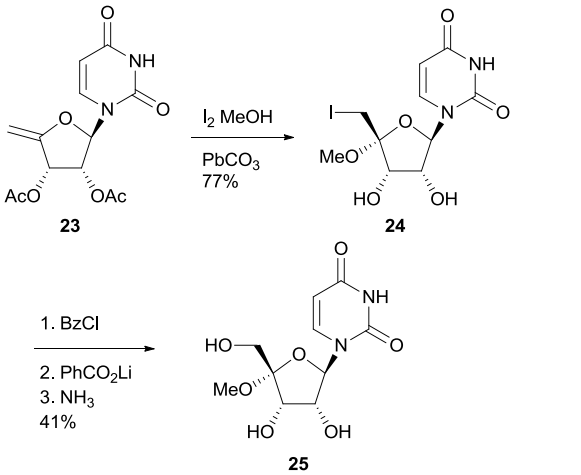


Scheme 6 Use of the 4'-methylene unit to prepare 4'-fluoride nucleosides

It should be noted that the fluoride group can also be introduced to the 4'-position by radical means[16] *via* the 4'-bromide, with similar yields.

The 4',5'-methylene unit has also been used to access 4'-methoxy substituted nucleosides (scheme 7).[17] The reaction of alkene **23** with iodine and methanol in the presence of lead carbonate was found to give **24** in greater than 95% isomeric yield and 77% chemical yield. The stereochemistry is controlled by the stereoselective addition of the iodine to the top face. Subsequent attack of the methanol group on the iodonium intermediate occurs from the bottom face. The iodide was converted to the hydroxyl *via* protection of the hydroxyls with BzCl, displacement of the iodide with lithium benzoate and subsequent hydrolysis. The authors also provide a thorough investigation of the effect the protecting groups at the 2'- and 3'-hydroxyls have on the stereochemical outcome of the iodination/methanol displacement.



Scheme 7 Use of the 4'-methylene unit to prepare 4'-methoxy nucleosides

Moffatt *et al* also used the 4',5'-methylene unit to prepare 4'-substituted azido nucleosides.[18] This methodology was later developed further in the same laboratories by Prisbe *et al* (scheme 8).[13] Treatment of the alkene **17** with iodine monochloride and sodium azide gave a 9:1 ratio of 4'-epimers in favour of the desired β-D-Ribo isomer over the undesired α-L-Lyxo isomer. The stereochemistry is controlled in a similar fashion to that described for the methoxy analogue (see above). Interestingly this stereoselectivity holds true for both ribose and 2'-deoxyribose nucleosides, but once the 3'-hydroxy, is removed, as in 2',3'-dideoxynucleosides, a 1:1 ratio of isomers is obtained. Conversion of the iodide **26** to the alcohol by nucleophilic substitution was again difficult due to the presence of an electron withdrawing substituent at the 4'-position. However the authors managed to circumvent this problem by oxidising the iodide **27** to the corresponding hypervalent iodide with *m*-CPBA. This allowed the benzoyl group at the 3'-position to internally attack the hypervalent iodide. This resulted not only in introduction of the benzoyl protected hydroxyl at the 5'-position but also

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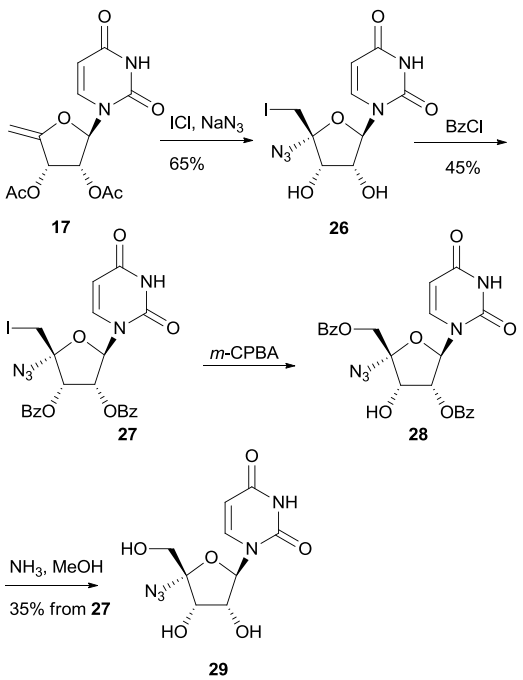
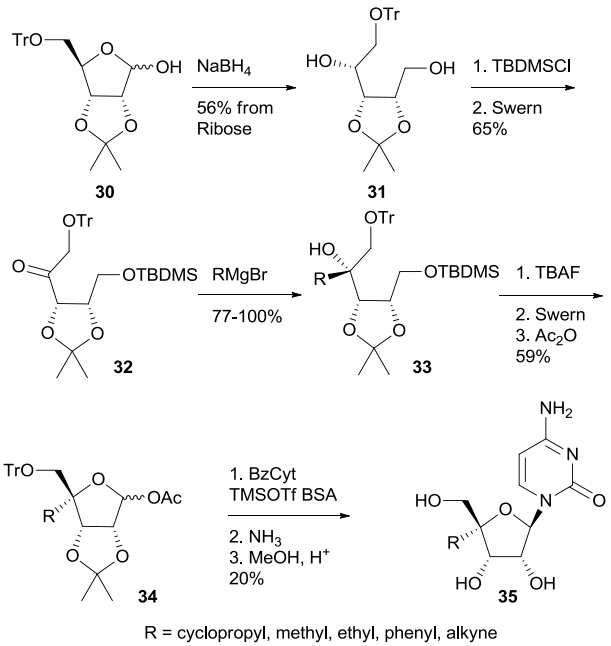
hydrolysis of the benzoyl group at the 3'-position to give **28**. The authors provide further details on the intermediates and nature of the mechanism for this reaction.



Scheme 8 Use of the 4'-methylene unit to prepare 4'-azide nucleosides

2.3 Stereocontrolled addition of Grignard reagents

Maddaford *et al* developed a route which uses the stereoselective reaction of Grignard reagents with ketones to access a range of C-linked 4'-substituted nucleosides (scheme 9).[19] The key step is the highly stereoselective addition of the Grignard reagent to ketone **32**. The existing stereochemistry embedded in the acetonide unit directs the addition to ensure only the desired isomer is formed. After manipulation of the protecting groups and oxidation of the primary hydroxyl, the cyclised lactol was trapped with acetic anyhydride, and then coupled to the base unit under Vorbruggen silyation conditions.



Scheme 9 Synthesis of C-linked 4'-substituted nucleosides via stereoselective Grignard reactions

Very similar chemistry was also used by Smith *et al* [6] but with a dimethylvinyl functional group[20] in place of the protected of the hydroxyl (compound **36**, scheme 10). The same high levels of stereoselectivity where obtained as for the Maddaford method. Ozonolysis was used to liberate the aldehyde required for lactonisation. Johnson and Kozak used the same synthon (**36**) to introduce a trifluoromethyl group to the 4'-position using Rupperts reagent and TBAF (compound **38**).[21] This resulted in a 4:1 mixture of isomers in favour of the desired D-Ribo isomer.

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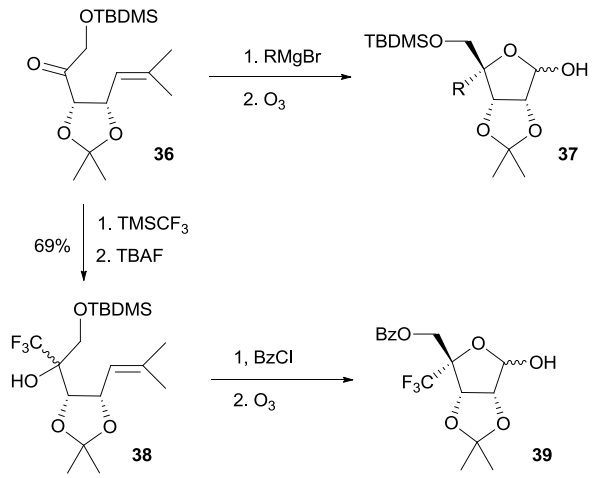


Scheme 10 Synthesis of C-linked 4'-substituted nucleosides

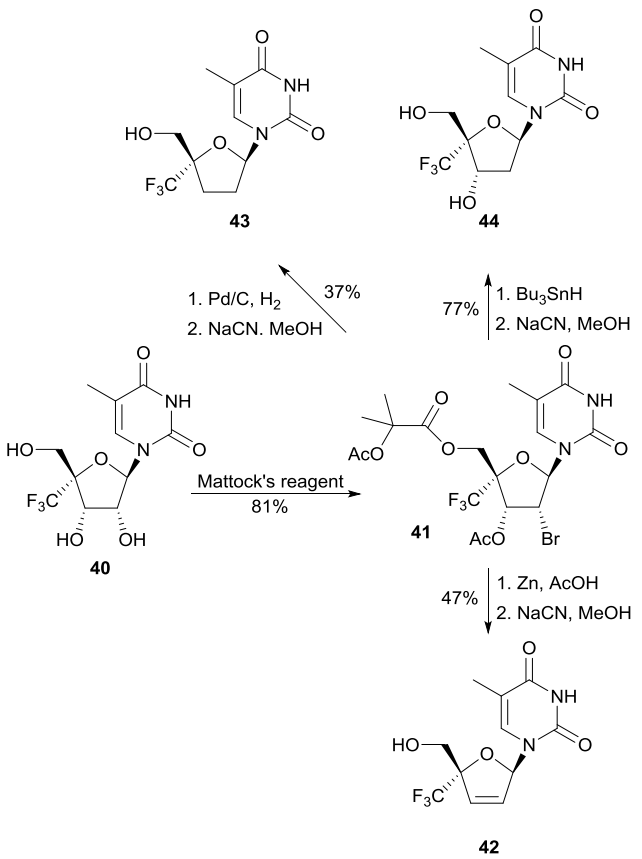
Both **37** and **39** were subsequently reacted to their corresponding nucleosides by using standard nucleoside coupling conditions.

3. Deoxyribose nucleosides

There are many varied approaches to 4'-substituted deoxynucleosides. The review will particularly highlight methods which involve deoxygenation of 4'-substituted ribose nucleosides, a summary of the Cannizzaro chemistry, synthesis of C-linked 4'-substituted deoxy nucleosides by activation with phenyl selenium or sulfones, regioselective opening of 4',5'-epoxides, alkylation of tartrate derivatives and oxidation of alkene precursors.

3.1 Deoxygenation of 4'-substituted ribose nucleosides

Perhaps the conceptually simplest approach to deoxy 4'-substituted nucleosides is to make the 4'-substituted ribonucleoside using the well precedented methods described in Section 2, and then removing one or both of the 2'- and 3'-hydroxyl groups.[22] For example, this approach has been used by Johnson (Scheme 11).[23] Reaction of **40** with Mattock's reagent (α-acetooxyisobutyryl bromide[24]) provided the bromide **41**. Tri-butyltin hydride was used to dehalogenate **41** to give the 2'-deoxyribose **44**. Alternatively, treatment of **41** with zinc in acetic acid gave the 2',3'-didehydro-2'3'-dideoxy product **42** and hydrogenation of **41** with with H_2 over Pd/C gave the 2',3'-dideoxy product **43**. In all cases final deprotection was achieved using sodium cyanide in methanol.



Scheme 11 Deoxygenation of ribose nucleosides *via* Mattock's reagent

Deoxygenation *via* conversion to a bromide and then radical reduction was also used by Ohrui *et al*.[25] The authors used acetyl bromide rather than Mattock's reagent to synthesise the 2'-bromo-3'-OAc intermediate.

Marx has demonstrated that if the 4'-substituent is not adversely affected by hydrogenation, the 3'-oxygen can be benzyl-protected and Barton-McCombie deoxygenation of the 2'-hydroxyl is a viable, high yielding and probably preferable route to 2'-

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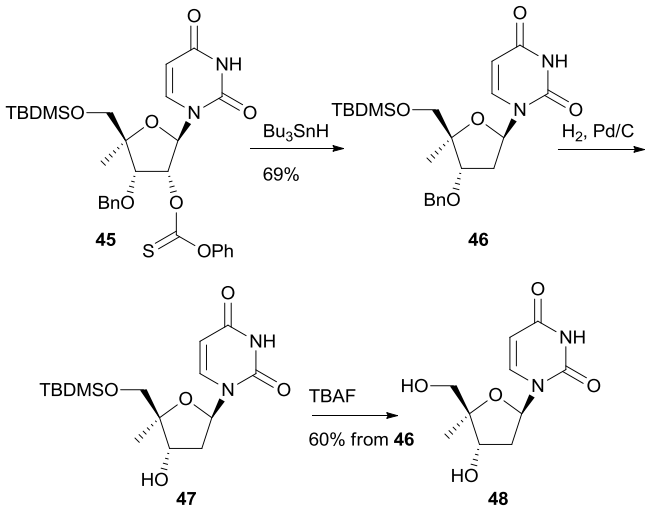
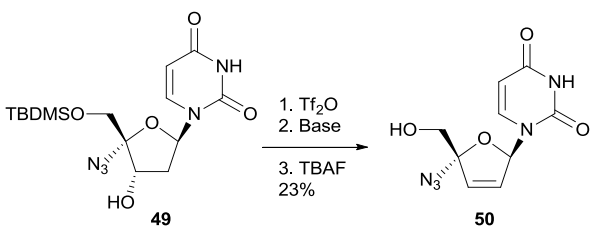
deoxyriboses (*e.g.* **45** to **46**, scheme 12). Hydrogenation to remove the benzyl group from **46** and then treatment with TBAF to deprotect the 5'-OTBDPS successfully gave the nucleoside **48**.[26]



Scheme 12 Deoxygenation of ribose nucleosides *via* Barton-McCombie reaction

Once the 2'-deoxy nucleoside was in-hand elimination of the 3'-hydroxy to give the 2',3-didehydro'-2'3'-dideoxy nucleoside was straightforward using methods not unique to 4'-substituted nucleosides. For instance, reaction of **49** with triflic anhydride followed by base catalysed elimination and deprotection gave **50**.[27]



Scheme 13 Elimination of a 3'-triflate with base

3.2 Cannizzaro approach to functionalise in the 4'-position

The commonly used Cannizzaro approach for incorporation of 4'-substituents described in Section 1 is equally applicable to the synthesis of deoxynucleosides. For instance, the 3'-O-TBS protected thymidine **51** has been converted to the diol **52** *via* the usual Moffatt oxidation/Cannizzaro sequence (scheme 14).[28] The authors did not use the three step DmTr-protection-TBS-protection-DmTr-deprotection strategy but instead utilised the greater reactivity of the α-hydroxy[29] by selectively oxidising the diol under Swern conditions to give a mixture of aldehydes which were converted to the oximes. These were separated and found to be in a 9:1 ratio in favour of the desired epimer **53**. When the diol **52** was oxidised using Moffatt conditions poorer selectivity was observed, the oximes were produced in a 3:1 ratio. The desired oxime was converted through to the nitrile **54** in 70% yield. The authors did not comment on the selectivity of the oxidation of the diol in the uridine case, except to mention the desired nitrile epimer was formed "predominantly".

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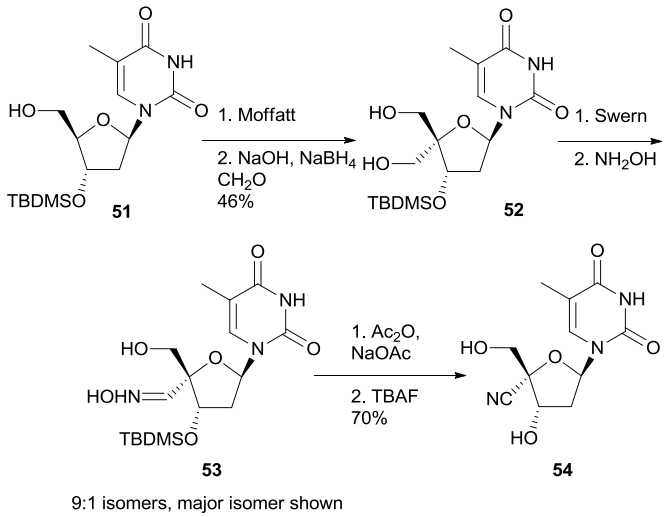
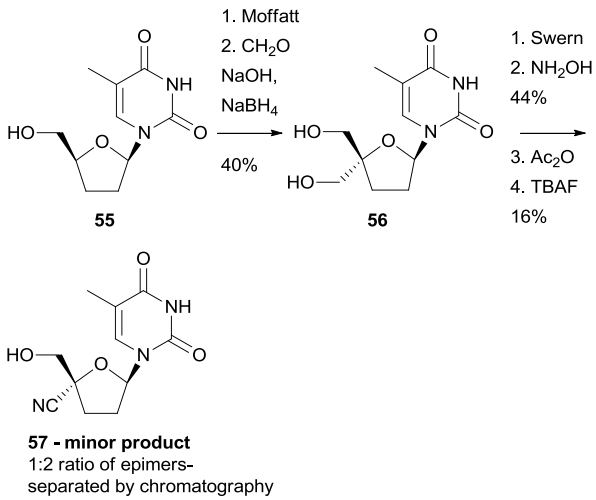


Scheme 14 Cannizzaro approach for 4'-substituted 2'-deoxyribose nucleosides

A similar process was used for the conversion of 3'-deoxythymidine **55** to the diol **56** (scheme 15).[28] Swern oxidation gave a mixture of aldehydes, which was converted, *via* a mixture of oximes, to the nitrile **57**, produced as a mixture together with its 4'-epimer. These were separated by flash chromatography. Interestingly, in the absence of a 3'-substituent (*cf* **51**), the desired epimer **57** is produced *as the minor product*. Evidently the Swern oxidation of the diol **56** gave the aldehydes in a 1:2 ratio, with oxidation of the β-hydroxyl predominating. It is interesting to compare the selectivity of oxidation of this dideoxynucleoside **56** (1:2, oxidation on the top face favoured) with the selectivity observed for the more sterically hindered 2'-deoxy-analogue **52** (9:1, oxidation on bottom face preferred).



Scheme 15 Cannizzaro approach for 4'-substituted 2',3'-dideoxyribose nucleosides

An imaginative method for manipulation of the diol **58** was published by Herdewijn.[30] The diol was converted to the ditriflate **59** in 85% yield. This ditriflate was stable to silica chromatography and just over 3 g was isolated. Reaction of **59** with sodium hydride in DMF in the presence of adenine gave **60** in 64% yield (1.4 g isolated). Hydrolysis using aqueous sodium hydroxide gave **61,** which was used in subsequent steps in order to phosphorylate on the 3'-hydroxyl. This chemistry was also demonstrated to work with thymine in place of adenine, albeit in lower yields with a more problematic purification.

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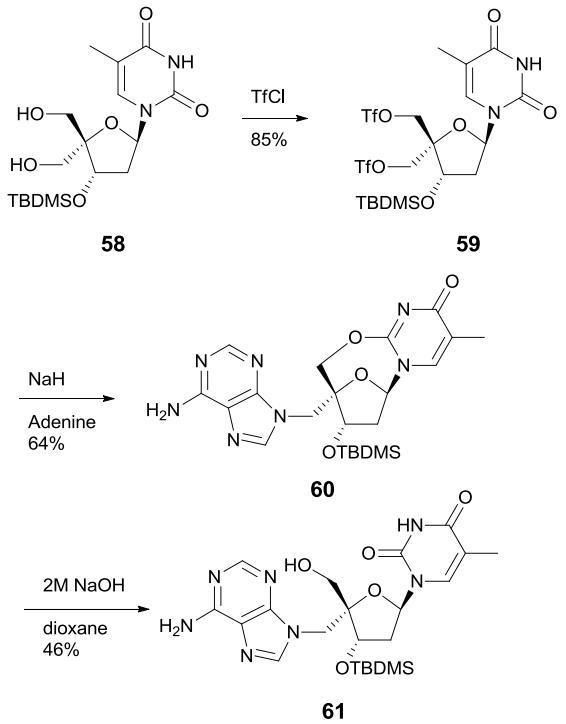
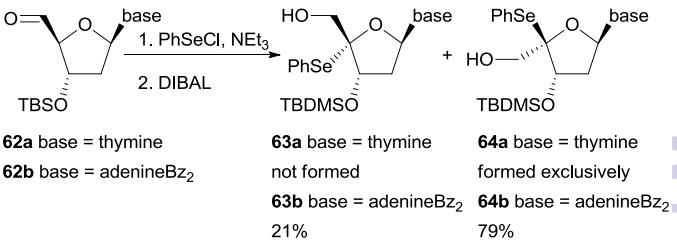


Scheme 16 Application of an intramolecular cyclisation with thymine to control selectivity at the 4'-position

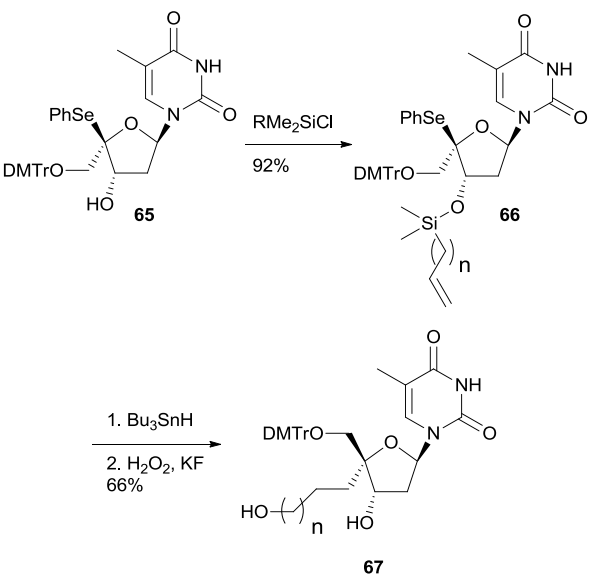
3.3 Introduction of leaving groups and radical pre-cursors to the 4'-position to access 4'-C-linked deoxy nucleosides

In 1994 Giese published reports on the reaction of the aldehydes **62a**[31] and **62b**[32] with PhSeCl (scheme 17). When the nucleoside base is thymine the reaction gives a single isomer of **64a**. When the bulkier benzoyl protected adenine was the base approximately 20% of the 4'-epimer **63b** was also formed. These epimers were separated by silica flash chromatography.



Scheme 17 Selective alkylation of the 4' formyl group with phenyl selenium chloride

This methodology was utilised by Matsuda to access compound **67,** where a silicon tether has been used to direct an intramolecular radical cyclisation onto the bottom face of the sugar ring (scheme 18).[33-34] The 4'-free-radical was generated by treatment of **66** with tributyltin hydride and this was trapped by the radical-acceptor alkene. The tether was cleaved by Tamao oxidation to give the 4'-substituted nucleosides.



Scheme 18 Application of a 3'-silicon tether to direct 4'-substitution

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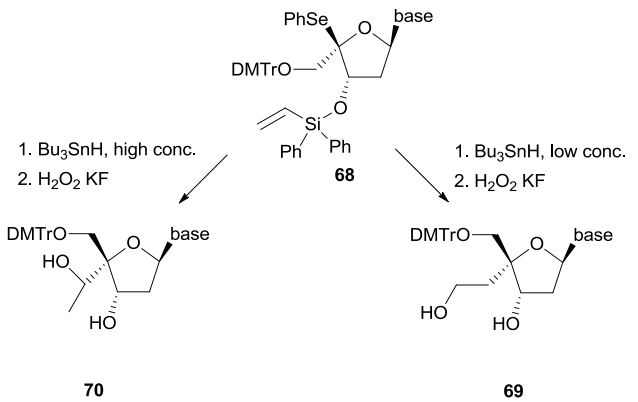
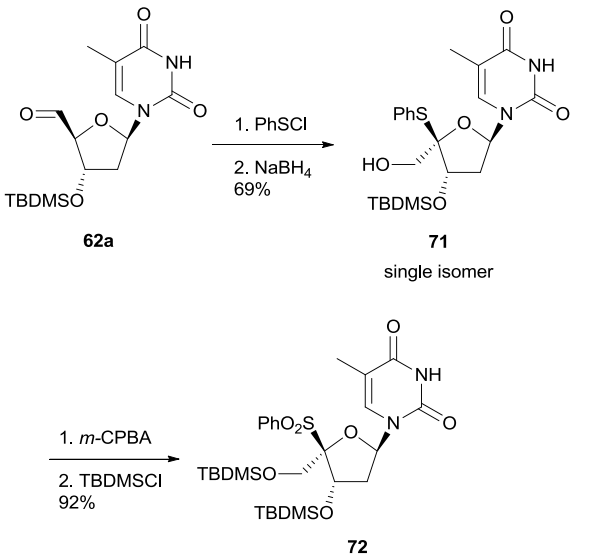
The regioselectivity of the reaction was found to be dependent on whether a high or low concentration of tri-butyltin hydride was used. Under high concentration conditions (3 equivalents of tri-butyltin hydride at 80 ˚C, together with AIBN) **70** was formed. When a solution of 1.1 equivalents of tri-butyltin hydride and AIBN was added slowly to **68** at 110 °C (low concentration conditions) the regioselectivity was completely reversed and **69** was the product.



Scheme 19 Selective radical substitution controlled by the number of equivalents of reagents

The group of Tanaka have used the Giese method for incorporation of a leaving group into the 4'-position (scheme 20).[35] The sulfone **72** was obtained from reaction of the corresponding aldehyde **62a** with PhSCl and triethylamine. Subsequent sodium borohydride reduction of the aldehyde gave the alcohol **71**. The product was isolated as a single distereoisomer. Oxidation to the sulfone to form the leaving group was achieved using *m*CPBA. The selectivity of the reaction of the benzenesulfenylation step was explained as being due to repulsion between the incoming electrophile and the bulky 3'-OTBS group. The reaction was repeated using the substrate with the 3' O-TBS group in the opposite ("up") configuration and again the benzenesulfenylation occurred *anti* to the 3'-OTBS.



Scheme 20 Stereoselective synthesis of 4'-sulfones

The stereochemistry of the addition of organosilicon reagents in the presence of Lewis acids with nucleosides such as **72** was studied (scheme 21). The reaction was found to be more complicated than a simple S_N2 displacement. The intermediacy of a 4'-chloro derivative was demonstrated, the $SnCl_4$ or $MeAlCl_2$ Lewis acid evidently act as chlorinating agents and they displace the benzenesulfonyl group of **72a** with inversion of configuration. The stereochemistry of this reaction is not influenced by the configuration at the 3'-position. In the examples of reactions using trimethylaluminium, displacement of the benzenesulfonyl of **74a** proceeded mostly with retention of configuration. The authors ascribe this to an S_Ni (ion-pair) mechanism.[36] Higher selectivities were observed in the less polar solvent carbon tetrachloride than were observed when dichloromethane was used, supporting the ion-pair mechanism.

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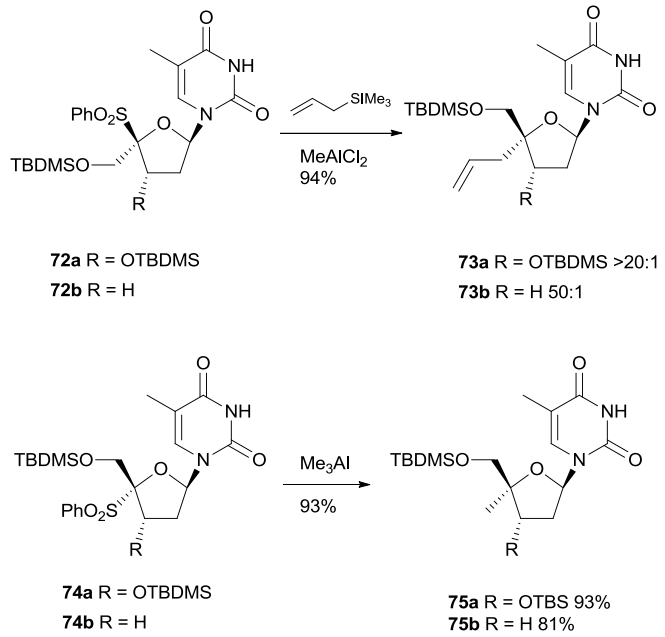
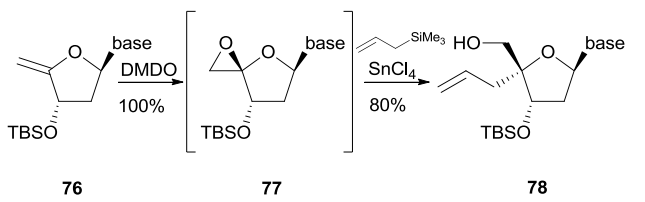


Scheme 21 Stereoselective substitution of 4'-sulfones

More recently Tanaka has published on the synthesis of 4'-substituted-dideoxy-nucleosides based upon nucleophilic additions to 4'-benzenesulfonyl-3'-deoxythymidine.[37] The epimers **72b** and **74b** were separated by prep HPLC. Reaction with both aluminates and silyl nucleophiles was investigated. The reactions from **74b** with aluminates proceeded mostly with retention of configuration, with the exception of $EtAl(CCSiMe_3)_2$, which gave a complex mixture of products. Excellent selectivity was observed in the reaction of a mixture of epimers **72b** and **74b** with allyl-TMS, **73b** was formed almost exclusively (50:1 mixture of epimers). Reactions with TMS-azide and TMS-CN were less selective, with the epimers formed in approximately a 2:1 ratio in both cases. The selectivity is temperature dependant, with better selectivities observed at lower temperatures.

3.4 Regioselective opening of 4',5'-epoxides

In 2003 Takeda disclosed the stereoselective epoxidation of **76** using dimethyldioxirane as the oxidant.[38] Opening of the epoxide with trimethylaluminium was regioselective, exclusive reaction at the 4'-carbon was observed. However, the stereoselectivity of this reaction was not perfect – a 93:7 ratio of 4'-β-isomer: 4'-α-isomer was obeserved. Greater success was enjoyed when the epoxide **77** was attacked with allyltrimethylsilane in the presence of $SnCl_4$ (scheme 22). **78** was isolated as a single isomer in 80% yield. The reaction is not limited to the introduction of an allyl group, (cyclopentyl)trimethylsilane, cyanotrimethylsilane and (2-bromoallyl)trimethylsilane also reacted selectively with **77**, albeit in yields of around 40%.



Scheme 22 Selective opening of 4',5'-epoxides

3.5 Stereoselective alkylation of tartrate derivatives

Crich developed a novel method for preparing 2'-deoxy 4'-substituted ribose nucleosides by stereoselectively alkylating the protected L-tartrate derivative **80** with BOM-Cl (scheme 23).[39] The synthesis began with the conversion of dimethyl L-tartrate to the cyclopentylidene acetal **80**. Deprotonation using LDA followed by stereoselective quench with BOM-Cl gave **81** as a single isomer in 60% isolated yield. The less hindered ester was

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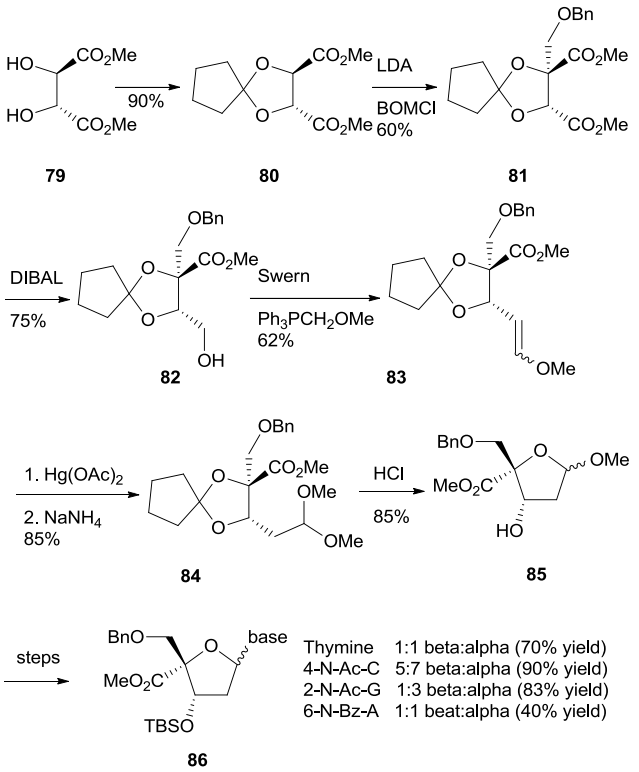
selectively reduced to the alcohol, then oxidised to the aldehyde and converted to **83**. Reaction with 3M HCl and then HCl in methanol gave the methyl glycoside **85**. Predictably, nucleoside couplings with protected bases proceeded with poor anomer selectivity but in each case they could be separated by silica chromatography. The spectroscopic identification of alpha and beta anomers is well documented, but it is interesting to note that Crich reported that all four beta anomers were faster eluting on silca than the alpha anomers. In a later publication Crich disclosed their attempts to direct the attack of the base to the β-face of the sugar by forming a temporary lactone between the 3'-hydroxy and the 4'-carboxyl.[40] The stereoselectivity of the couplings of such bicylic systems was solvent dependant. At best, in acetontirile, a 5:1 ratio in favour of the desired β-anomer was observed.



Scheme 23 Stereoselective alkylation of tartrate derivatives

3.6 Chiral oxidation of alkene precursors

Various groups have independently reported syntheses of single enantiomers of lactones such as **88**. Lopp's key step in the synthesis of dideoxy sugar **89** was the asymmetric oxidation of 3-substituted-2-hydroxy-2-cyclopenten-1-ones **87a-g** using ^{t}BuOOH-diethyl tartrate-Ti($O^{i}Pr$)$_4$ complex (scheme 24).[41(b)-42] The absolute configuration of the lactones is dictated by the use of either (+)- or (-)-diethyl tartrate. Enantiomeric excess of 96% for lactones **88a-g** was improved upon to >99% by recrystallisation. Lopp has demonstrated how substituted chiral lactones such as **89** can be converted to a variety of 4'-substituted deoxynucleosides.[43-44]

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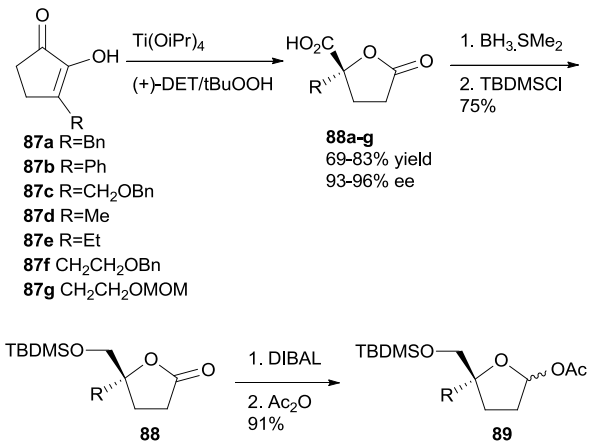
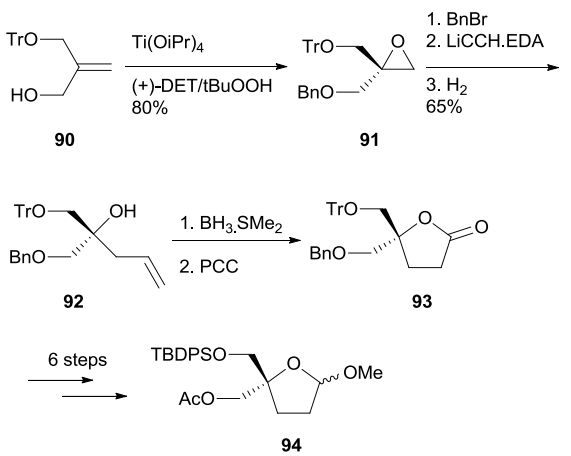


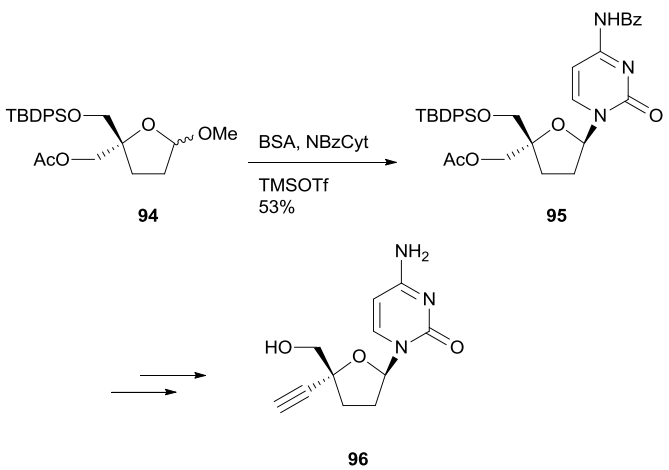
Scheme 24 Chiral oxidation of enones

The Marquez group's asymmetric route to the lactones similar to **88** is slightly different (scheme 25).[45] They were able to synthesise differentially protected lactone **93** in >96% ee over 6 steps from commercial starting materials. Once again, the chirality is introduced by utilisation of Sharpless asymmetric oxidation conditions.



Scheme 25 Chiral oxidation of terminal alkenes

Once the key lactone **93** was in-hand as a single enantiomer it was straightforward to manipulate the sugar to the acetate **94,** the key partner in the nucleoside coupling. Marquez decided to protect the α-4'-CH_2OH with an acetate group, in the hope that they might find some distant neighbouring group participation to guide the incoming base to the β-face. In their hands the Vorbruggen coupling (scheme 26) proceeded to give a mixture of anomers in a 1:1.14 ratio, showing a slight preference for attack from the desired face. This is an improvement on the 2:1 alpha:beta ratio observed when there isn't the opportunity of distant neighbouring group participation. The anomers were separated by flash chromatography and identified using the fact that the anomeric proton of the β-anomer appears as a pseudotriplet in the ^{1}H NMR spectra.



Scheme 26 Nucleoside coupling of 2',3'-dideoxynucleosides

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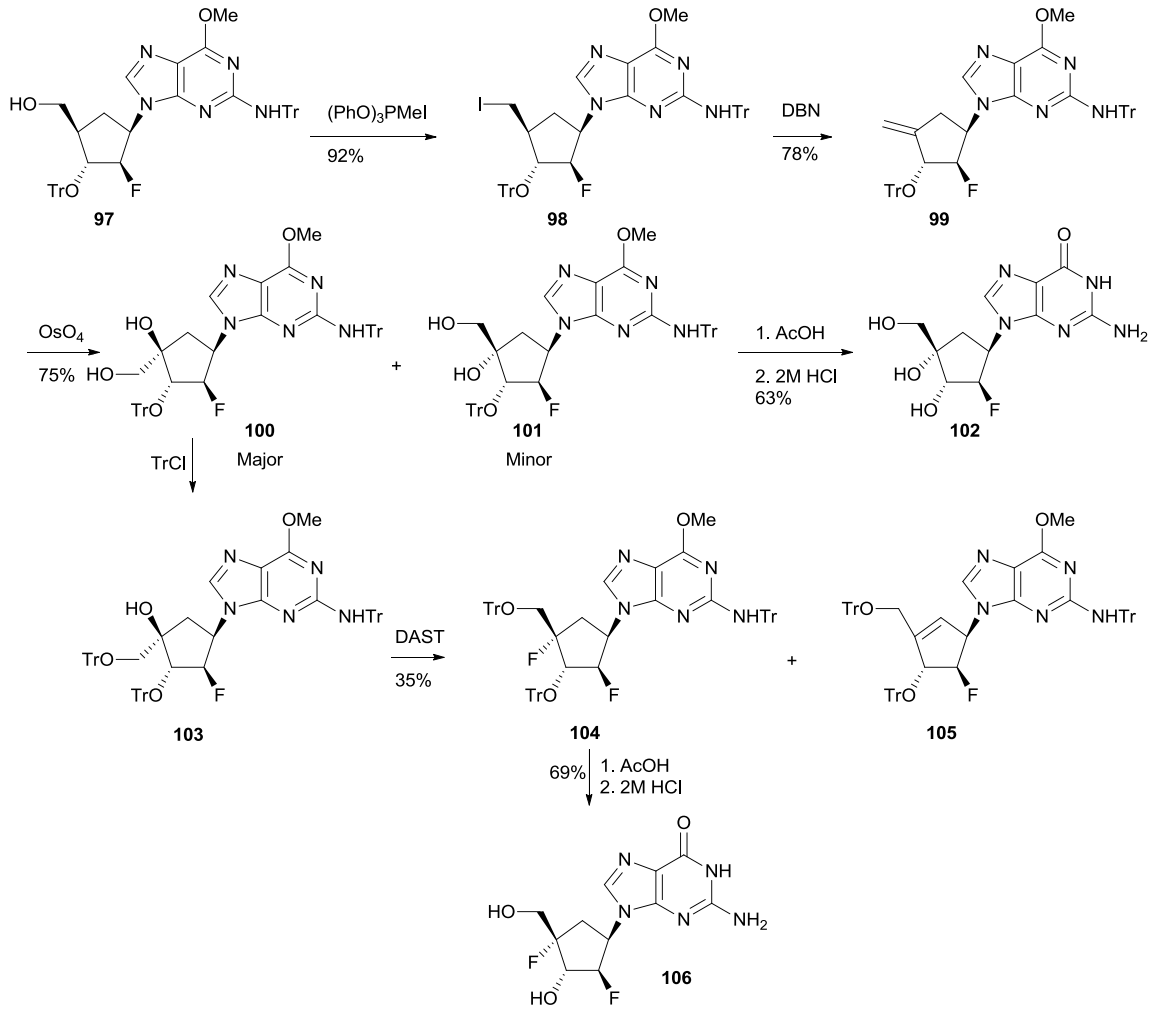
4. Carbocyclic nucleosides

The approaches to 4'-substituted carbocyclic nucleosides include manipulation of an existing nucleoside, use of Grubbs catalyst to cyclise a diene precursor, introduction of the 4'-substituent by stereoselective addition to an enone sugar, and utilisation of chiral auxiliaries to induce stereochemistry at the 4'-position. Shorter racemic syntheses of 4'-substituted carbocyclic nucleosides are noted[46-47] but are not detailed further here. For the general synthesis of carbocyclic nucleosides, and particularly the techniques for coupling the sugar and base unit together, the reader is directed to the recent excellent review by Castillon *et al*.[48]



Scheme 27 Introduction of 4'-hydroxy and fluoride substituents *via* 4',5'-methylene carbacycles

4.1 Introduction of 4'-hydroxyl and fluoride *via* a 4'-alkene

Biggadike *et al* introduced fluoro and hydroxyl substitutents to the 4'-position of carbocyclics by the method outlined in scheme 27.[49] To access the required functionality at the 4'-position, they prepared the alkene **99** *via* elimination of the iodide **98**. Osmylation of the alkene gave a mixture of the two

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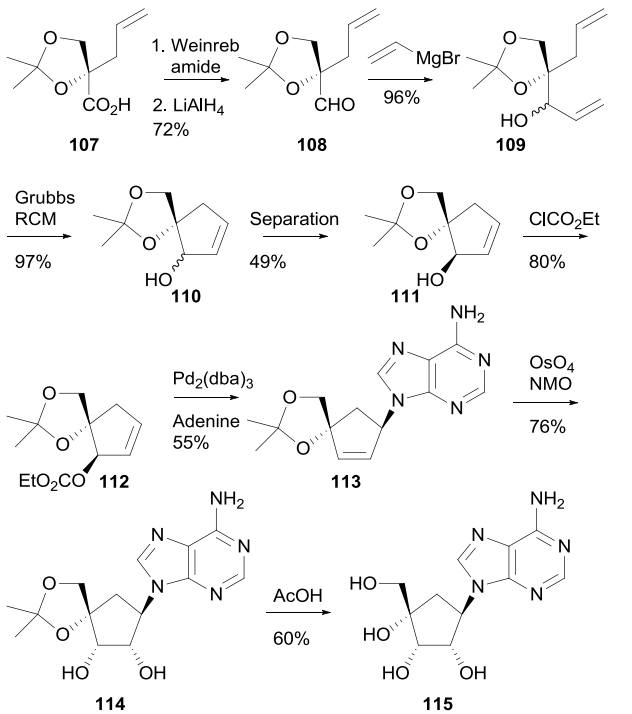
diastereoisomers **100:101** in a 3:1 ratio. The osmylation predominantly occurs on the opposite face to the O-trityl in accordeance to Kishi's rule.[50] The minor isomer **101** was deprotected with acetic acid to give the hydroxyl analogue **102**. The fluorine analogue was accessed by first protecting the β-hydroxy with a trityl and then treating the hydroxyl on the α-face of **103** with DAST. This reaction proceeds with inversion of stereochemistry, although a little of the eliminated side product **105** was also isolated. Deprotection with acetic acid gave the final 4'-fluoro substituted nucleoside.

4.2 Grubbs approach to 4'-substituted carbocycles

Hong *et al* later developed a more efficient route to the 4'-hydroxy carbacycle nucleoside utilising Grubbs chemistry (scheme 28).[51] Carbacyclic nucleosides prepared by the Grubbs reaction are well documented.[48] This requires the preparation of a diene such as **109**, which, when treated with Grubbs catalyst ($Cl_2(Cy_3P)_2RuCHC_6H_5$) cyclises to the cyclopentene. Hong utilised this work by synthesising intermediate **107** (prepared from commercially available D-Lactose in 5 steps[52]) where the hydroxyl was already in place in what will become the 4'-position. The cyclisation of **109** proceeded in 97% yield, although the product was produced as a 1:1 mixture of diasteroisomers. The two isomers were readily separated and the desired isomer **111** confirmed by NMR studies. This specific isomer was required for the Trost coupling step of **112** to **113**. The palladium based coupling procedure proceeds with retention of stereochemistry to give the desired nucleoside with both the correct regio- and stereo-chemistry. The alkene was then shown to undergo selective *cis* dihydroxylation on the α-face due to the steric hindrance on the β-face. Removal of the acetonide protecting group revealed the final nucleoside.



Scheme 28 Grubbs approach to 4'-hydroxy carbocycles

The Grubbs catalyst based approach has also been used to access a range of 4'-substituted 2',3'-dideoxy carbocyclic nucleosides, a selection of which is detailed in scheme 29.[53-55]

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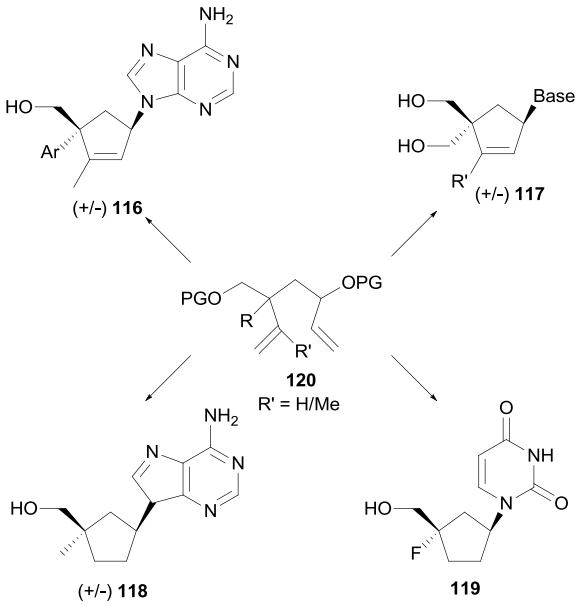
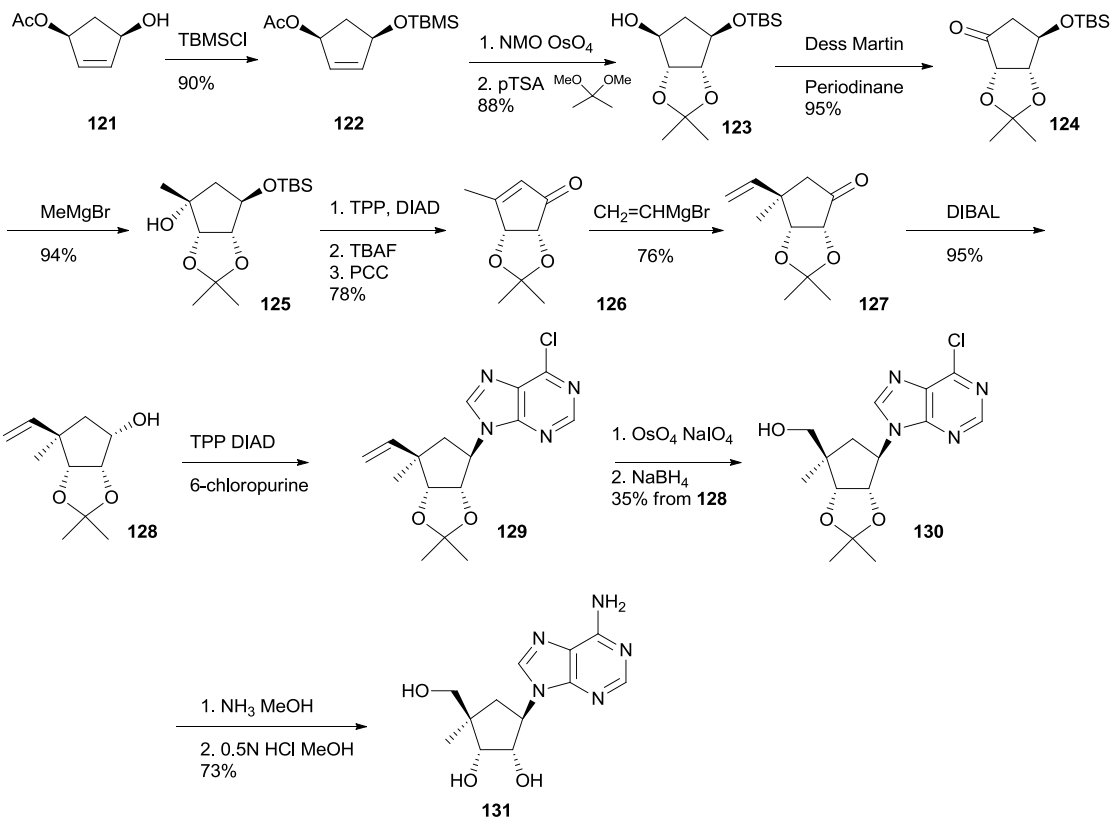


Scheme 29 Grubbs approach to some 4'-substituted carbocycles

Schneller *et al* developed an alternative route which introduces a Grignard reagent stereoselectively to the 4'-position of an enone (scheme 30).[56] The 4'-methyl group was introduced to the molecule early in the synthetic route *via* Grignard addition to the ketone **124**. The subsequent hydroxyl was then eliminated by use of a Mitsunobu reaction to give enone **126**. Vinyl magnesium bromide was added to the enone in 76% yield. The addition was completely selective for attack of the Grignard on the convex face of the bi-cycle. The ketone was stereoselectively reduced to the alcohol **128** in 95% yield to allow for introduction of the 6-chloropurine *via* a Mitsunobu reaction on the *β*-face. The alkene was finally converted to the 5'-hydroxyl *via* oxidative cleavage and subsequent reduction to **130**. A similar approach for the same nucleoside has also been developed by Chu *et al*.[57]

4.3 Stereoselective addition of a Grignard reagent to an enone



Scheme 30 Stereoselective addition of a Grignard to an enone

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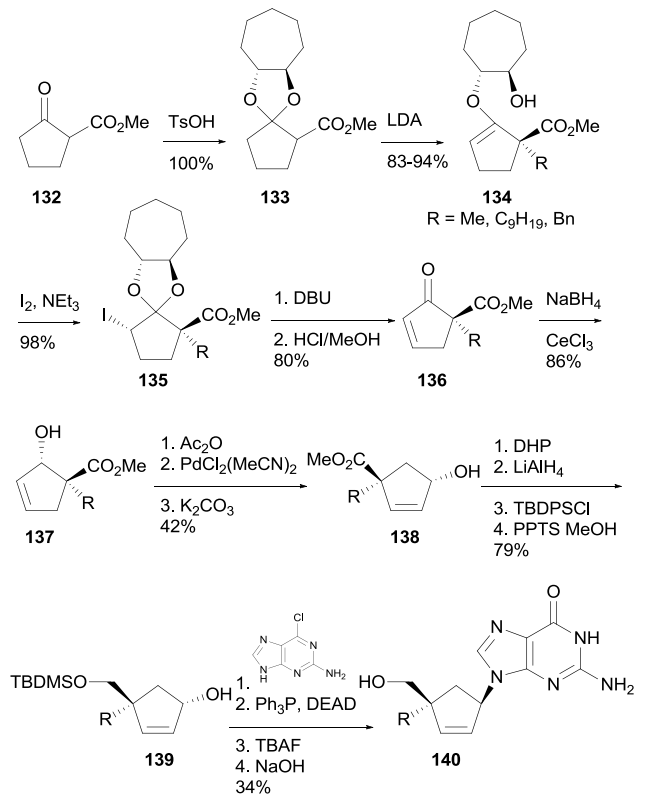
4.4 Introduction of the 4'-subsitutent stereoselectively *via* use of chiral auxiliaries

Kato *et al* developed an asymmetric synthesis of 4'-substituted nucleosides *via* the use of a chiral auxiliary to control the stereoselective addition of a range of alkylating agents to lithium enolates (scheme 31).[58] The synthesis started with the preparation of the chiral acetal **133** from condensation of (*R,R*)-cycloheptane-1,2-diol with ketone **132**. Enolisation of **133** with LDA at -78 °C followed by quenching with a variety of alkylating agents gave **134** with excellent diastereoselectivity (>99%). Iodoacetalization with iodine reformed the acetal as a single diastereoisomer. The iodide was then eliminated by treatment with DBU and the acetal was cleaved with HCl/MeOH to give the ketone **136**. Luche reduction selectively reduced the ketone, and the alcohol **137** was then protected with acetic anhydride. A palladium catalysed allylic rearrangement gave the allylic alcohol **138**. The ester was reduced with lithium aluminium hydride and after protection of the hydroxyl group, the base was coupled to **139** under Mitsunobu conditions. A similar approach was used by the same authors to access racemic C-linked 4'-substituted nucleosides.[59]



Scheme 31 Application of chiral acetal to induce stereoselectivity

Hegedus *et al* also made use of a chiral auxiliary to control the 1,4-addition of nucleophiles to substituted cyclopentenones (scheme 32).[60] Addition of $Me_2CuLi/BF_3.OEt_2$ to the enone **141** gave the product **142** in 52% yield and 9:1 diastereoselectivity in favour of the desired isomer. The auxiliary was then cleaved with TBAF, but the Luche reduction proceeded with little selectivity and the isomers of **144** needed to be separated. After further transformation the carbocycles were coupled to thymine and adenine under optimised Trost coupling conditions. The authors also demonstrated the same approach was applicable for 4'-substituted cyano carbocycles, but utilising Et_2AlCN to introduce

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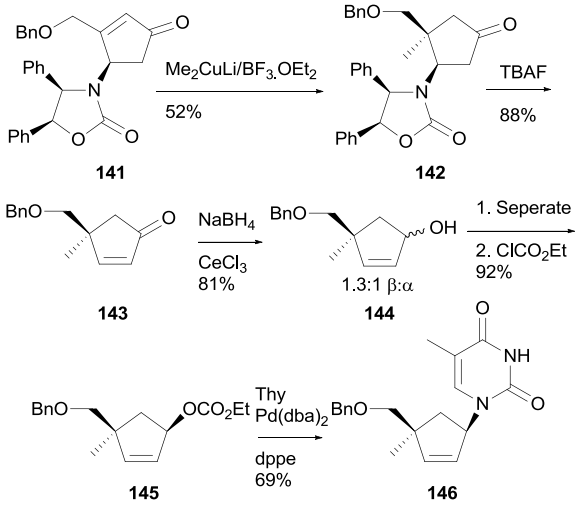
the cyanide group.



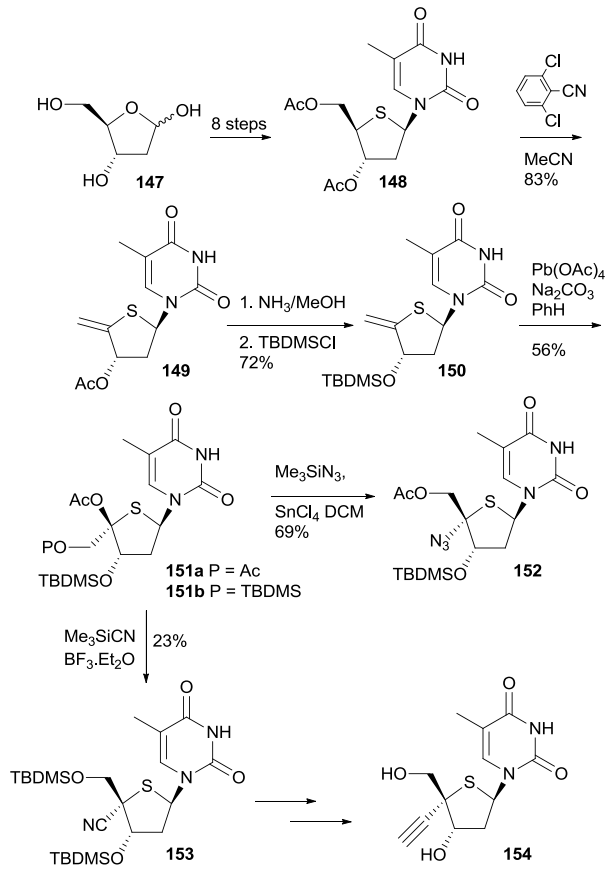
Scheme 32 Application of a chiral auxiliary to control the introduction of a 4'-substituent *via* a 1,4-addition

5. 4'-Thionucleosides

The review will detail two approaches to introduce an additional 4'-substituent into 4'-thionucleosides. The first of these is the displacement of a 4'-O-acetyl group (obtained through oxidation) by other nucleophilic groups. Secondly, a Cannizzaro approach has been used to introduce a 4'-hydroxymethyl group which has been further modified to other functional groups.

5.1 Introduction and displacement of a 4'-O-acetyl group

In 2008 Haraguchi *et al* described a method of introducing a 4'-O-acetyl group on the *β*-face of a thioribonucleoside (scheme 33).[61] This was done by elimination of the 5'-O-acetyl group of **148** to synthesise the exocyclic methylene compound **149**. After an exchange of protecting groups, compound **150** was oxidised to acetate **151** using lead tetraacetate. The O-acetate group in this molecule could be displaced with inversion under acidic conditions. Thus trimethylsilyl methanol (TMS-methanol), TMS-azide and TMS-thiophenol all reacted with **151a** to give inverted *β*-products such as azide **152**. When TMS-cyanide was tried in the reaction, it was found that the O-acetyl group in the 5' position interfered with the simple nucleophilic displacement reaction by cyanide at the neighbouring position. Replacing the 5'-O-acetyl group with an O-TBDMS group (**151b)** allowed this reaction to proceed in 23% yield to give **153**. This compound was converted via an intermediate formyl group to acetylene **154**.



Scheme 33 Introduction and displacement of a 4'-O-acetyl group

5.2 Introduction of 4'-hydroxylmethyl group via Cannizzaro reaction and subsequent manipulation

In 2011 Haraguchi's group published an improved method for introducing an acetylene group into the 4'-position of a thioribonucleoside (scheme 34).[62] Compound **155** was converted in five steps to a thioribose compound **156** containing a 5'-formyl group. A crossed aldol reaction between **156** and formaldehyde

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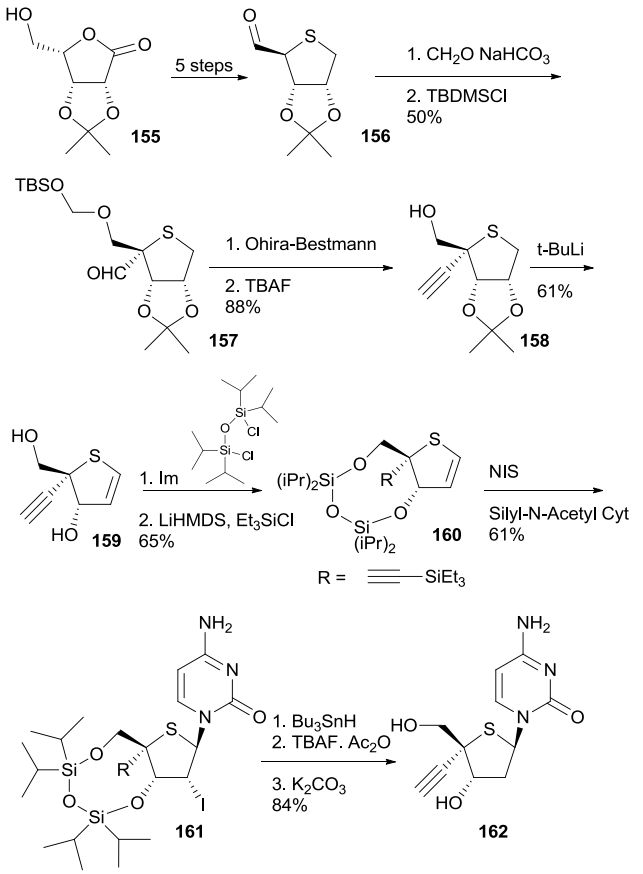
was used to install a 4'-hydroxymethyl substituent which was trapped by a second molecule of formaldehyde and the silylating agent to give a 50% yield of **157**. The formyl group on the α-face was converted to an acetylene substituent using the Ohira-Bestmann reagent, and then the 2'-substituent was eliminated using t-butyl lithium to give the vinyl thioether **159**. The alcohol and acetylene groups were protected before the cytosine unit was installed *via* the iodonium intermediate to give compound **161** in 61% yield. The iodine atom was removed using tributyl tin hydride and subsequent deprotection steps yielded the target compound **162.**



Scheme 34 Application of an aldol reaction to access the 4'-hydroxymethyl group

Haraguchi's group had used a similar, albeit racemic, approach to access 4'-substituted 4'-thiostavudine nucleosides (scheme 35).[63]

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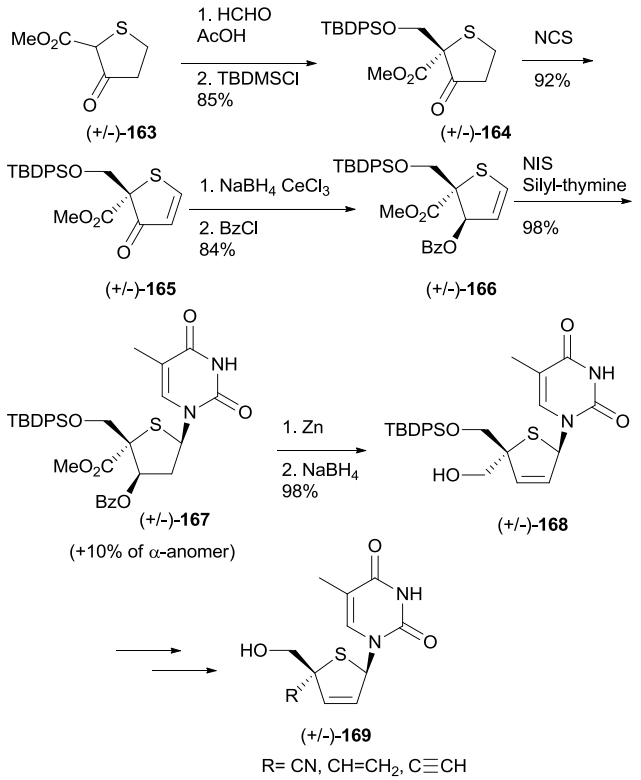

Scheme 35 Application of an Aldol reaction to access the 4'-hydroxymethyl group

Aldol reaction between **163** and formaldehyde, followed by protection gave **164** in 85% yield. The enone was introduced by Pummerer-type reaction with NCS. The ketone was then reduced diastereoselectively with sodium borohydride and protected as the benzoate. The nucleoside was introduced by a reaction of the alkene with NIS, followed by reaction with the silyated thymidine to give the nucleoside in a 10:1 diastereoisomeric ratio in favour of the desired β-isomer. The selectivity is likely due to the steric bulk of the benzoate on the β-face forcing the iodine to add to the α-face, which in turn allows the thymine to add to the β-face. After purification by recrystallisation, **167** was found to undergo elimination with zinc, and then the ester group was reduced with sodium borohydride to give **168** in 98% yield. The alcohol was used as a handle to access the vinyl, alkenyl, and nitrile groups by methods described previously in this review.

6. Conclusions

Over the last 50 years chemists have developed a variety of excellent synthetic approaches to 4'-substituted nucleosides. These have allowed medicinal chemists to explore the impact of functional groups at this position in research fields such as anti-virals, antisense therapies, cancer and antimicrobials. Future medicinal research is expected to continue to focus on chemical modifications to DNA/RNA and their monomer components. Therefore synthetic chemists will be required to unlock access to new classes of 4'-substituted nucleosides, or develop shorter and more efficient approaches to existing desirable targets.

Notes and references

[a] *Peakdale Molecular, Sheffield Road, Chapel-en-le-Frith, Derbyshire, SK23 0PG, UK. Fax: +44(0)1298 816701; Tel: +44(0)1298 816700; E-mail: mark.betson@peakdale.co.uk*

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