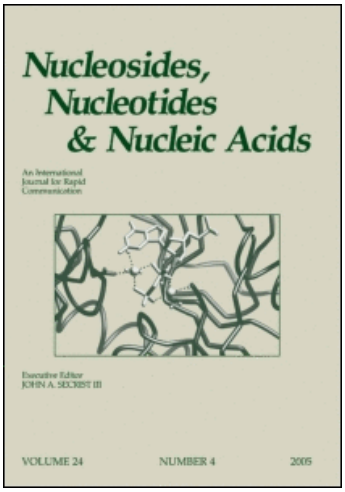

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The Chemistry of 2'-Deoxyribo-C-Nucleosides

Lars J. S. Knutsen[a]
[a] CNS Drug Discovery, CNS Division, Novo Nordisk A/S, Novo Nordisk Park, Måløv, DENMARK

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THE CHEMISTRY OF 2'-DEOXYRIBO-*C*-NUCLEOSIDES

Lars J.S. Knutsen

CNS Drug Discovery, CNS Division, Novo Nordisk A/S,
Novo Nordisk Park, DK 2760 Måløv, DENMARK.

Abstract: The various synthetic approaches to 2'-deoxyribo-*C*-nucleosides are summarized. These approaches are divided into four groups. Emphasis is placed on the techniques used in determination of anomeric configuration in the products.

Introduction

A substantial number of both synthetic and natural ribofuranosyl *C*-nucleosides have been prepared and some of the many ingenious approaches to such nucleosides have already been reviewed[1-5]. These *C*-nucleosides have in many cases been prepared as synthetic analogues of naturally occurring *N*-nucleosides. In the same manner, the somewhat narrower range of 2'-deoxyribofuranosyl-*C*-nucleosides which have been synthesized are often analogues of naturally occurring 2'-deoxy-*N*-nucleosides.

In many cases, the target molecules are designed to mimic the biological activity of the analogous natural nucleosides, especially as potential antiviral[6-8] or antitumor[9] agents, whilst incorporating the more stable C-C bond between the 2'-deoxyribose moiety and the aglycone and thereby, for example, hindering possible enzymatic cleavage. No 2'-deoxy-*C*-nucleosides have apparently as yet been discovered as natural products.

The Synthesis of 2′-Deoxy-*C*-Nucleosides

When reviewing the large range of synthetic approaches used to prepare 2′-deoxy-*ribo*-*C*-nucleosides, it becomes apparent that four main routes have been followed, as listed below:-

1. The reaction of a metallated heterocycle with a protected 2′-deoxyribose derivative.

2. Construction of the heterocyclic moiety from a suitably C-1 functionalized sugar derivative.

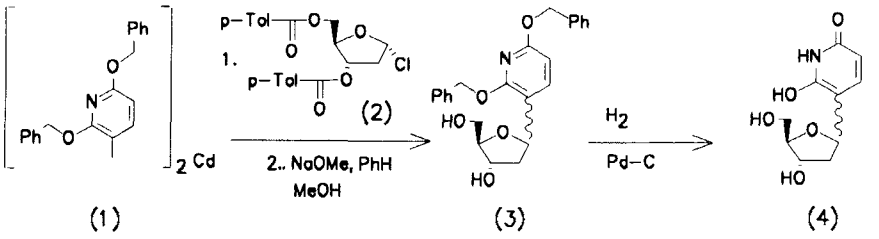
3. Stepwise formation of a 2′-deoxyribose derivative from a ribofuranosyl-*C*-nucleoside.

4. Total synthesis from non-ribose precursors.

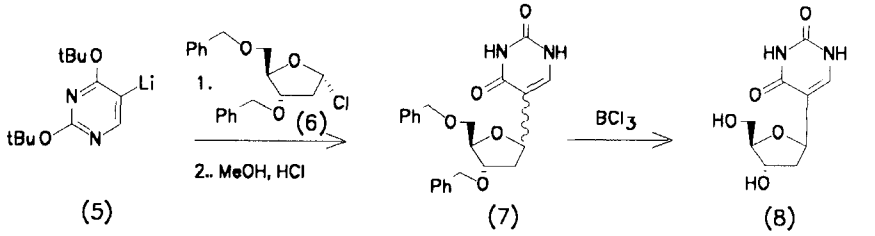
These four approaches will be dealt with in turn.

1. The reaction of a metallated heterocycle with a protected 2′-deoxyribose derivative.

The first recorded synthesis of a 2′-deoxyribo-*C*-nucleoside, namely 2′-deoxy-1-deazauridine **4** (Scheme 1), was claimed by Mertes and co-workers[10], who were aiming for agents which would inhibit thymidylate synthetase. This nucleoside was formed by reaction of 2-deoxy-3,5-bis-*O*-*p*-toluoyl-α-*D*-*erythro*-pentofuranosyl chloride **2** and the bis-(2,6-dibenzyloxypyridin-3-yl) cadmium **1** providing a dibenzylated product **3** which after two deprotection steps afforded an anomeric mixture of 2′-deoxy-1-deazauridines **4**. However, these compounds apparently decomposed too rapidly for full characterization and investigation.



Scheme 1



Scheme 2

A similar approach, also involving a metallated heterocycle, was later used by Bridges *et al*[11] in an early preparation of 2'-deoxypseudouridine **8** (Scheme 2). These workers employed 2,4-di(t-butoxy)-5-lithiopyrimidine **5** in condensation with 3,5-di-O-benzyl-2-deoxy-*D-erythro*-pentofuranosyl chloride **6** to afford two epimeric 5-pyrimidinyl polyols which were cyclized with methanolic hydrogen chloride to provide a separable mixture of the 3',5'-di-O-benzyl nucleosides **7**. Treatment of either anomer with boron trichloride furnished **8**, its α-anomer, and a small amount of a pyranose isomer. However, purification was possible by column chromatography. The anomeric configuration was assigned by comparison of the ^{1}H NMR of these compounds with anomeric pairs of pyrimidine 2'-deoxy-*N*-nucleosides and by an independent synthesis of **8** from pseudouridine using a method originally described by Kondo *et al*[12].

Eaton and co-workers, attempting to produce nucleoside analogues for incorporation into synthetic DNA strands, have published an eleven step synthesis of a 3-pyridyl-2′-deoxy-*C*-nucleoside **12**[13](Scheme 3). Their starting point, 2′-deoxy-ribopyranose **9** was converted into the protected dithioacetal **10** and from there into an aldehyde with careful manipulation of protecting groups. Reaction with 3-lithiopyridine followed by cyclization of the resulting alcohol **11** gave the protected 3-(2′-deoxy-*D-erythro*-pentofuranosyl)pyridine **12**. Separation of epimers was effected by chromatography of the 3′-(4-methoxybenzoyl) derivatives.

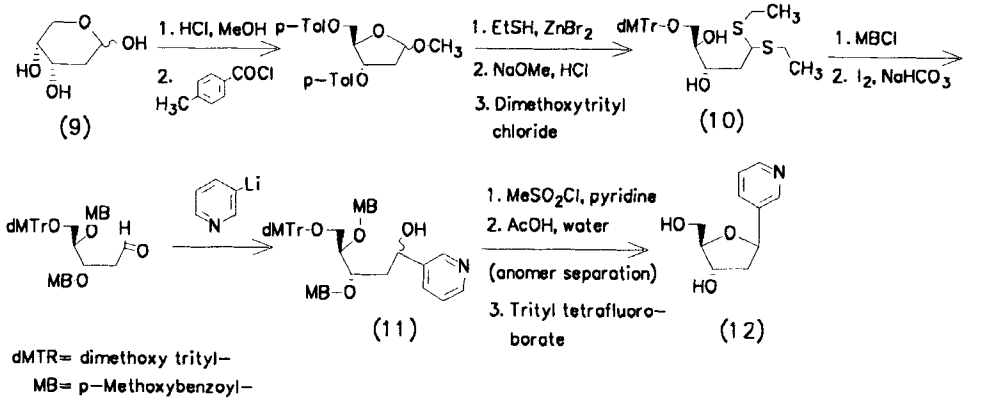
The deprotected α-anomer was crystalline and its anomeric configuration was confirmed independently by X-ray crystallography[14].

Solomon and Hopkins[15] adopted a similar approach which also utilized intermediate 3-lithiated pyridine derivatives, but in reaction with a more easily prepared sugar precursor.

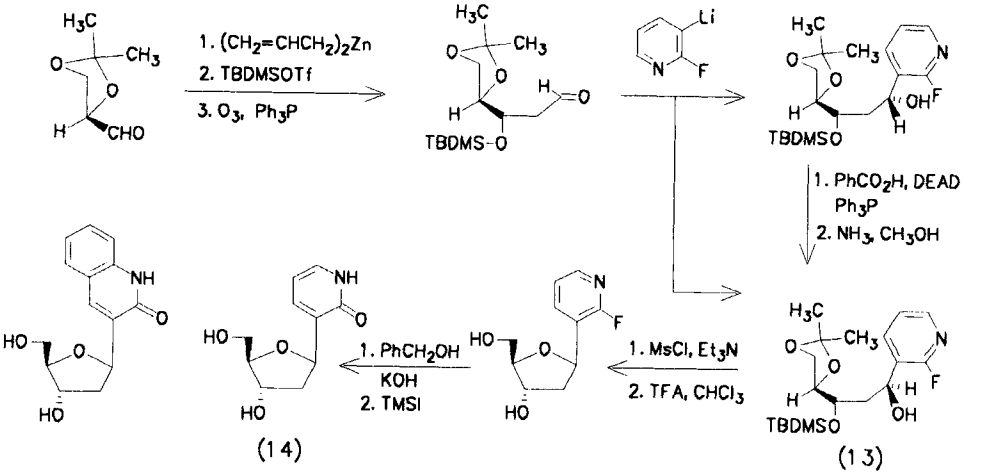
It was found that the product from reaction of 3-lithio-2-fluoropyridine with the aldehyde shown, gave two diastereomeric products which could be epimerized under Mitsonobu conditions. The isomer **13** was carried through to the final product 3-(2′-deoxy-*D-erythro*-pentofuranosyl)-2-hydroxypyridine **14** (Scheme 4). The same synthetic route was used for the corresponding isoquinoline derivative.

Russian workers[16] have synthesized a 6-nitro-3-indolyl-2′-deoxy-*C*-nucleoside as an anomeric mixture (Scheme 5). Reaction of 6-nitroindole with 2-deoxy-3,5-bis-*O*-*p*-toluoyl-α-*D*-*erythro*-pentofuranosyl chloride **2** in the presence of silver oxide and molecular sieve provided **15**, which was deblocked to the target compound. The isomeric *N*-nucleoside was also isolated from the reaction mixture.

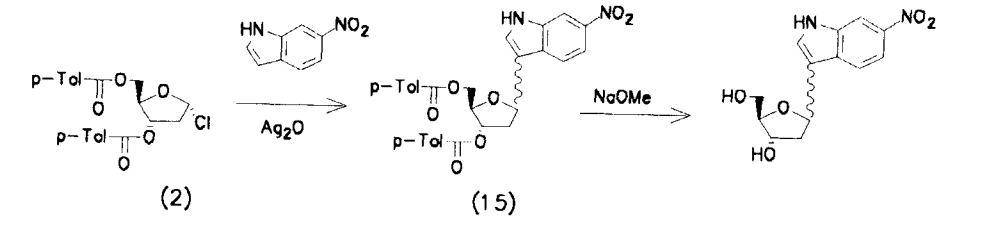
Hacksell and Daves[17] have investigated a new route to 2′-deoxy-*C*-nucleosides involving palladium-mediated addition



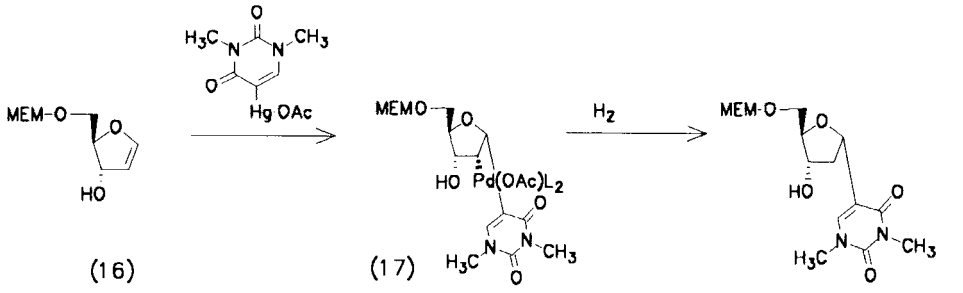
Scheme 3



Scheme 4



Scheme 5



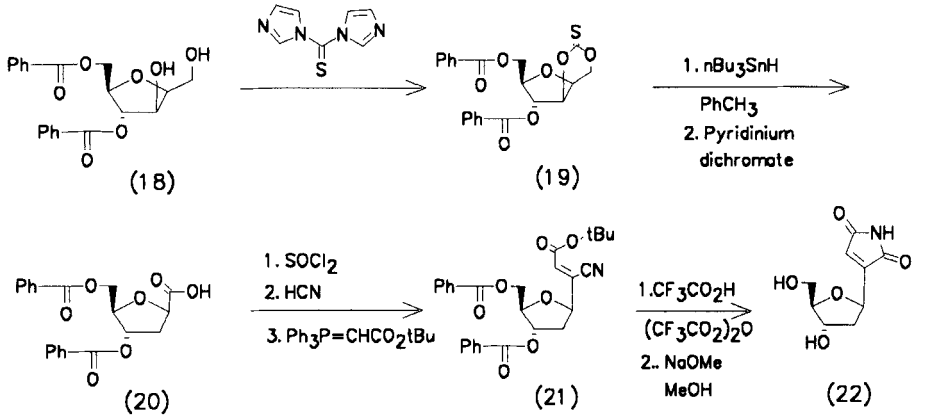
Scheme 6

of a mercurated uracil to the furanoid glycal **16** (Scheme 6). Depending on the bulk of the protecting groups used in the glycal moiety, the adduct formation can provide either α- or β-anomers of product *C*-nucleosides, reflecting which face of the glycal is least sterically hindered. It was found that the intermediate palladium complex **17** could be hydrogenated to a protected 1,3-dimethylpseudouridine.

These same authors have produced a useful analysis[18] of their observed ^{1}H and ^{13}C n.m.r. data, discussing their anomeric assignments on the basis of a combination of characteristic coupling constant and chemical shift criteria.

2. Construction of the heterocyclic moiety from a suitably C-1 functionalized sugar derivative.

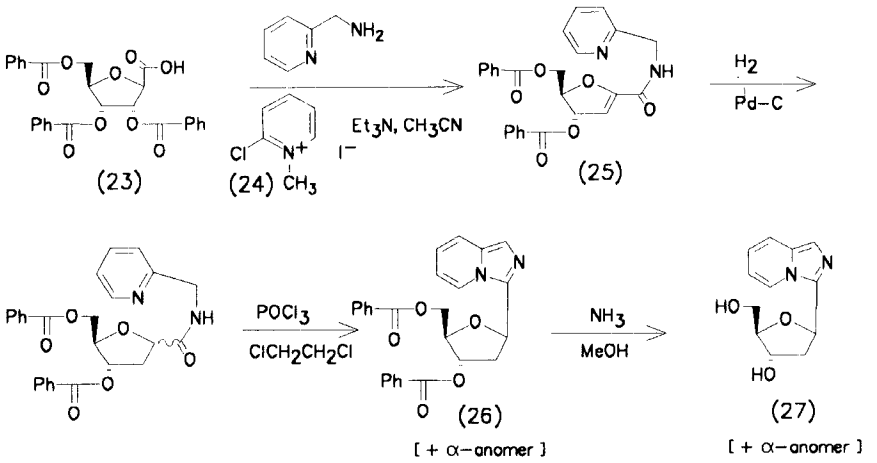
Some investigators prefer this approach, which can start either with a synthetic or a natural 2′-deoxy sugar moiety. Amongst those who favour the former method are Mubarak and Brown[19]. Their preparation of this class of *C*-nucleoside, namely 2′-deoxy showdomycin [3-(2′-deoxy-β-*D*-*erythro*-pentofuranosyl)maleimide] **22** (Scheme 7) began with the readily available 2,5-anhydro-4,6-di-*O*-benzoyl-D-glucitol **18** which was deoxygenated in two steps *via* the



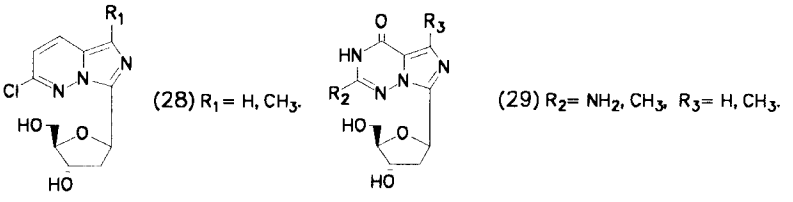
Scheme 7

cyclic 1,3-*O*-thiocarbonate **19**. The resultant alcohol was oxidized to provide 2,5-anhydro-3-deoxy-4,6-di-*O*-benzoyl-β-*D-ribo*-hexonic acid **20**. This acid was converted into the 2'-deoxy-*C*-nucleoside **22** *via* the cyano ester **21** using a method originally developed by Kalvoda[20] for the synthesis of the naturally-occurring ribose analogue, showdomycin.

Another attractive method for the synthesis of 2'-deoxy ribose derivatives falling within this classification is the β-elimination of a suitable group from the 2-position of a substituted ribose, thereby forming a 1,2-double bond, which can be hydrogenated to provide a 2'-deoxyribose derivative. This new synthesis of 2'-deoxy-*C*-nucleosides, reported by Scopes, Knutsen and co-workers, was successfully applied to the preparation of the useful diastereomeric precursors 2,5-anhydro-3-deoxy-4,6-di-*O*-benzoyl-β-*D-ribo*-hexonic acid **20** and 2,5-anhydro-3-deoxy-4,6-di-*O*-benzoyl-α-*D-ribo*-hexonic acid[21], in addition to providing a short synthetic route to novel imidazo[1,5-a]pyridine 2'-deoxy-*C*-nucleosides. The starting point of the synthesis was the readily synthesized 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid **23**[22] which



Scheme 8



Scheme 9

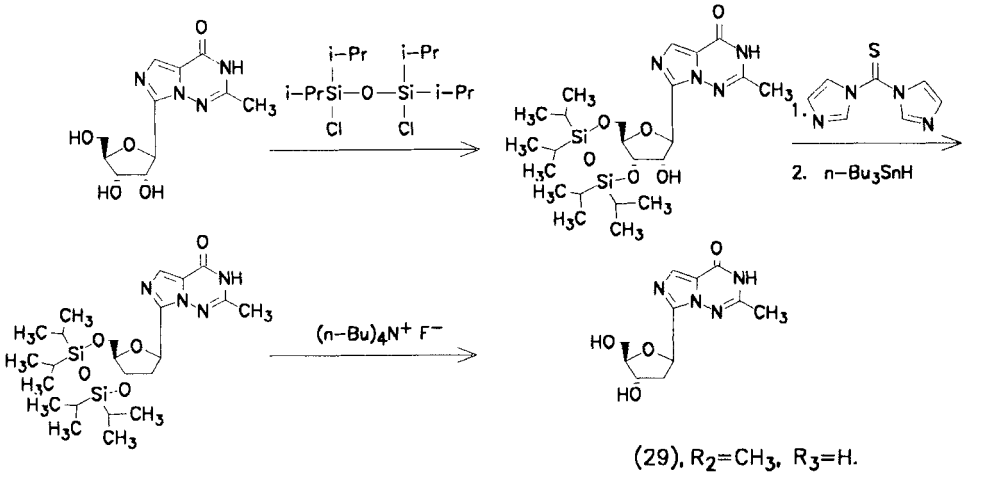
was reacted with 2-aminomethylpyridine in a coupling-elimination reaction (Scheme 8). This involved 2-chloro-*N*-methylpyridinium iodide **24** in acetonitrile with triethylamine as base to afford the novel, crystalline α,β-unsaturated amide **25** which was hydrogenated and cyclized using phosphorus oxychloride in the presence of pyridine. The protected α- and β-anomers **26** which were obtained were separated in a single fractional crystallization and deblocked to give the imidazo[1,5-*a*]pyridine 2′-deoxy-*C*-nucleosides **27**[23,24].

Other imidazo-fused systems were exemplified, giving the novel imidazo[1,5-*b*]pyridazine **28** and imidazo[5,1-*f*]-triazinone **29** 2′-deoxyribo-*C*-nucleosides (Scheme 9).

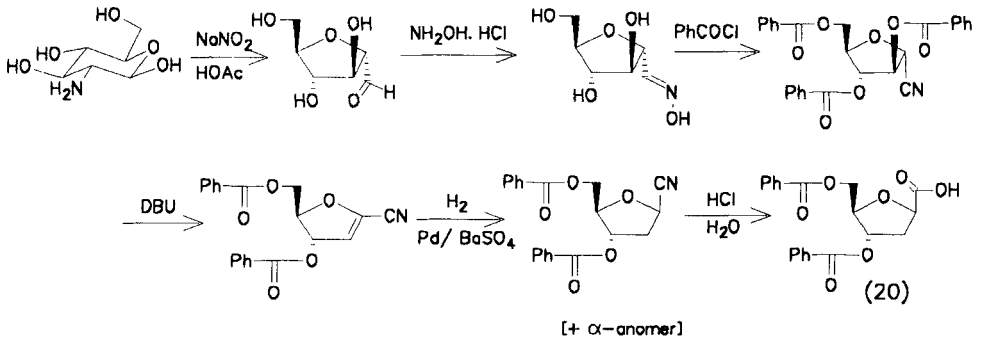
The anomeric assignments of this series of nucleosides were the subject of an extensive investigation. Deviations from the "triplet-quartet" peak-width rule[25] have prompted Srivastava *et al.*[26] to offer an alternative criterion for determination of the anomeric configuration of 2'-deoxy-*N*- and *C*-ribonucleosides (as reviewed by Chu *et al.*[27]). These investigators indicated that the methylene protons 2'-H_a and 2'-H_b adjacent to the anomeric centre in α-2'-deoxy-D-ribonucleosides display more NMR chemical shift non-equivalence than those of the corresponding β-anomer, and they have presented data for five anomeric pairs to support this proposal, backed up with some crystal structure data[28]. An approach to anomeric assignments based on ^1H-^1H coupling constants has recently been proposed by Francois *et al.*[29].

The background of ambiguity surrounding the assignment of configuration of this class of nucleosides, coupled with the notion that generalizations could only reliably be made within a given series of 2'-deoxyribo-*C*-nucleosides, led to the development of a self-consistent method of determination of anomeric configuration[23,24]. This procedure was based on a key nuclear Overhauser effect (n.O.e.) experiment which made use of the known *ribo*-configuration at C-3' and C-4'. Thus for the β-anomers it was confirmed that H-1' and H-4' were on the same face of the furan ring and for the α-anomers, H-1' and H-3' were on the same face.

Further confirmation of structural assignment was made by unambiguous synthesis of the 2'-deoxy-*C*-nucleoside **29** (R_2=CH_3, R_3=H), from the previously prepared *ribofuranosyl* β-anomer[30] by the same authors (Scheme 10). This ribose to 2'-deoxyribose conversion, which closely paralleled those exemplified earlier by Robins *et al.*[31], Lessor and Leonard[32] and Pankiewicz *et al.*[33], is currently the method of choice for this type of transformation and proceeded with retention of configuration at C-1'.

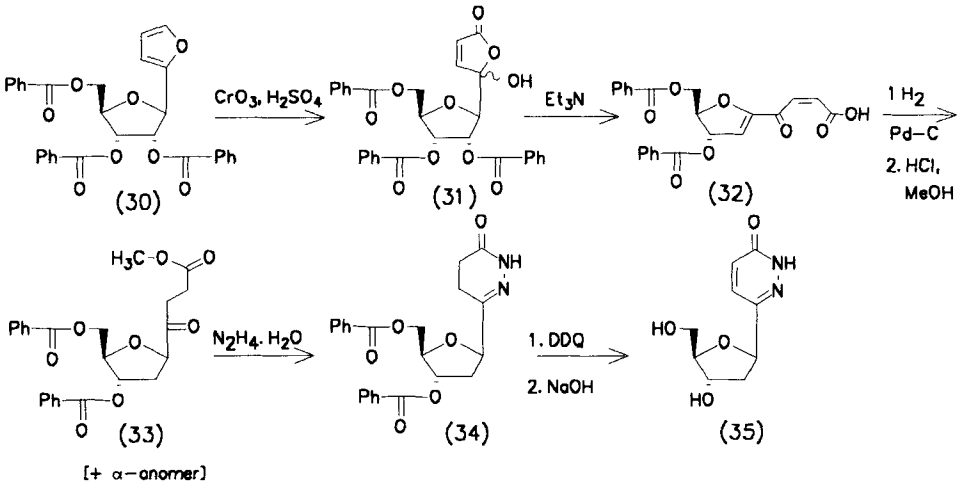


Scheme 10



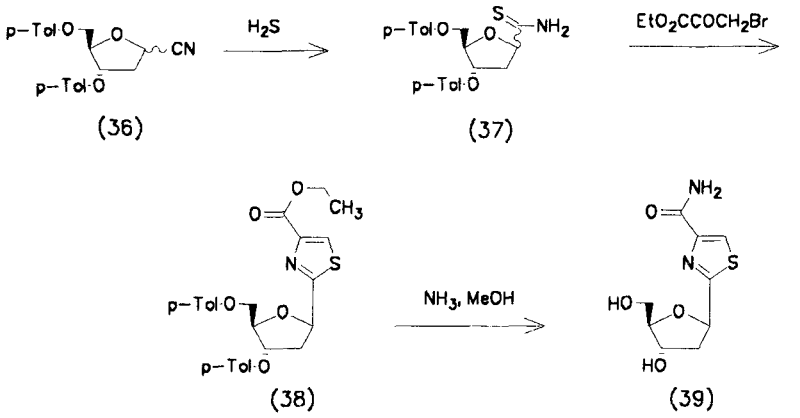
Scheme 11

Jung and co-workers[34] have also utilized the protected β-*D*-*ribo*-hexonic acid **20** and the corresponding nitrile as a pivotal point for 2′-deoxyribo-*C*-nucleoside synthesis, preparing the 2′-deoxy analogues of tiazofurin[31], showdomycin and the 2′-deoxy-*C*-nucleoside analogue of ribavirin (Scheme 11). The later stages of these syntheses were known, but the route used for the preparation of **20** was new. However, it contained elements of the above coupling-elimination procedure[21,24].



Scheme 12

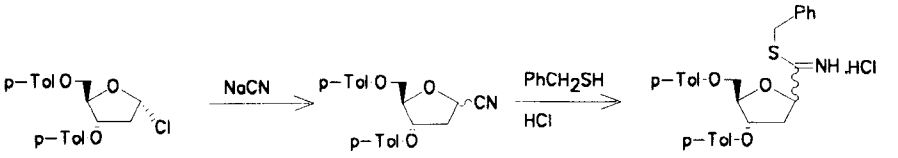
Another route to 2'-deoxy-C-nucleosides with similarities to the preceding reactions, in that elimination of a benzoyl group across the 1,2-bond of the oxidized furan **31** is involved, has recently been published by Maeba and coworkers[35]. Their approach is based on the familiar and useful starting material 2-(2',3',5'-tri-O-benzoyl-β-*D-ribo*-furanosyl)furan **30** (Scheme 12). Oxidation[36] of the furan ring provided the unsaturated alcohol **31** which was subjected to an elimination reaction to give the α,β-unsaturated ketoacid **32**. Hydrogenation provided the saturated acid which was esterified to the ketoester **33** at which stage anomer separation took place. Compound **33** was readily converted into the tetrahydropyridazinone derivative **34**. Aromatization, followed by deprotection provided the 2'-deoxypyridazinone ribo-C-nucleoside **35**, and elucidation of anomeric configuration took place essentially by the n.O.e. method described previously[23,24].



Scheme 13

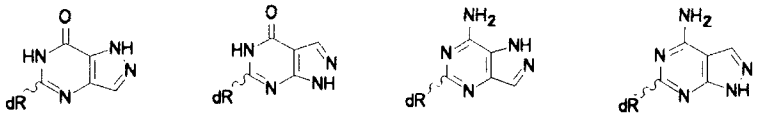
Srivastava and Robins[26] have published a preparation of the 2′-deoxy analogue **39** of the antitumour agent tiazofurin (2-β-*D*-*ribo*-furanosylthiazole-4-carboxamide) (Scheme 13). Their synthesis began with the protected nitrile **36** which was smoothly converted into 2,5-anhydro-3-deoxy-4,6-di-*O*-toluoyl-D-*ribo*-*hexono*-thiamide **37**. Compound **37** was treated with the ethyl ester of bromopyruvic acid to give the ethyl thiazole-4-carboxylate **38** as a mixture of anomers, which were readily separable by chromatography. Deprotection of the β-anomer afforded 2-(2′-deoxy-β-D-*erythro*-pentofuranosyl)thiazole-4-carboxamide **39**, the configuration of which was confirmed by an X-ray crystal structure determination[28]. These authors also provided a detailed discussion of their n.m.r. data.

Igolen and co-workers have prepared many examples of 2′-deoxyribo-*C*-nucleosides, exploiting a key intermediate thioformimidate **40**, made as a mixture of anomers from the useful 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-*D*-*erythro*-pentofuranosyl chloride **2** *via* the cyano 2′-deoxysugar **36** (Scheme 14).

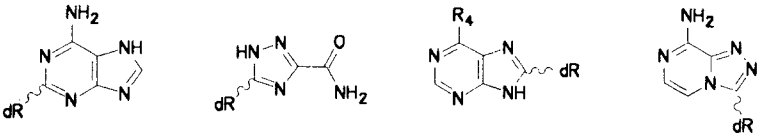


(2) (36) (40)

Scheme 14

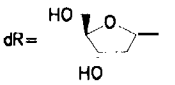


(ref. 37) (ref. 37) (ref. 38) (ref. 39)



(ref. 40) (ref. 41) (ref. 42) (ref. 43)

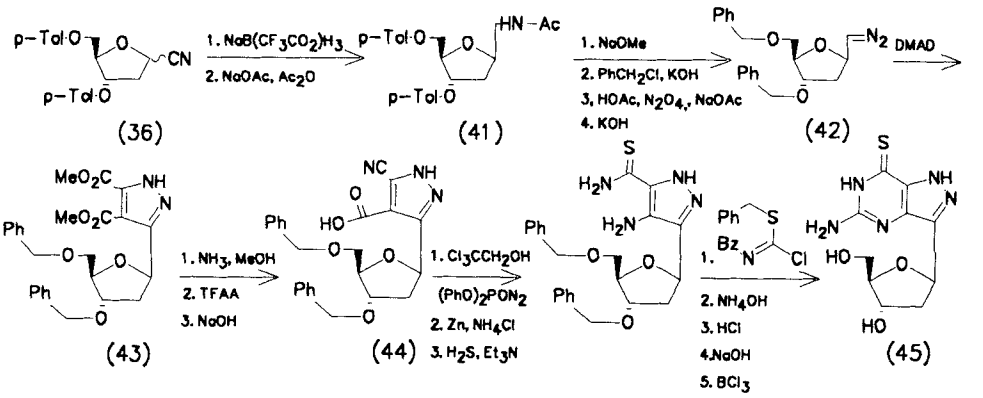
(R_4=OH, NH_2, SH)



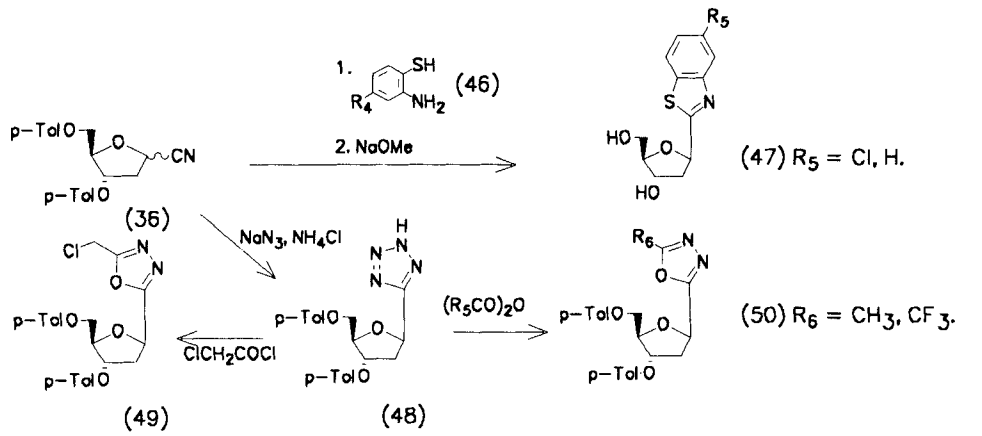
Scheme 15

The thioformimidate **40** could be further functionalized by condensation with several substituted heterocycles. In this manner a whole series of new 2'-deoxy-C-nucleosides were prepared. The structures obtained are shown overleaf with their corresponding literature references (Scheme 15).

The nitrile **36** has indeed proved to be a very popular starting point for the preparation of novel 2'-deoxy-ribo-C-nucleosides. Acton and Ryan[44] have published a synthesis of C-nucleosides isosteric with thioguanosine, aiming to retain the parent compound's antitumor effects (Scheme 16).



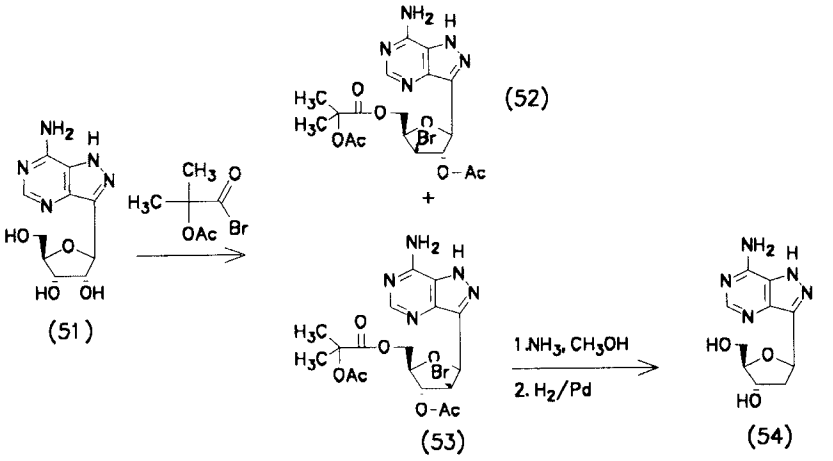
Scheme 16



Scheme 17

Reduction of the nitrile **36** followed by acetamide **41** formation, exchange of protecting groups and diazotization provided the reactive diazomethane glycal **42**. 1,3-Dipolar addition, involving dimethyl acetylene dicarboxylate and stepwise formation of the cyano acid **44** [*via* the diester **43**] followed by treatment with diphenylphosphoryl azide and pyrazolo[4,3-d]pyrimidine ring formation, provided the novel thioguanosine isostere **45**.

The final synthetic approach to 2'-deoxy-*C*-nucleosides which to be summarized in this section also uses the



Scheme 18

ubiquitous nitrile **36** as a starting point. Farkas and co-workers[45,46] have converted this versatile intermediate directly into the benzothiazole derivative **47**, by use of the aminothiol **46** and *via* a tetrazole **48** into the 1,3,4-oxadiazoles **49** and **50** [47] (Scheme 17).

3.Stepwise formation of a 2'-deoxyribose derivative from a ribofuranosyl *C*-nucleoside.

A range of synthetic methods have been developed which make it possible to prepare a 2'-deoxy-*ribo*-*C*-nucleoside from a *ribo*-*C*-nucleoside. An early example of these was published by Moffatt in 1973[48] (Scheme 18).

When formycin A **51** was treated with 2-acetoxyisobutyryl bromide, a mixture of the protected halides **52** and **53** was isolated. After separation and deblocking, followed by hydrogenolysis of the C-Br bond, 2'-deoxyformycin **54** was obtained.

Some twelve years later, Rosowsky and co-workers[49] published a different conversion of formycin A into 2′-deoxyformycin **54** which used the diisoproyldisiloxane/ deoxygenation route pioneered in the *C*-nucleoside field by M.J. Robins *et al.*[25] and also used by others[24,33]. Revankar and co-workers[50] have published a similar procedure, but instead they converted 5-chloroformycin into a corresponding 2′-deoxy analogue.

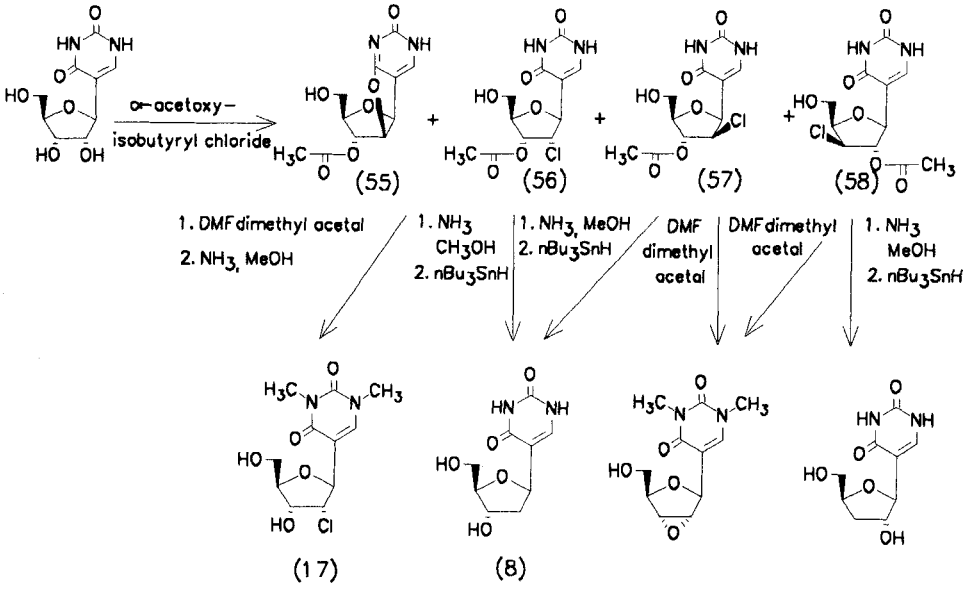
The chemistry of the corresponding 2-acetoxyisobutyryl chloride in reaction with the natural *C*-nucleoside pseudouridine was investigated by other workers[51] and as a result of this, a series of articles were published giving some controversial results[52,53,54]. The matter was eventually clarified when a definitive paper was published by Watanabe and co-workers in 1985[55]. In this article the products were confirmed as the 2′,4-anhydro derivative **55** as well as the three different chloro compounds **56**, **57** and **58**, and some of the earlier presumed structures were rescinded (Scheme 19).

Several of the structural assignments were confirmed by synthesis, e.g. the anhydro compound **55**. 5-(2′-Deoxy-β-*D*-*erythro*-pentofuranosyl)-1,3-dimethyluracil **17** had been isolated previously[33]. Watanabe *et al.* have also devised syntheses of various methylated 2′-deoxypseudouridines[56] and isocytidines[57].

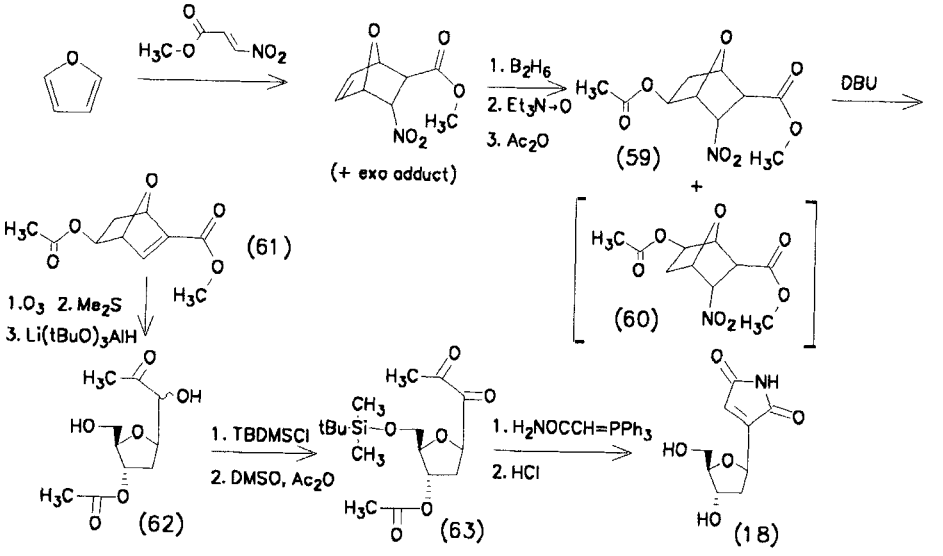
4. Total synthesis from non-ribose precursors.

One example of a total synthesis of a 2′-deoxyribo-*C*-nucleoside has been published by Just and co-workers[58] as part of a series of nucleoside syntheses[59,60,61](Scheme 20).

This synthesis started with a Diels-Alder reaction between methyl β-nitroacrylate and furan, and conditions were chosen to favor the formation of the *endo*-nitro adduct.



Scheme 19



Scheme 20

Hydroboration and oxidation of the resulting borane with triethylamine *N*-oxide gave two isomeric alcohols which were acetylated to afford **59** and **60**. Elimination of nitrous acid provided the 2-*exo*-acetoxy-5-carbomethoxy-7-oxabicyclo-[2.2.1]hept-5-ene **61** which was ozonolyzed and reduced under mild conditions to give the diol ester **62**. Selective silylation and oxidation led to the α-keto ester **63** which was treated with carbamoylmethylene triphenylphosphorane[62] to provide the protected 2'-deoxy showdomycin in fair yield. Deblocking under acidic conditions gave **18** as a mixture of enantiomers.

A total synthesis of 8-(2'-deoxy-β-*D*-*erythro*-pentofuranosyl)-9H-adenine from furan has been reviewed elsewhere[63].

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