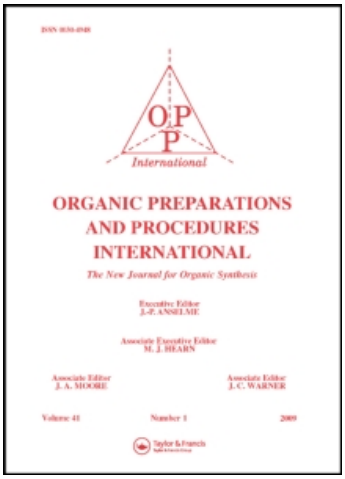

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SYNTHESIS AND PROPERTIES OF *PSICO*-NUCLEOSIDES

Stewart K. Richardson[a]; Amy R. Howell[a]; Rosa Taboada[a]
[a] Department of Chemistry, University of Connecticut, Storrs, Connecticut

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SYNTHESIS AND PROPERTIES OF *psico*-NUCLEOSIDES

Stewart K. Richardson, Amy R. Howell* and Rosa Taboada
Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060
E-mail: amy.howell@uconn.edu

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Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060
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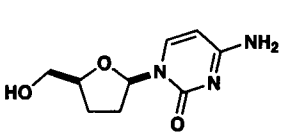
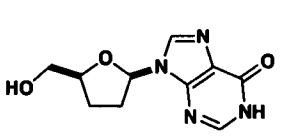
INTRODUCTION

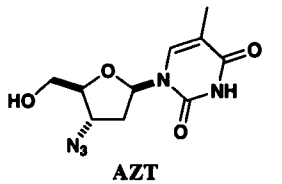
The design and synthesis of molecules for the fight against aggressive and potentially fatal diseases, such as cancer and bacterial and viral infections, remain important challenges.[1] Indeed, the existence of emerging and established viral diseases (*e. g.*, HIV, HSV, HBV, CMV, EBV, VSV), as well as the growing incidence of drug-resistant bacterial and viral infections, means that the need for new, effective therapies is increasingly urgent. These diseases, involving nucleic acid replication as a vital component, have, not surprisingly, been targeted by nucleosides and their analogs. In the area of antiviral research there has been considerable success with the development of such drugs as ddC, ddI, and AZT for the treatment of HIV.[2] More recently, HBV, HSV and CMV have been successfully treated with nucleosides.[3] Problems, however, have emerged, including the development (sometimes rapid) of viral resistance, chemical or enzymatic instability of the nucleoside analogs, poor pharmacokinetics or dynamics and drug-induced toxicity, caused by the affinity of the nucleosides or their derivative/metabolites for other essential enzymes. For these reasons the search for more effective nucleosides with a low incidence of side effects continues.



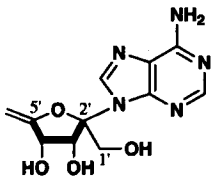
ddC



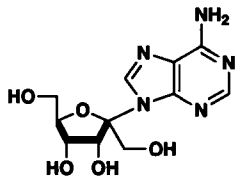
ddI



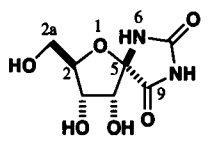
AZT



angustmycin A



angustmycin C



hydantocidin

The design of chemotherapeutic agents has often been inspired by nature's supply of structures and has subsequently focused on identifying analogs with improved spectra of activi-

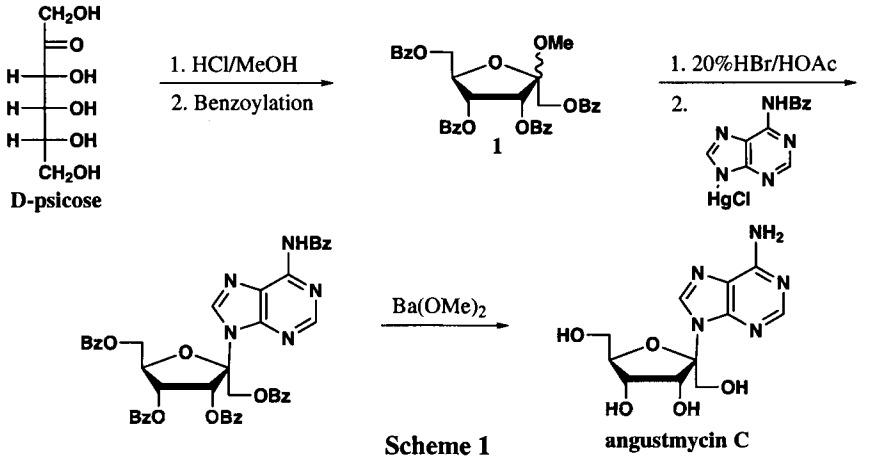
ties. From 1956 several groups isolated the same two natural products from different sources. They were given the names angustmycin A and C, and, following some initial confusion about the structure of angustmycin A, both structures were correctly assigned.[4] Interestingly, they were found to belong to a new class of nucleosides in that they had an alkyl (specifically hydroxymethyl) substituent on the ribose adjacent to the base. They were shown to be derived from the keto sugar D-psicose and were given the general name *psico*-nucleosides.[5] More recently, a novel spirocyclic *psico*-nucleoside, also the first of its class, called hydantocidin was isolated and shown to have potent herbicidal activity.[6] *psico*-Nucleosides represent a relatively unexplored class of nucleosides. However the biologically activity demonstrated by the two lead compounds, angustmycin (Section I) and hydantocidin (Section IV), has prompted interest from a number of industrial and academic research laboratories. This research is reviewed here in three sections: 1. *psico*-nucleosides with a substituent at C2 (Sections I and II); 2. Conformationally locked *psico*-nucleosides (Section III) and 3. Spirocyclic *psico*-nucleosides (Section IV). All of the compounds have both a nitrogen and carbon attached to the "anomeric" carbon of the cyclic sugar (or an isostere of it). Although the review is largely focused on synthetic efforts, any significant biological activity demonstrated by these compounds is placed briefly in context.

I. C1'-HYDROXYMETHYL *psico*-NUCLEOSIDES

1. *psico*-Nucleosides: Angustmycin A and C

Angustmycins A and C, isolated in 1956 and 1959, respectively, were reported to have antibacterial and antitumor activity *in vitro*.[7,8] Moreover, in fermentation with *Streptomyces hygroscopius var. decoyicus*, it was postulated that these two antibiotics existed in equilibrium.[4e] Given the structural similarity of the two compounds, their syntheses are frequently interlinked. In addition, because the enol ether of angustmycin A is relatively unstable, it is frequently prepared from an advanced angustmycin C intermediate with late introduction of the enol ether moiety.

Not surprisingly, D-psicose is a widely used starting material for angustmycin C synthesis, as illustrated by the synthesis of Farkas and coworkers (*Scheme 1*).[9] Treatment with

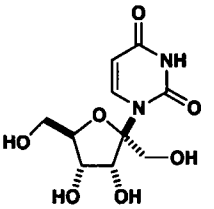


Scheme 1

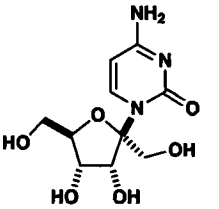
angustmycin C

methanolic HCl, followed by benzoylation, provided 1,3,4,6-*tetra*-benzoylated intermediate **1**. The anomers of **1** were separated by chromatography on neutral alumina. Formation of the glycosyl bromide, introduction of the nucleobase and global deprotection gave angustmycin C in 4.7% yield (from **1**). This approach was similar to the one reported earlier in brief outline by Schroeder and Hoeksema.[4d]

A second paper by the Farkas group employed a similar approach to the preparation of uracil and cytosine angustmycin C analogs **2** and **3**.[10] This time, coupling of the base to the sugar was achieved with the glycosyl bromide and silylated base in the presence of $Hg(OAc)_2$.

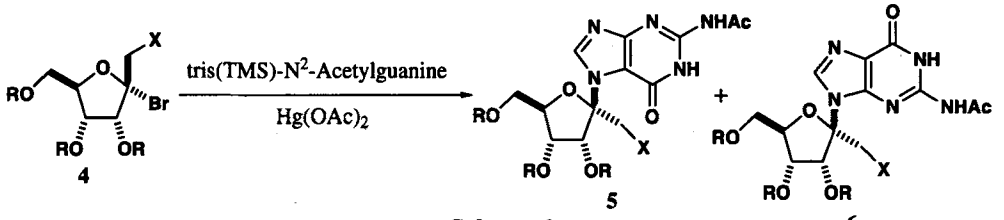


2



3

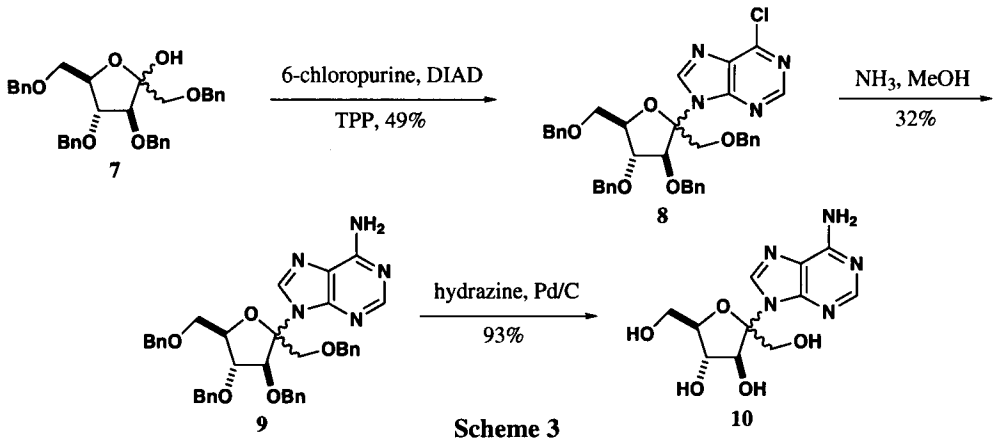
In a third paper Farkas and Hrebabecky completed a synthesis of *psico*-furanosylguanine, as shown in *Scheme 2*.[11] Reactions between a number of guanine derivatives and *psico*-furanosyl bromides were investigated, but the yields and selectivities were poor. For example, a mixture of the N7 **5** and N9 **6** (R = Bz, X = OBz) isomers (3:1) was obtained in 17% yield with **4** and tris(trimethylsilyl)-N^2-acetylguanine. On the other hand, reaction of bromide **4** (R = *p*-MeBz, X = Br) with the same base gave 28% of a mixture in which the N^9 isomer **6** predominated by 45:55. In each case the isomers were separable by chromatography. The guanine derivative of angustmycin C was prepared from **6** (R = Bz, X = OBz) by ammonolysis of the protecting groups.



4 **5** **6**

Scheme 2

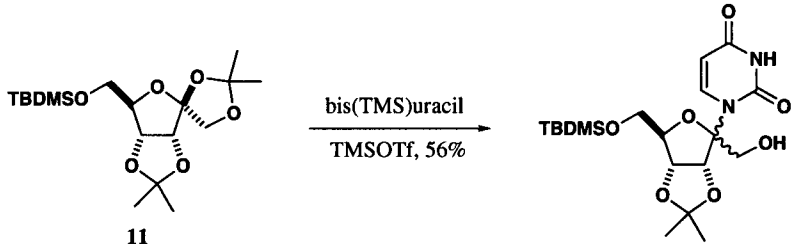
Bouali *et al.* used a Mitsunobu protocol for construction of the nucleoside bond in a synthesis of a fructose isomer of angustmycin C (*Scheme 3*).[12] Coupling of the fructose derivative **7** with 6-chloropurine gave **8** as a 3:1, β:α ratio in 49% yield. When benzoyl was used as a protecting group, the α-isomer predominated, presumably due to neighboring group participation. Treatment of this mixture with ammonia in methanol gave **9** (β:α, 2;1). The anomers of **9** could not be separated, but were deprotected to give **10** from which the desired β-anomer was isolated by HPLC.



7 8 9 10

Scheme 3

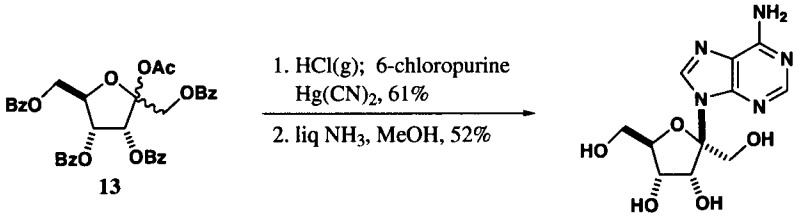
An efficient method for the construction of angustmycin analogs was reported by Sarma *et al.* (*Scheme 4*).[13] The key coupling reaction involved sugar **11**, which was more readily available than some of the glycosyl bromides already discussed. Although the two product anomers (*e. g.* **12**) were formed in an approximately 1:1 ratio, they were separable by chromatography. In addition to uracil, 5-hydroxyuracil, 5-bromouracil and 6-chloropurine were successfully coupled with **11**.



11 12

Scheme 4

Grouiller *et al.*[14] published a stereoselective version of the transformation from a protected/activated psicofuranose to a protected *psico*-nucleoside, as shown in *Scheme 5*. The *psico*-furanose tetrabenzoyl acetate **13** was activated as the anomeric chloride with HCl gas and

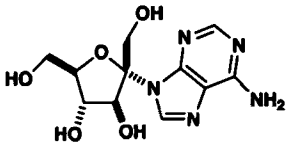


13 14

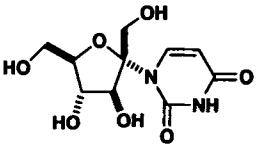
Scheme 5

then treated with 6-chloropurine in the presence of $Hg(CN)_2$ in nitromethane. Less than 5% of the undesired α-anomer was observed under these conditions. The resultant chloropurine was converted to adenine **14** with simultaneous deprotection of the benzoate groups using liquid

ammonia in methanol in a sealed tube. Uracil analog **2**, as well as the α-anomers of adenine **15** and uracil **16** fructofuranose, were prepared by a similar procedure. The stereochemical outcomes of these reactions, *i. e.* the high β-selectivity of **14** and **2** and α-selectivity of **15** and **16** were partially explained by the participation of the neighboring C3' benzoate group.

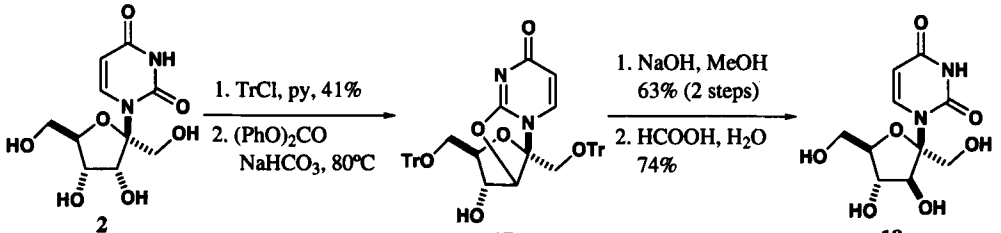


15



16

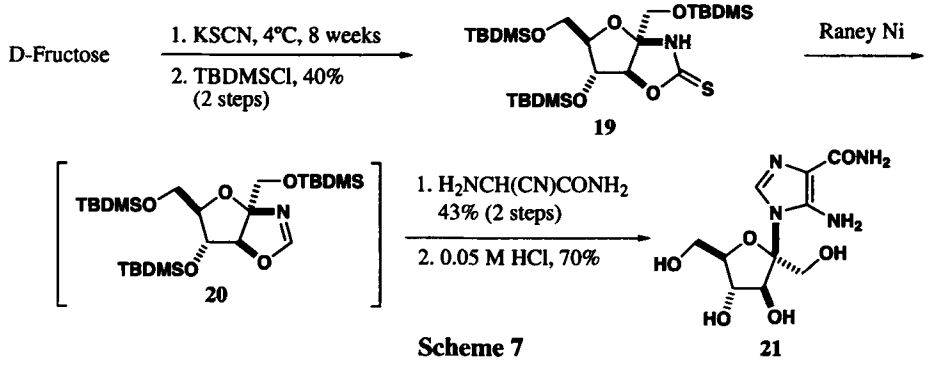
The desired β-anomer **18** of uracil fructofuranose was obtained as shown in *Scheme 6*.[14] Thus, angustmycin C analog **2** was treated with trityl chloride to protect both primary alcohols. The product was exposed to diphenyl carbonate to give cyclic ether **17**, which was hydrolyzed with base then deprotected to give **18**. This product was also prepared by Holy using a similar procedure.[15]



2 **17** **18**

Scheme 6

In a later paper by the Grouiller group, the problem of anomeric selectivity in the fructofuranoside series was solved as shown in *Scheme 7*.[16] Protracted treatment of D-fructose with KSCN under acidic conditions at 0°C, followed by silylation of the crude reaction mixture



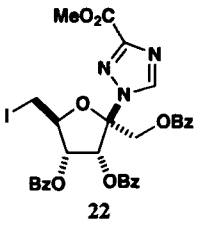
19 **20** **21**

Scheme 7

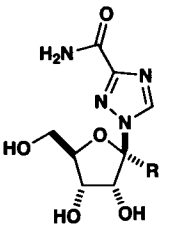
with TBDMSCl, gave oxazolidine-2-thione **19** in 40% yield. This was desulfurized with freshly activated Raney nickel, and the presumed oxazoline intermediate **20** was condensed with α-amino-α-cyanoacetamide and deprotected to give **21**. Aminoimidazole carboxamides like that

contained in **21** have been readily converted into a variety of purine containing nucleosides by established procedures.

In Moffat's synthesis of angustmycin A[17] (described in more detail in *Scheme 11*) the iodide group in compounds like **22** was displaced by acetate and this ultimately led to angustmycin A. Such iodides were also used to prepare angustmycin C analogs. For example, compound **23** (R=CH_2OH) is the *psico*-nucleoside analog of the antiviral agent virazole (ribavarin) (R=H). However, unlike virazole, **23** (R = CH_2OH) was completely inactive in antiviral, antibacterial and antitumor screens.

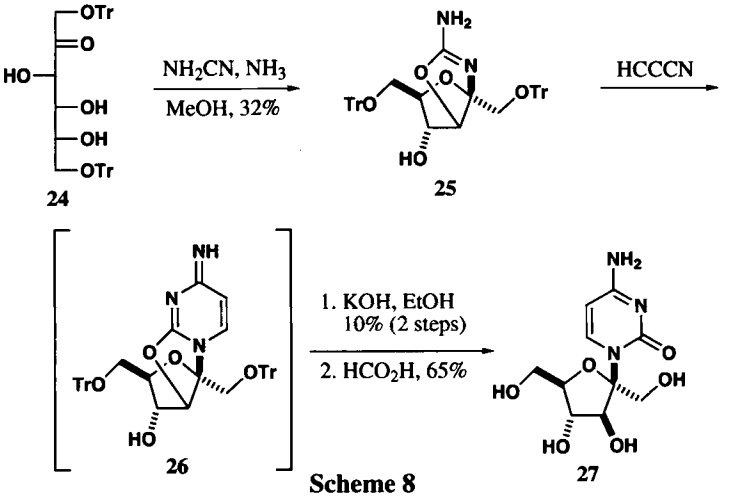


22



23

Tolman and Robins prepared cytosine-*psico*-fructofuranose **27**, as shown in *Scheme 8*.[18] 1,6-di-*O*-Trityl-D-fructose **24** was treated with cyanamide to give oxazoline **25**, according to a method developed earlier by Sanchez.[19] Treatment of **25** with cyanoacetylene gave anhydronucleoside **26**, which was not isolated but hydrolyzed *in situ* and deprotected to provide **27**.

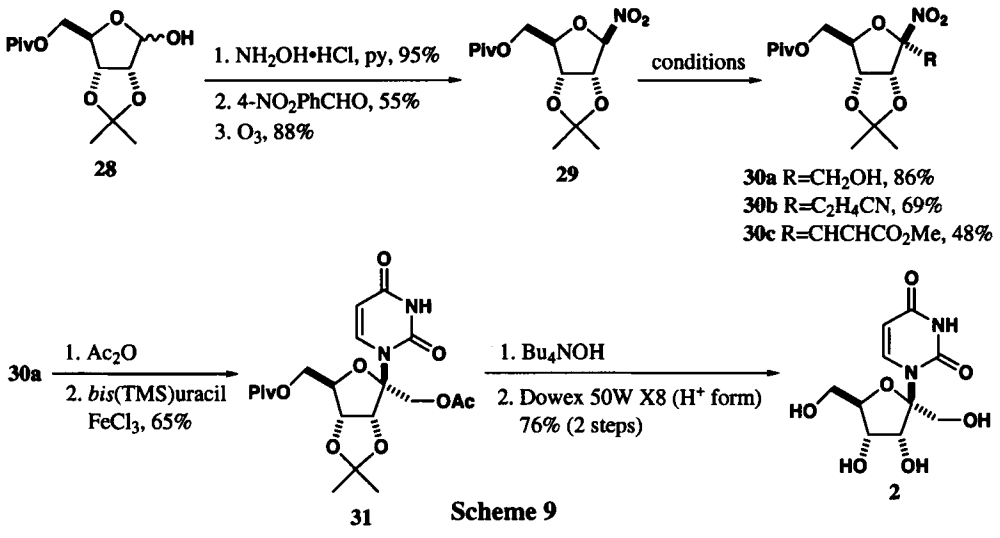


24 25 26 27

Scheme 8

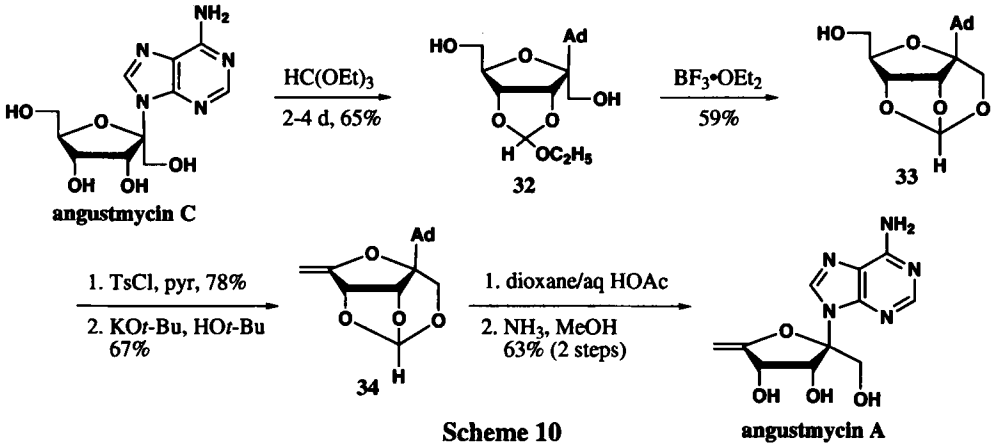
Vasella and coworkers prepared uracil derivatives of angustmycin C using the alkylation of nitronate anions to introduce the C2' substituent (*Scheme 9*).[20] 2,3-*O*-Isopropylidene-5-*O*-pivaloyl-D-ribofuranose (**28**) was converted to the corresponding oxime, which gave, without purification, the anomeric nitrones on treatment with 4-nitrobenzaldehyde. These were separable by chromatography, and the major β-anomer (β:α, 2.5:1) was oxidized with ozone to give **29**. The nitronate anion derived from **29** underwent addition to formaldehyde, acrylonitrile and

methylpropiolate, providing **30a-c**. In each case the major product was the anomer having the β-nitro group (β:α. 11:1 to 2:1). The hydroxymethyl group of **30a** was acetylated and the product reacted with *bis*(TMS)uracil. Double deprotection of the resultant uracil **31** gave *psico*-nucleoside **2**. Angustmycin C itself was prepared from **30a** by acetylation, followed by reaction with N^6-benzoyl-N^6,9-*bis*(TMS)-9*H*-adenine and subsequent deprotection.



Scheme 9

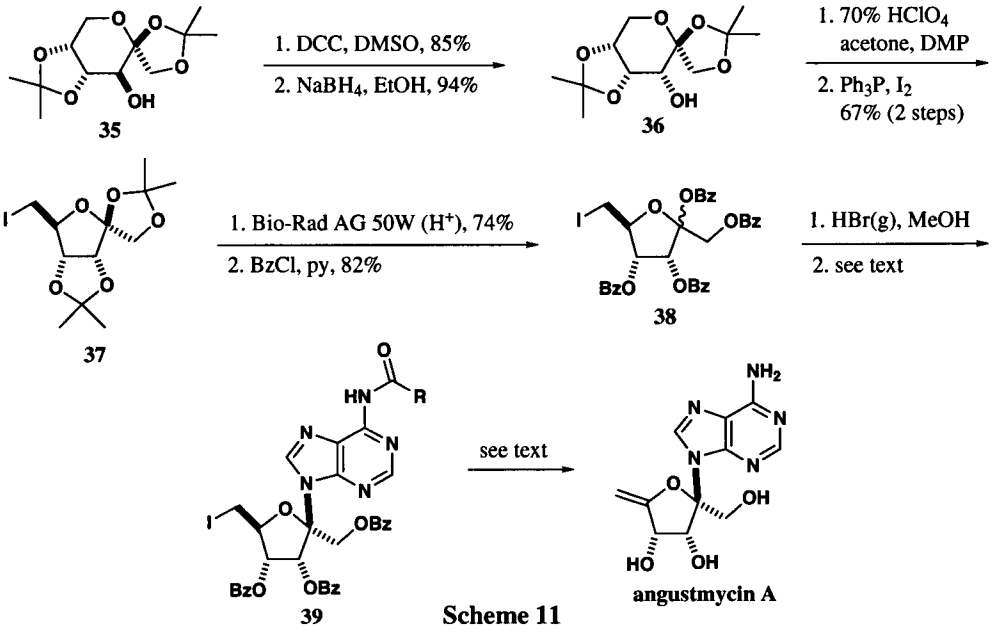
The synthesis of angustmycin A from angustmycin C was reported by McCarthy *et al.* (*Scheme 10*).[7] Treatment of angustmycin C with triethylorthoformate gave protected diol **32** in 65% yield. Conversion of this to orthoformyl tridendate **33**, achieved by treating **32** with BF_3•OEt_2, also confirmed the β-configuration at C2' in **32**. Tosylation of the free C6'-hydroxyl group, followed by elimination using KO*t*-Bu, gave **34**. Finally, hydrolysis of the orthoformyl tridendate and removal of the formyl group with ammonia in MeOH provided angustmycin A.



Scheme 10

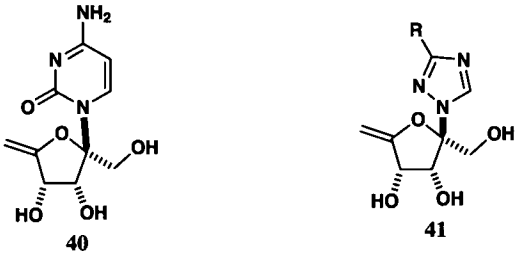
Moffatt and coworkers have also described a synthesis of angustmycin A.[17] Fructose was converted to 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**35**) in 38% yield on a scale of

over 600 g using perchloric acid and dimethoxypropane (DMP) in acetone. Although one other diisopropylidene isomer was formed concurrently, pure **35** could be isolated by recrystallization. The remaining hydroxyl group in **35** was inverted by oxidation with DCC and DMSO, followed by stereoselective reduction with sodium borohydride. The product **36** was isomerized to the furanose form with perchloric acid and DMP in acetone, and the primary hydroxyl was converted to the iodide, providing **37**. The acetonide groups were removed with an ion exchange resin, and the alcohol moieties were reprotected with base sensitive, benzoyl protecting groups to give **38** as a 2:1 mixture of anomers. The anomeric position was activated by conversion to the



Scheme 11

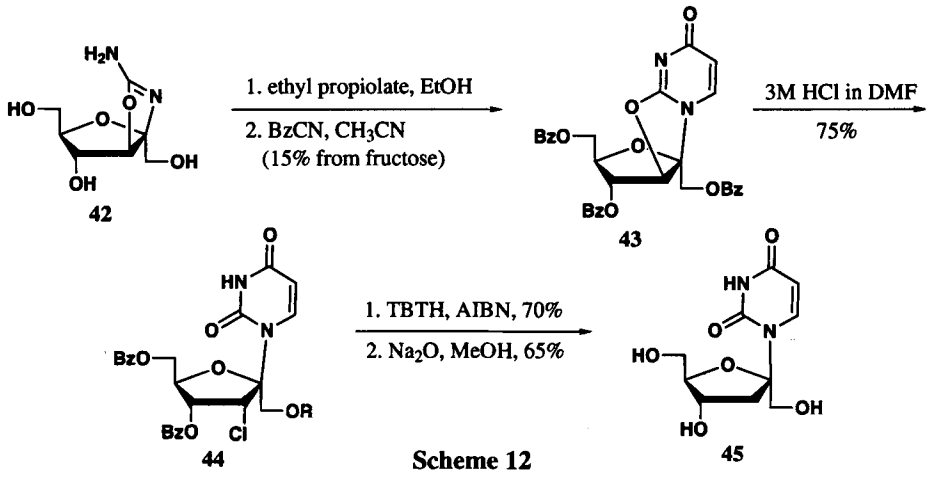
bromide, and treatment with N^6-hexanoyladenine in the presence of $SnCl_4$ and $HgCN_2$ gave mainly the β-nucleoside **39** (46%), along with some α-anomer (12%). Alternatively, reaction of **38** with the chloromercury salt of N^6-benzoyladenine resulted in the β-anomer exclusively (49%). Completion of the synthesis of angustmycin A was achieved either in two steps by elimination of HI with DBN, followed by removal of the acyl groups with ammonium hydroxide, or, more efficiently, in one step with sodium methoxide. In the same paper, cytosine analog **40**, as well as triazole *psico*-nucleosides **41**, were prepared by similar strategies.



2. 3'-Deoxy-*psico*-nucleosides

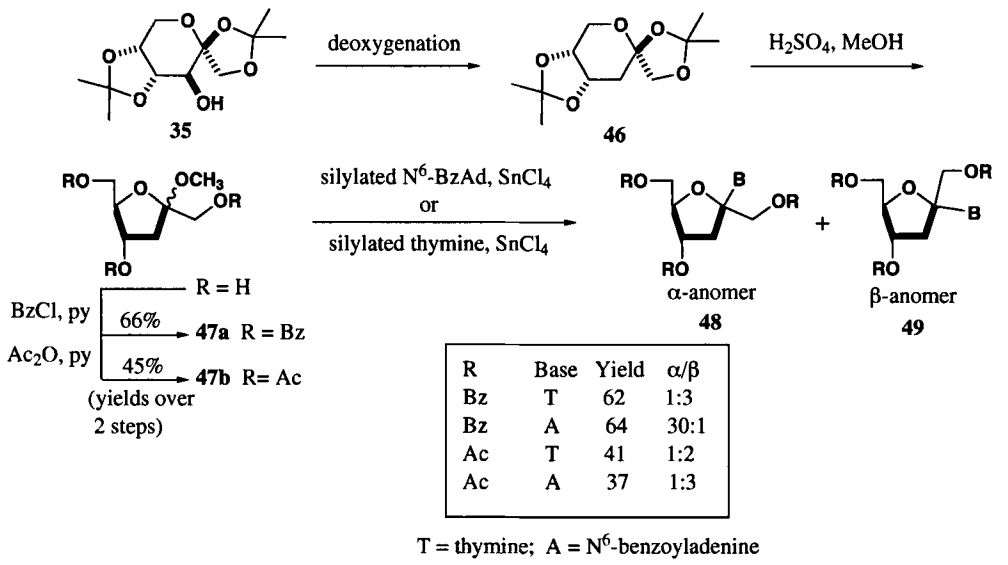
It had been postulated that 3'-deoxy-*psico*-nucleosides could be of interest because they might be more stable toward hydrolysis than angustmycin. Also, Azhayev *et al.*[21] proposed that, in addition to this greater chemical stability, these *psico*-nucleosides would retain properties similar to the biologically active 2'-deoxyribonucleosides, while including additional functionality (an anomeric hydroxymethyl group) for further modification.

Holy synthesized 1-[3'-deoxy-β-D-*psico*-furanosyl]uracil (**45**) (*Scheme 12*).[15] D-Fructose was treated with cyanamide, as described above by Tolman and Robins, to give oxazoline **42**, which could not be purified and was used immediately. Condensation with ethyl propiolate afforded the anhydronucleoside, which was converted to tri-benzoyl ester **43**. Reaction with dry HCl caused S_N2 ring opening of the ether. The resulting chloride in **44** was then removed with *tri-n*-butyltin hydride (TBTH). Deprotection gave target *psico*-nucleoside **45**, which did not inhibit the growth of *E. coli B* culture. The chloride was later removed in higher yield (92%) with $(TMS)_3SiH/AIBN$.[22]



Scheme 12

Azhayev's synthesis[21] of 3'-deoxy-*psico*-nucleoside analogs **48** and **49** began with deoxygenation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**35**) using a Barton approach to give **46**. Methanolysis to the furanose form and alcohol protection (as benzoyl or acetyl) gave methylglycosides **47a** or **b**, which were then glycosylated with silylated-thymine or -N^6-benzoyladenine under various conditions. The separable mixture of α- and β-anomers (for ratios see *Scheme 13*) was then deprotected, and their physical properties were studied. It was determined from acid-catalyzed hydrolysis experiments that 3'-deoxy-*psico*-nucleosides were less stable than 2'-deoxyribonucleosides.

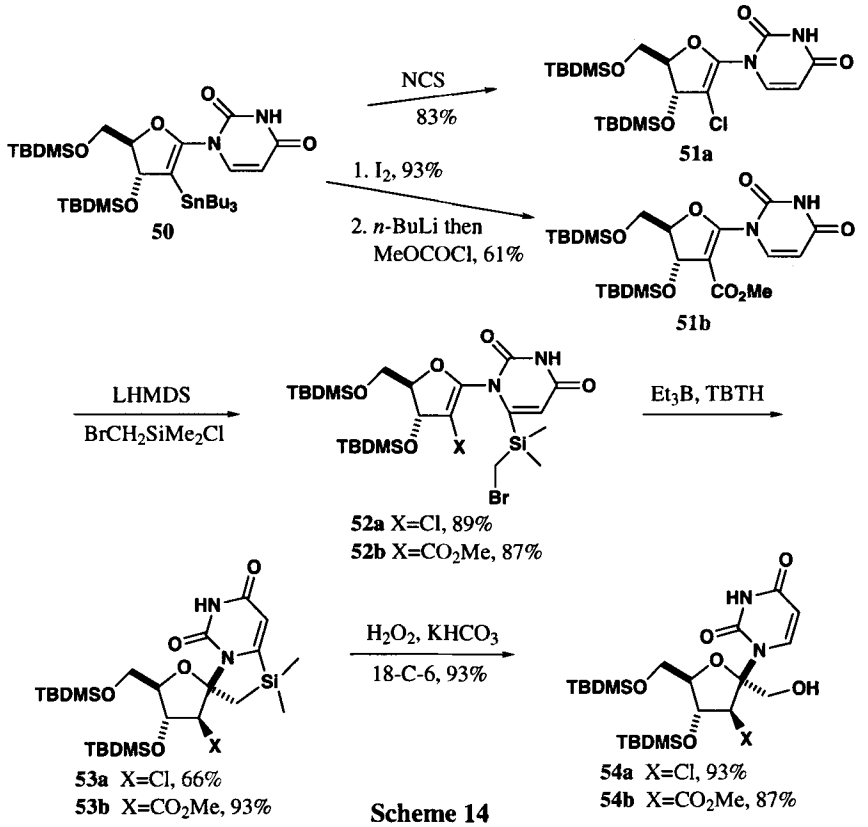


R	Base	Yield	α/β
Bz	T	62	1:3
Bz	A	64	30:1
Ac	T	41	1:2
Ac	A	37	1:3

T = thymine; A = N^6-benzoyladenine

Scheme 13

Tanaka and coworkers[23] utilized stannane **50** as a valuable intermediate for the synthesis of 3'-substituted-3'-deoxy-*psico*-nucleosides (*Scheme 14*). Treatment of the stannane

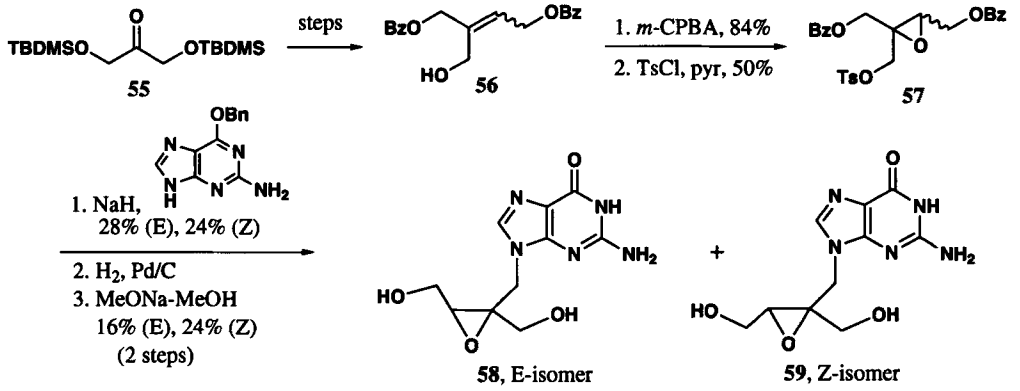


Scheme 14

with NCS gave vinyl chloride **51a**. Alternatively, reaction with iodine, followed by lithium/iodine exchange and carboxymethylation, afforded **51b**. The bromomethylsilyl group was then introduced at C6 of the uracil by treatment with LHMDS and $BrCH_2SiMe_2Cl$, providing **52a** or **52b**. Radical cyclization then gave exclusively the 5-*exo*-products **53a** or **53b**. Fleming-Tamao oxidation of these gave the protected 3-substituted 3-deoxy-*psico*-nucleosides **54a** or **54b**.

3. Epoxide-containing Analogs

Doubly protected α,α'-dihydroxyacetone **55** served as the starting point for the synthesis of epoxide-containing *psico*-nucleosides **58** and **59** (*Scheme 15*).[24] Compound **55** was converted in 4 steps to a 1:1 mixture of E/Z isomers **56**, which was epoxidized and tosylated. Coupling of the resultant **57** with a protected guanine, followed by separation and deprotection, provided analogs **58** and **59**.

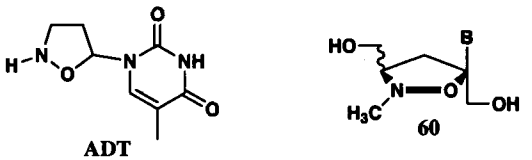


Scheme 15

In inhibition studies with HSV-1 Tomioka strain it was found that *E*-epoxide **58** was weakly active, while *Z*-**59** was inactive. It was speculated that the low activity might be due to the decomposition of the epoxide-analogs under assay conditions. It is noteworthy that analogs **58** and **59** also fall in the homo-nucleoside category (Section II.6).

4. *N,O-psico*-Nucleosides or *psico*-Isoxazolidine Nucleosides

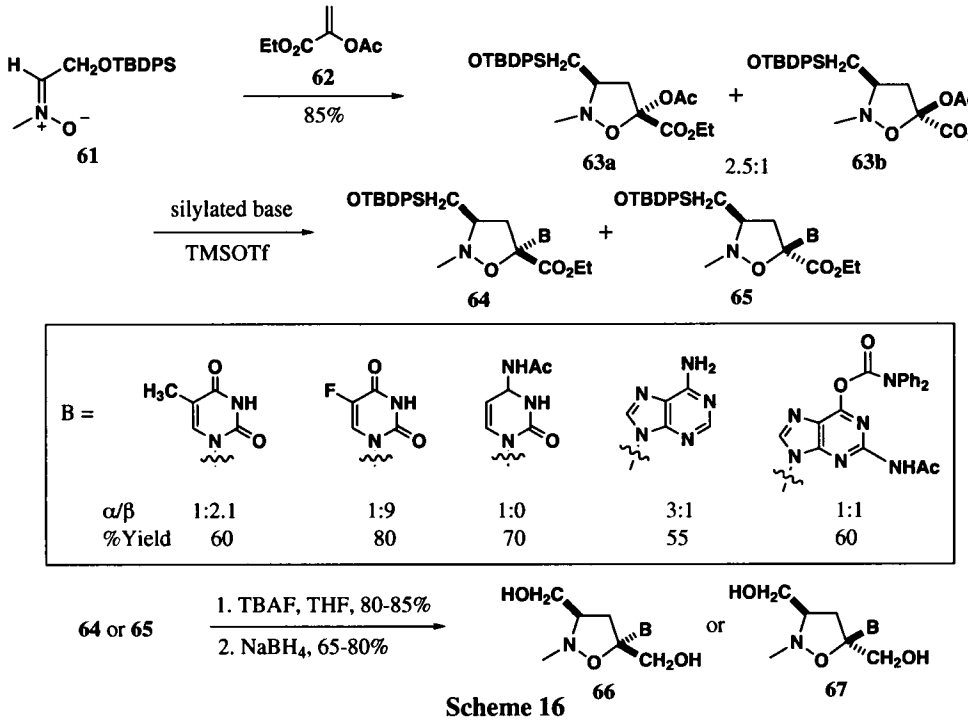
One area of focus in designing nucleoside analogs has been the replacement of the furanose in nucleosides with other heterocyclic rings. One such system has been the isoxazolidines. Interest in these systems was sparked by the discovery that analogs such as ADT showed



antiviral activity *in vitro*. Following on from this, *N,O-psico*-isoxazolidine nucleoside analogs **60** have been developed by Romeo and coworkers.

a) *Diastereoselective Synthesis*

The methodology developed for the formation of isoxazolidine-based analogs **66** and **67** centered on diastereoselective 1,3-dipolar cycloaddition reactions of *C*-α-silyloxymethyl-*N*-methyl nitrones with enol esters (*Scheme 16*). First, nitrone **61**, readily obtained from D-mannitol, was reacted with enol acetate **62** to provide separable isoxazolidines **63a** and **63b** (2.5:1) in 85% yield.[25] Lewis acid catalyzed coupling of the appropriate silylated pyrimidine or purine nucleobases with either **63a** or **63b** afforded isoxazolidinyl nucleosides **64** and **65**. The resulting α/β mixtures were separated by flash chromatography and the relative configuration determined using nOe studies. Deprotection of the pure anomers, followed by $NaBH_4$ reduction of the ester moiety, provided the desired *N,O-psico*-nucleosides **66** and **67**. This protocol offered a slight improvement over a previously published, but closely related, report from the same group.[26]

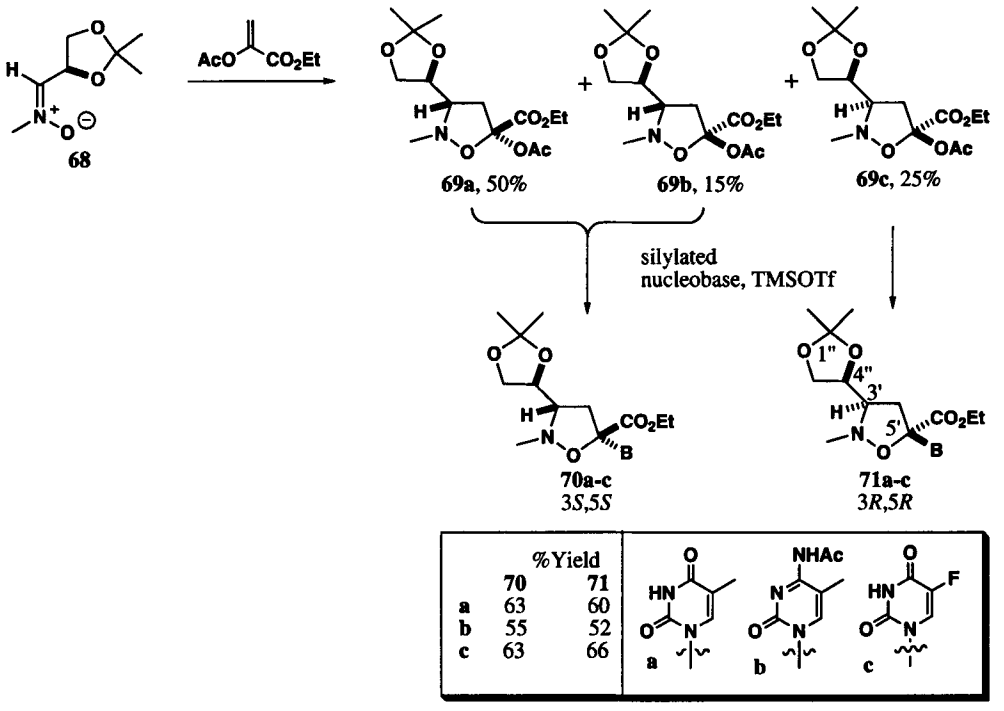


Scheme 16

b) *Enantioselective Synthesis*

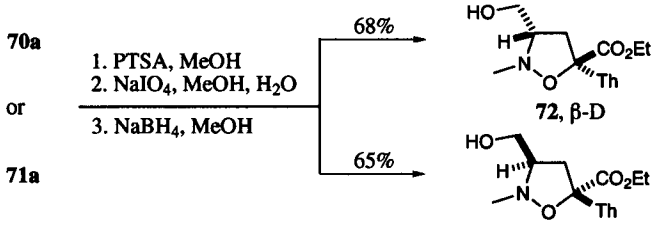
The enantioselective synthesis of *N,O-psico*-isoxazolidine nucleosides has been realized using homochiral nitrone **68**, obtained from readily available 2,3-*O*-isopropylidene-D-glyceraldehyde (*Scheme 17*).[27] The reaction proceeded in good global yield (90%) with a *cis/trans* diastere-

oselectivity of 5:1 (**69a+69c:69b**). Once separated, the stereoisomers were coupled with a series of nucleobases to give protected *psico*-nucleoside analogs **70** and **71**. It is noteworthy that the protected nucleosides were obtained exclusively as the desired *cis*-isomers. This was rationalized by temperature effects on the selectivity of the reaction.[28]



Scheme 17

Finally, deprotection and oxidative cleavage of the diols was effected, using **70a** and **71a** as examples, as shown in *Scheme 18*, to afford β-D-(**72**) and β-L-(**73**). Biological studies are reported to be underway for these compounds.

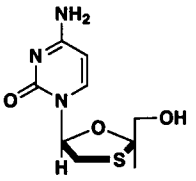


Scheme 18

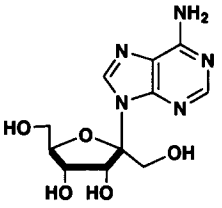
5. Thiofuranoid Glycals

Nucleoside analogs containing thiosugars have shown potent antiviral and antitumor activity.[29,30] One example is the 1,3-oxathiolane-containing anti-HIV and anti-HBV agent, 2',3'-

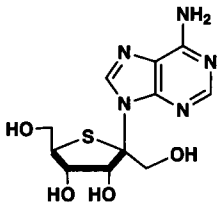
dideoxy-3'-thiacytidine (3TC). Interest in sulfur-containing *psico*-nucleosides can also be seen, as evidenced by the synthesis of 5'-thioangustmycin C.[31]



3TC

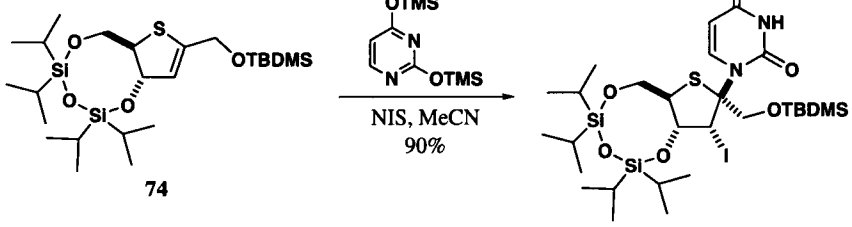


angustmycin C



4'-thioangustmycin C

Haraguchi *et al.* reported the synthesis of sulfur-containing *psico*-nucleosides derived from 4,5-dihydrothiofuran **74**.[31] Thus, NIS promoted glycosidation of **74** gave exclusively the β-anomer **75** in high yield (*Scheme 19*). It had previously been determined on similar substrates that the α,β selectivity can be directed by the silyl protecting groups at the 4'- and 6'-positions.[32] Either the TIPDS-(tetraisopropyldisiloxane-1,3-diyl) or the DTBS-(di-*t*-butylsilylene) group provided the β-anomer with high selectivity in good yield. Unfortunately, the NIS mediated glycosylation of other substrates provided lower yields and undesired byproducts, which led to the investigation of alternative methods.

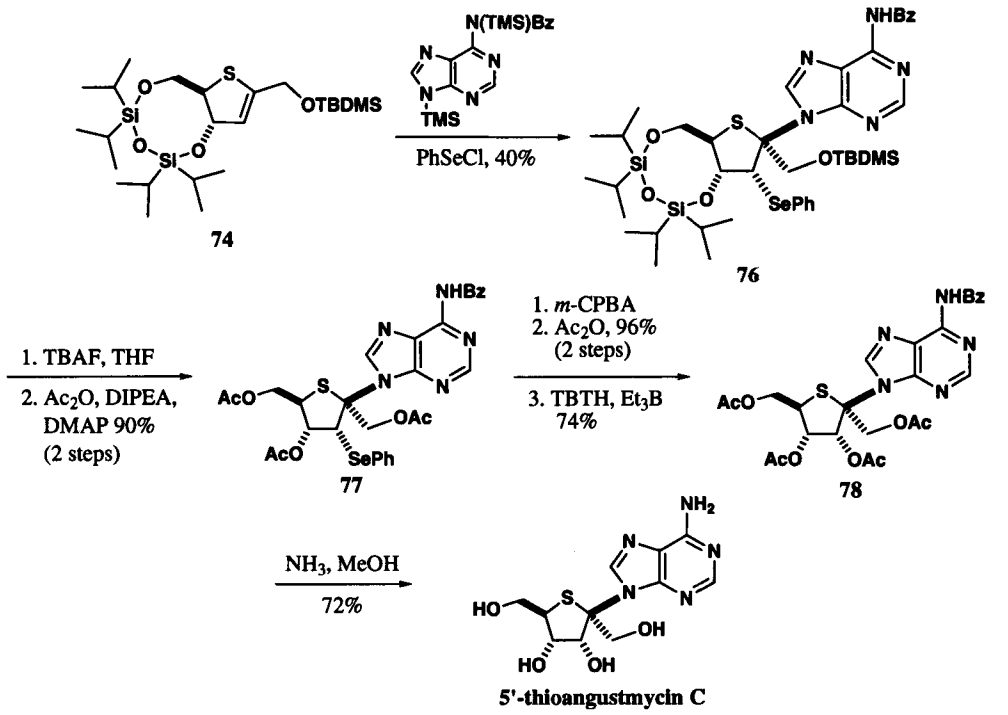


74

Scheme 19

75

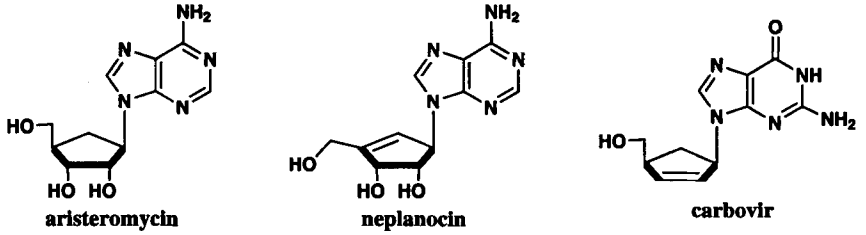
The synthesis of a 5'-thioangustmycin C was next examined with PhSeCl as the electrophile (*Scheme 20*).[31] The coupling of **74** with *bis*(TMS)-N^6-benzoyladenine produced only the β-anomer **76** in 40% yield. Silyl group deprotection and acetylation proceeded in good yields to give **77**. Oxidation and seleno-Pummerer reaction of **77** gave the α-selenoacetate as a mixture of isomers. The stereoselectivity of the subsequent radical selenide cleavage was highly dependent on temperature and the best results (74% plus 8% C3' epimer) were obtained at –70°C. Global deprotection of **78** gave 5'-thioangustmycin C. Other silylated bases (thymine, cytosine) also participated in the seleno-glycosylation strategy to give a range of thio-*psico*-nucleosides.[32]



Scheme 20

6. Carbocyclic Nucleosides

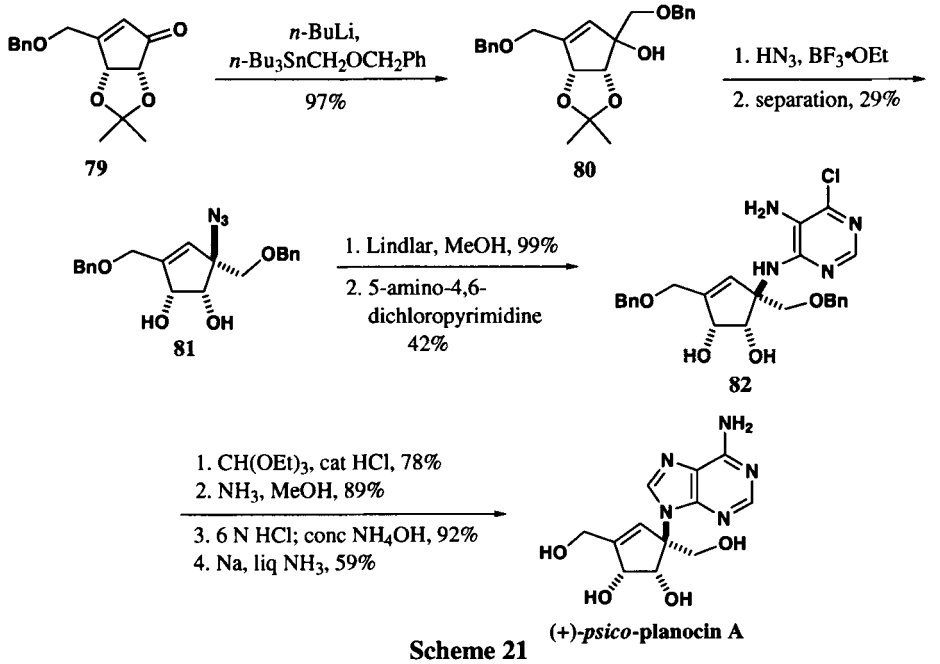
Carbocyclic nucleosides, a category in which the furanyl oxygen has been replaced by a carbon atom, are important nucleoside analogs as they can retain biological activity but are more stable to acid or enzymatic degradation. Examples of bioactive carbocyclic nucleosides include aristeromycin,[33] neplanocin[34] and carbovir.[35]



a) *psico-Planocin A*

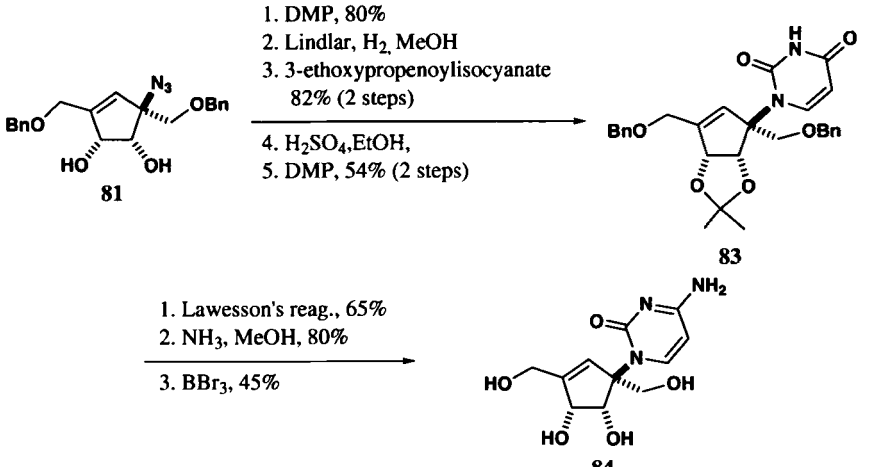
The antitumor antibiotic neplanocin A has an alkene which flattens the ribose ring in a manner similar to that found in angustmycin A. Combining this feature with the C2'-hydroxymethyl group of angustmycin C led to the target *psico*-planocin A, which mimics the structure of both. Marquez's synthesis of (+/-)-*psico*-planocin A started from racemic cyclopentenone **79** (*Scheme 21*).[36] 1,2-Addition of benzyloxymethylithium produced alcohol **80**. Subsequent reac-

tion with hydrazoic acid gave a partially deprotected tertiary azide in which the undesired α-azide predominated (β:α, 2:3). Chromatographic separation of the isomers provided β-azide **81**, which was then reduced to the amine. Condensation with 5-amino-4,6-dichloropyrimidine under forcing conditions (140°C, 2.5 d) provided pyrimidine-containing *psico*-nucleoside **82**. Ring closing, ammonolysis and two step removal of the protecting groups afforded *psico*-planocin A.



Scheme 21

Cytosine analog **84** was prepared in a similar manner from azide **81** (*Scheme* 22).[37]



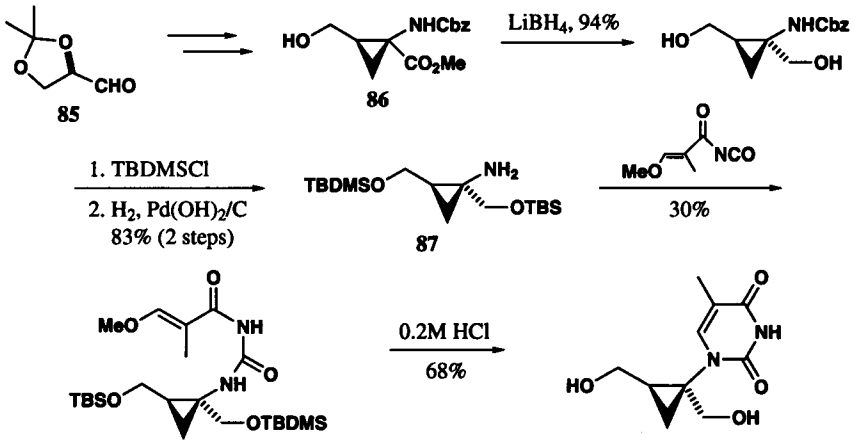
Scheme 22

In this case protection of the diol preceded reduction of the azide to the amine, which was condensed with 3-ethoxypropenoylisocyanate. Cyclization to the uracil under basic condi-

tions failed, and, so, following acid catalyzed cyclization, the diol had to be reprotected, providing **83**. Conversion of the uracil to cytosine was achieved using Lawesson's reagent, followed by ammonia. Final cleavage of the acetonide and benzyl groups gave desired nucleoside analog **84**. Biological studies on both *psico*-planocin A and **84** revealed no *in vitro* cytotoxicity to Molt 4 cells.[38]

b) Cyclopropyl psico-Nucleosides

With the identification of **160**[24] as a potent antiviral compound (*vide infra*), the synthesis of cyclopropyl *psico*-nucleoside **88** was targeted. The synthesis of **88**[39] commenced with homochiral cyclopropylaminoester **86**, obtained from D-glyceraldehyde (**85**) as described by Ortuno and coworkers.[40] Reduction of the ester, protection of the diol and deprotection of the amine gave **87**. Thymine target **88** was obtained from the condensation of **87** with 3-methoxy-2-methacryloyl isocyanate, prepared *in situ*, followed by simultaneous deprotection and acid catalyzed cyclization (*Scheme 23*).

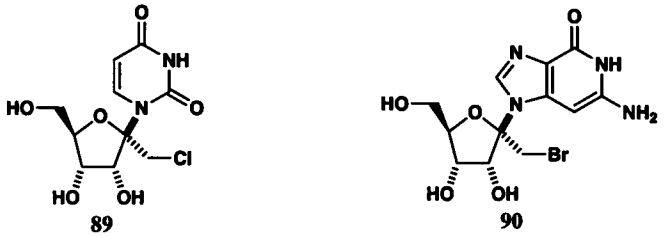


Scheme 23

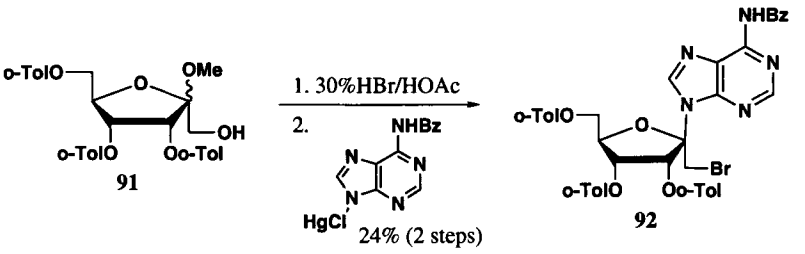
II OTHER C1'-BRANCHED NUCLEOSIDES

1. C1'-Halomethyl Analogs

The most direct synthesis of C1'-halomethyl-*psico*-nucleosides involves the direct halogenation of angustmycin C derivatives. In fact, long before the biological potential of this modification was probed, several groups had prepared C1'-halomethyl-*psico*-nucleosides. Examples included uracil-containing derivative **89**,[10] the guanine derivative **90**[11] and protected



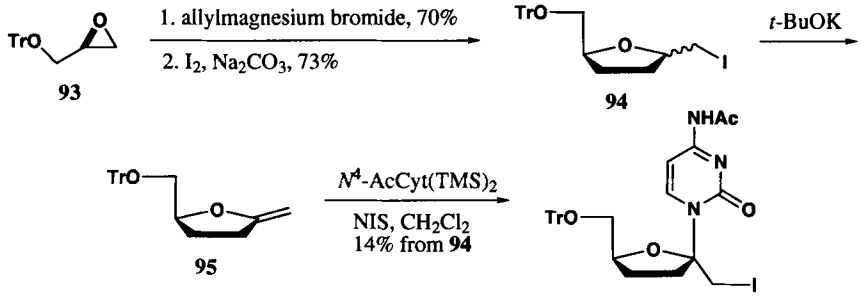
adenine **92** (*Scheme 24*), prepared from alcohol **91** *via* the C1',C2'-dibromide.[41] The primary purpose for these compounds was the synthesis of C1'-alkyl derivatives (Section II.5) by radical dehalogenation.



Scheme 24

2',3'-Dideoxynucleosides such as ddC and d4T have had a powerful impact due to their effectiveness in the treatment of HIV. Combining this feature with the C2'-branching found in angustmycin gives 3',4'-dideoxy-*psico*-nucleosides. *e. g.* C1'-halomethyl ddC, which have attracted some interest.

The syntheses of iodomethyl **96** and fluoromethyl **98** ddC analogs are shown in *Schemes 25* and *26*.[42] Ring opening of trityl-protected *R*-glycidol (**93**) with allylmagnesium bromide followed by direct cyclization *via* iodoetherification gave **94** as a 1:1 mixture of diastereoisomers (*Scheme 25*). Elimination with KO*t*-Bu provided unstable *exo*-methylenetetrahydrofuran **95**. N-Glycosylation with silylated N^4-acetylcytosine using NIS gave a low yield

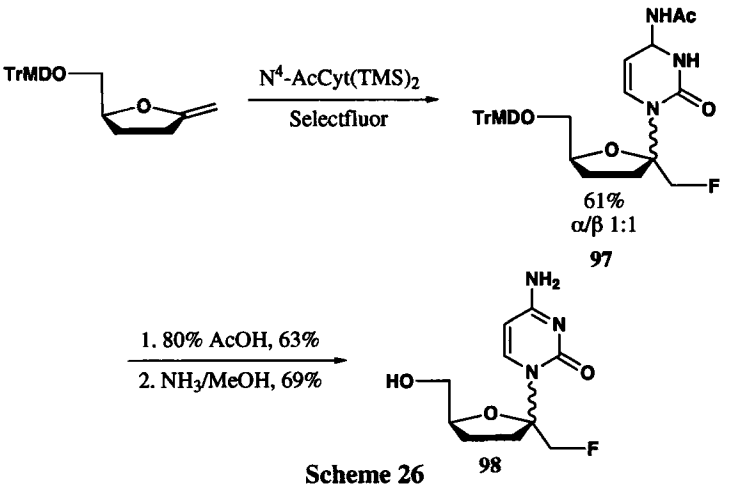


Scheme 25

of the unstable β-anomer **96**. Due to the low efficiency of this reaction and the instability of the products, activation with fluoride instead of iodide was attempted. This approach was successful

for the fluoromethyl analog of **96**, but removal of the trityl group was not possible without hydrolysis of the glycoside bond. Consequently, a switch to the more labile dimethoxytrityl (DMTr) group was made.

The mild electrophilic fluorinating reagent, selectfluor, and silylated N^4-acetylcytosine provided an inseparable mixture of α/β anomers (1:1) **97**. Final DMTr and acetyl deprotections lead to **98**, also as an inseparable mixture.

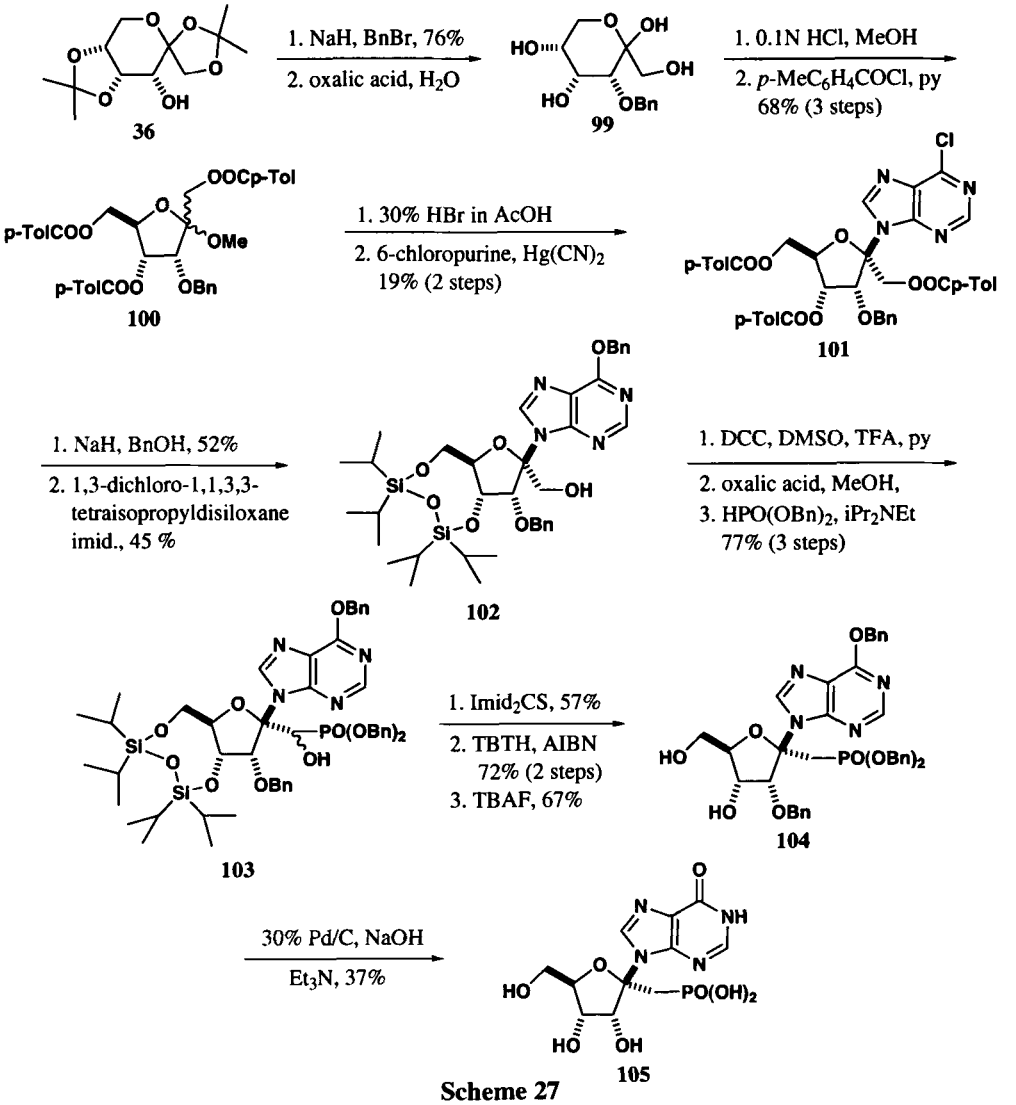


Scheme 26

2. C1'-Phosphorus Substituted Analogs

The guanine *psico*-furanose phosphate **105** was designed as an inhibitor of purine nucleoside phosphorylase (PNP), an enzyme involved in regulation of T-cell populations and, hence, a potential target for therapy for autoimmune diseases. An inhibitor of PNP could also potentiate the cytotoxicity of antitumor agents by inhibiting their degradation by the enzyme. The synthesis of **105** is shown in *Scheme* 27.[43] 1,2:4,5-Diisopropylidene-β-D-psicopyranose (**36**), available in three steps from δ-fructose, was benzylated at the remaining hydroxyl group and the protecting groups hydrolyzed to give **99**. Anomeric methylation (α:β, 1:1) was followed by acylation with *p*-toluoylchloride to give **100**. Activation of the sugar at the anomeric position by bromination was followed by coupling with 6-chloropurine in the presence of $Hg(CN)_2$ to give a separable mixture of the anomers (α:β, 1:1 total yield 38% from methoxide **100**). Simultaneous chloride displacement and partial deprotection of the pure β-anomer **101** using sodium hydride in benzyl alcohol, followed by reprotection at C4 and C6, gave **102**. Oxidation of the remaining alcohol to the aldehyde, isolated as the hemiacetal, was followed by reaction with dibenzyl phosphite to give **103**. The two isomers were separable and isolated in 47% (less polar) and 30% (more polar) yield over the three steps, which were carried out without purification of the intermediates. The major isomer was deoxygenated under radical conditions and the silyl protecting group removed to give **104**. Final debenzylation was complicated by the instability of the

product to the free phosphonic acid groups, but in the presence of triethylamine and sodium hydroxide **105** was isolated in 37% yield. Although **105** was weakly active in the assay of PNP inhibition, this was attributed to the formation of its degradation product hypoxanthine, which is also an inhibitor of PNP.

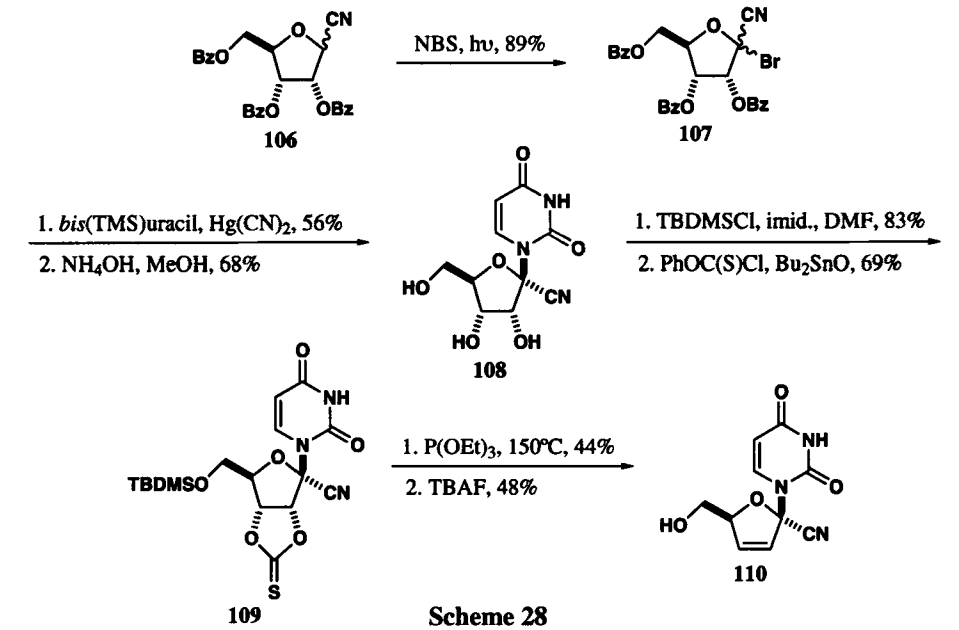


Scheme 27

3. C1'-Cyano Analogs

There has been considerable interest in the preparation of *psico*-nucleosides having electron withdrawing groups (EWG) at the anomeric position. The rationale for this is that the

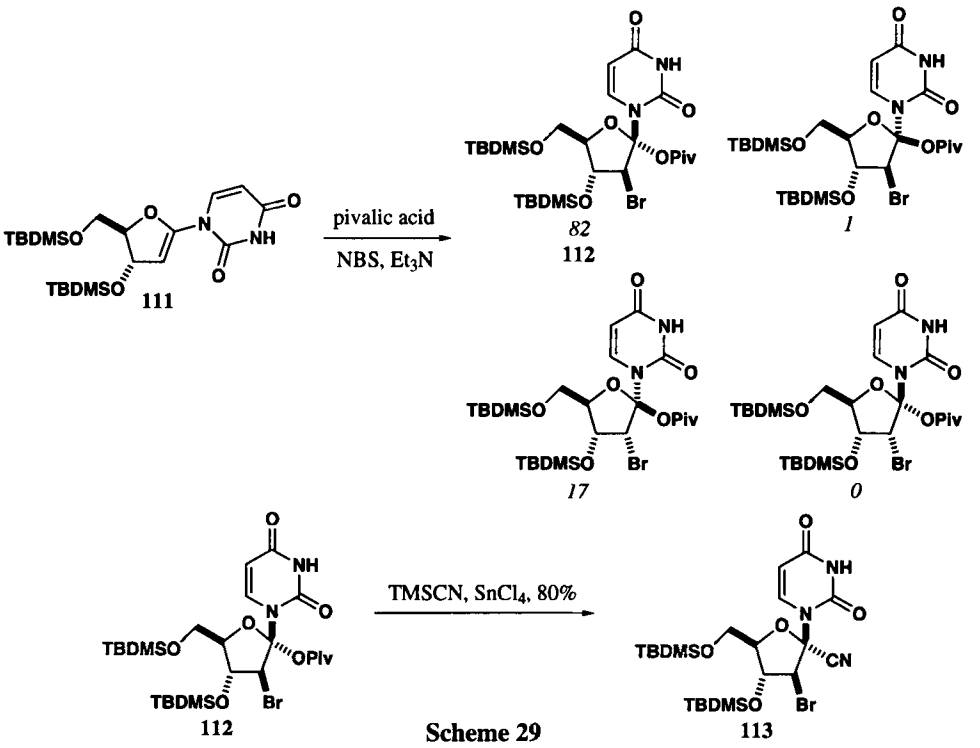
ion formed by solvolysis of the base would be destabilized by the presence of an EWG and hence the *psico*-nucleoside would possess enhanced stability. If the EWG had low steric bulk then bioactivity should be retained. One series of compounds that appeared to fit these criteria was the 1'-cyanonucleosides, such as **108** and **110**,[44] the latter a *psico*-nucleoside analog of d4T. These which were prepared as shown in *Scheme 28*. Photochemical free radical bromination of known cyanide **106** provided **107** as a mixture of anomers. Stereoselective introduction of the base from the β-face and deprotection gave **108**. Protection of the primary alcohol and deoxygenation *via* the cyclic thionocarbonate **109**, afforded **110** after deprotection. Although both cyano-*psico*-furanosides **108** and **110** had prolonged stability at various pH's, they were inactive in assays of HIV inhibition.



106 **107** **108** **109** **110**

Scheme 28

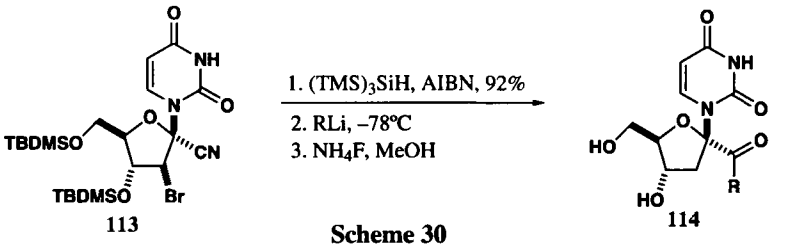
Cyano-*psico*-nucleosides have also been prepared by a method that appears to be sufficiently flexible to incorporate other groups at a later stage. In two papers from the same group, Tanaka and coworkers used the unsaturated sugar **111** (*Scheme 29*).[45] Electrophilic bromoacylation gave up to four compounds, depending on the facial selectivity of the electrophilic addition and the *syn* to *anti* ratio of the subsequent nucleophilic attack. The best yield was obtained with pivalic acid and NBS in diethyl ether, providing a 4.6:1 β:α selectivity and a *syn*:*anti* ratio of 99:1. The desired product **112** was separated easily from this mixture by chromatography and recrystallization in 55% yield. Treatment of **112** with TMSCN gave the C1'-cyanide **113** in 80% yield.



Scheme 29

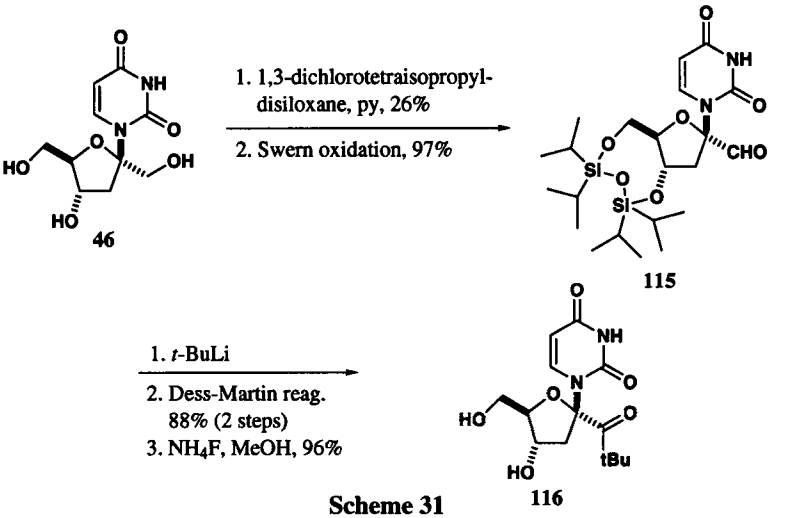
4. C1'-Keto- and Hydroxyalkyl(aryl) Analogs

Keto-substituted *psico*-nucleosides have attracted interest because they can be used in generating anomeric radicals, which are useful in studying the mechanism of oxidative damage in DNA.[46] Cyanides are susceptible to nucleophilic addition, and this has been exploited as a direct route to keto-*psico*-nucleosides, as exemplified by two papers by Chatgilialoglu *et al.*[22,47] Radical debromination of **113**, prepared as shown above, with tris(trimethylsilyl)silane and AIBN, followed by addition of an alkyl lithium reagent and deprotection, afforded **114** (*Scheme 30*).



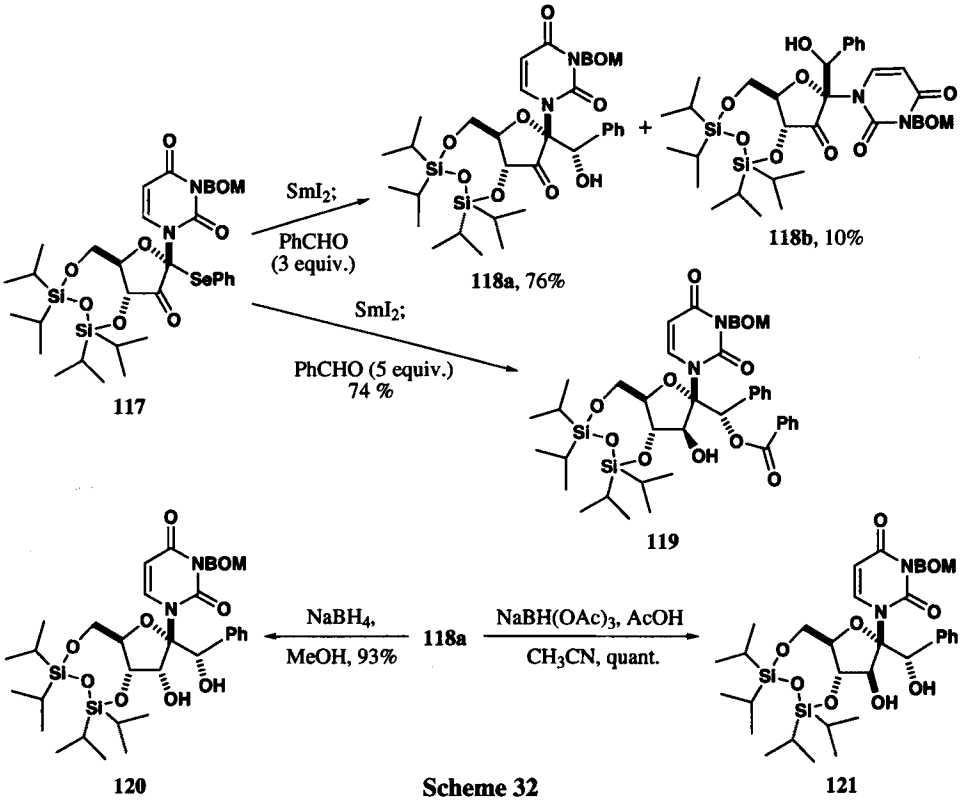
Scheme 30

An earlier publication had reported the preparation of similar ketones, as illustrated in *Scheme 31*.[48] Protection of known C3'-deoxypsicofuranose **45** as the disiloxane proceeded in low yield, but subsequent oxidation under Swern conditions was almost quantitative. Aldehyde **115** was treated immediately with *t*-butyllithium to give an unstable mixture of secondary alcohols, which was oxidized to the corresponding ketone with the Dess-Martin periodinane. Final deprotection gave **116**.



Scheme 31

Shuto, Matsuda and coworkers have developed a samarium promoted aldol reaction for the preparation of C1'-phenyl-substituted *psico*-nucleosides.[49] The benzyloxymethyl (BOM) protected nucleoside **117** was treated with SmI_2, providing a samarium enolate, which reacted with benzaldehyde to give **118a** and **118b** in 76% and 10% yield, respectively (*Scheme 32*). The

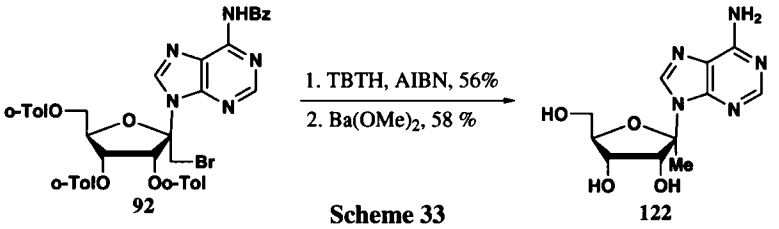


Scheme 32

absolute stereochemistry at the newly formed secondary alcohol was almost exclusively *S*. Acetaldehyde and isobutyraldehyde also reacted, although the distribution of products varied with the aldehyde and the stoichiometry. For example, with a greater excess of benzaldehyde, the aldol-Tishchenko product **119**, having the *arabino* configuration, was formed in 74% yield. Reduction of ketone **118a** could be achieved with excellent stereoselectivity, and epimeric alcohols **120** and **121** were prepared. In this same publication the uracil analog **2** of angustmycin C was prepared by the condensation of **117** with formaldehyde, followed by reduction with $NaBH_4$ and deprotection.

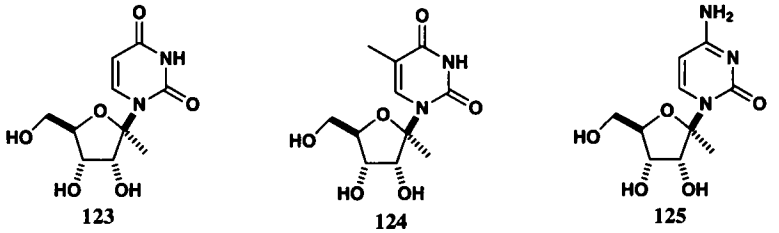
5. C1'-Alkylated Analogs

A typical approach to the preparation of simple C1'-methyl-*psico*-nucleosides has involved the reduction of C1'-halomethyl compounds (see Section II.1). This is illustrated by the preparation of C1'-deoxyangustmycin C **122** (*Scheme* 33).[41] Previously described C1'-bromomethyl-*psico*-nucleoside **92** (*Scheme* 24) was subjected to a radical reduction with TBTH and AIBN, followed by global deprotection with barium methoxide, to give **122**. This showed no growth inhibition of *E. coli*.



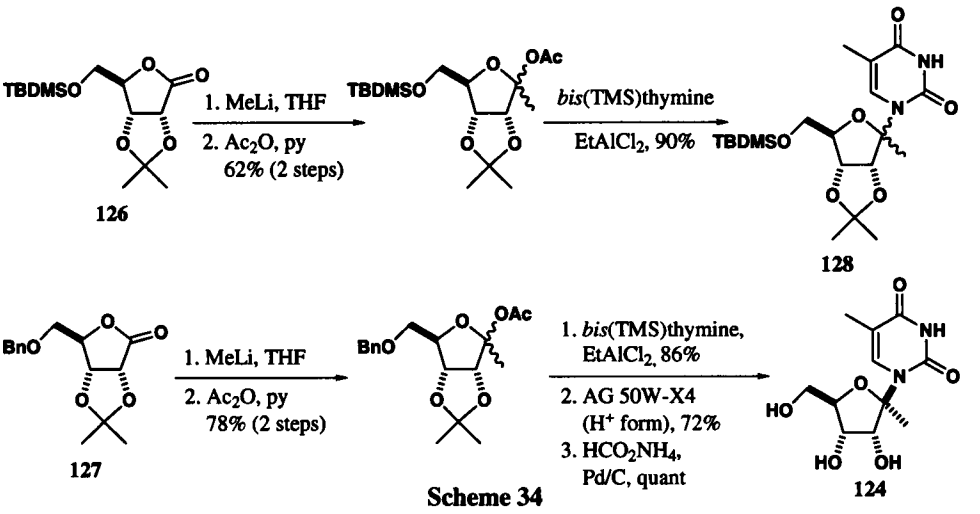
92 **Scheme 33** 122

The simple anomeric C1'-deoxy uracil **123**, thymine **124** and cytosine **125** *psico*-nucleosides were also prepared by reduction of halomethyl derivatives.[50]



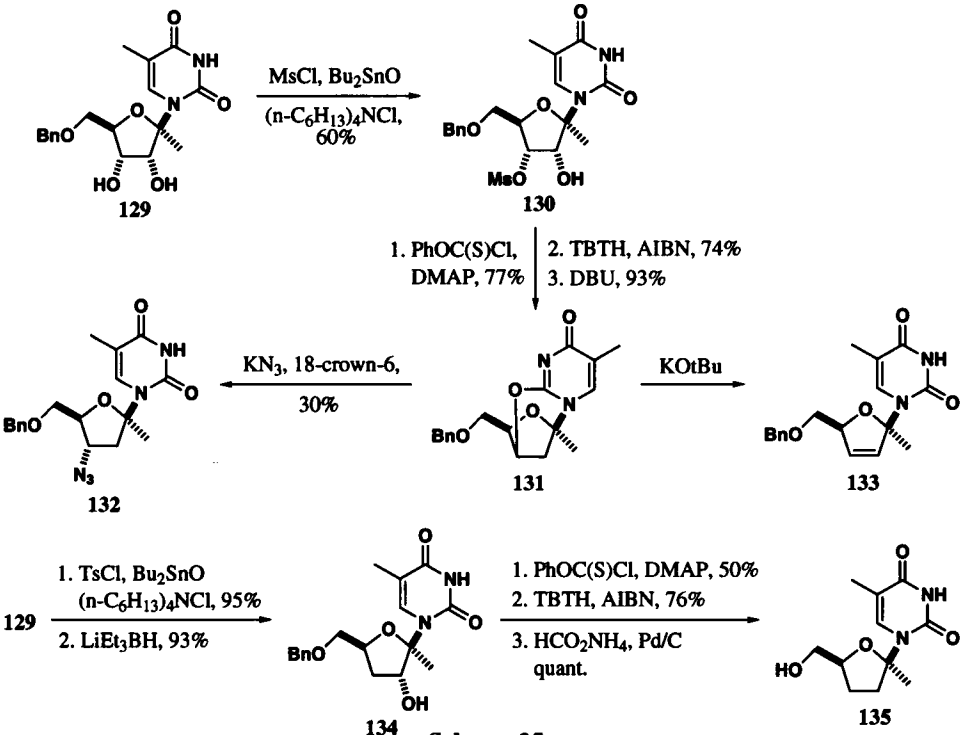
123 124 125

In an improved preparation of the thymine C1'-deoxy-*psico*-furanose **124**, Grouiller and coworkers used TBDMS **126** or Bn **127** protected isopropylidene-D-ribonolactone as the starting material (*Scheme 34*).[51] Addition of methyllithium to **126** gave the hemiketal, which was directly acetylated to give a single anomer (anomeric stereochemistry not specified). Reaction of this with *bis*(TMS)thymine using $EtAlCl_2$ as the Lewis acid gave an inseparable mixture of anomers **128** in 90% yield in which the β-anomer was preferred (3:1). Better results were obtained with Bn derivative **127**, which gave a 9:1 preference for the desired β-anomer in similar yield. Following deprotection of the acetonide, the two anomers were separated, and transfer hydrogenation with HCO_2NH_4 gave target *psico*-nucleoside **124** in 49% overall yield.



Scheme 34

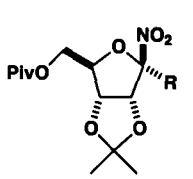
One of the intermediates (not shown) in the above approach was used in the preparation of C1',C3',C4'-trideoxy-*psico*-nucleosides **132**, **133** and **135**, analogs of the biologically important nucleosides AZT, d4T and 3'-deoxythymidine.[52] Thus, **129**, when treated with MsCl and dibutyltin oxide in the presence of a phase transfer catalyst, unexpectedly gave the C4'-mesylate **130** (*Scheme 35*). This was deoxygenated at C3' *via* the thionocarbonate and converted to cyclic



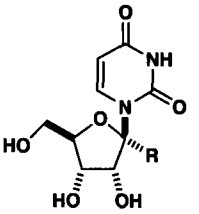
Scheme 35

anhydride **131**. The inversion at C4' was completed by ring opening with azide to give **132**. Alternatively, elimination with KOtBu gave alkene **133**. The instability of the glycoside bond in **132** and **133** meant that neither of these compounds could be successfully deprotected. The final compound in this series, **135**, was also prepared from **129**. C4'-deoxygenation was accomplished *via* a tosylate, which was reduced with lithium triethylborohydride. The C2'-hydroxy of the resultant **134** was removed *via* the thiocarbonate, and reductive cleavage of the benzyl group provided **135**.

Nitrile **136** and unsaturated ester **137** were prepared from the corresponding nitrosugars **30b** and **30c**, respectively, by a similar route to that outlined earlier (*Scheme* 9).[20]

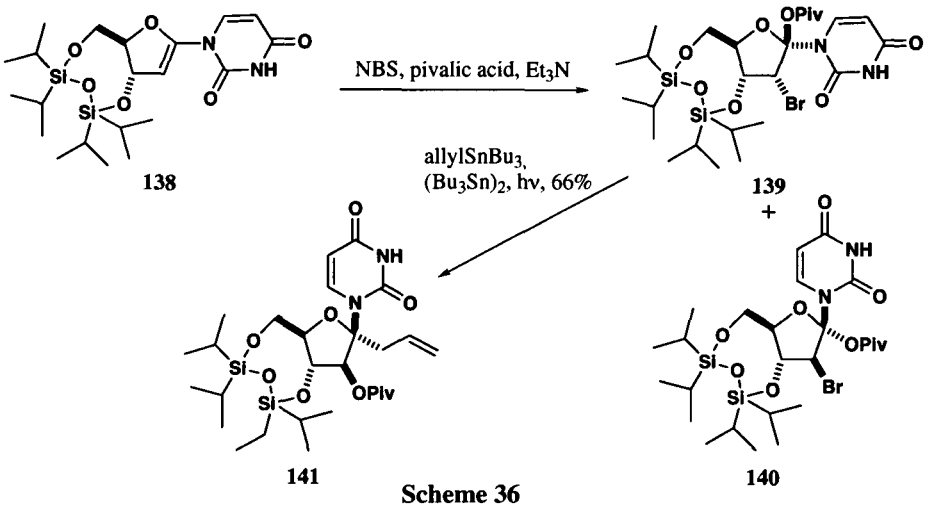


30b R=CHCHCN
30c R=CHCHCO$_2$Me



136 R=CHCHCN
137 R=CHCHCO$_2$Me

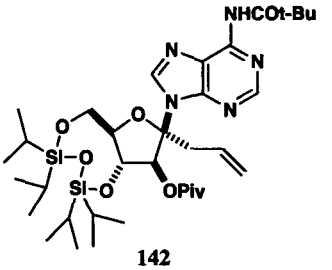
Tanaka, Haraguchi and coworkers have developed several conceptually elegant methods for the synthesis of alkylated-*psico*-nucleosides (*Scheme 36*). Following on from their



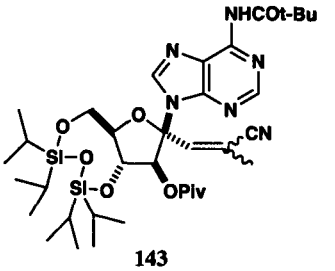
Scheme 36

work on the bromopivalation of TBDMS glycals described earlier (Section II.3), treatment of **138** under the same conditions (*Scheme 29*)[53] gave a separable mixture of **139** and **140** in 52 and 26% yields. respectively. Thus, the nature of the protecting groups has a clear effect on the outcome of the reaction. Allylation of **139** with photochemical initiation gave **141** in 66% yield. The mechanism involves radical generation *via* C-Br bond homolysis, then a 1,2-acyloxy migration, followed by trapping of the anomeric radical. This procedure also worked with adenine

derivatives to give, for example, **142** and with other alkenes, such as 3-bromo-2-methylacrylonitrile, which provided **143**.

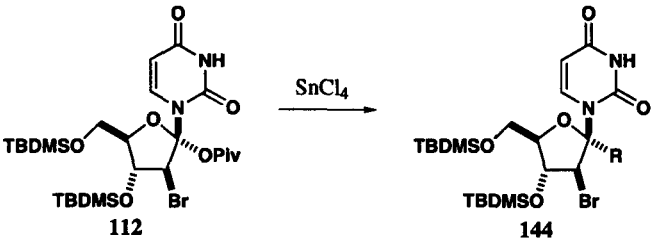


142



143

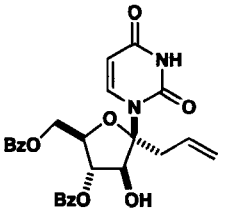
In an earlier paper, straightforward substitution of a C1'-pivalate had been achieved under Lewis acid catalyzed conditions.[45] This approach was previously shown in the conversion of pivalate **112** to the C1'-cyano derivative **113** (*Scheme 29*). Examples of the Lewis acid catalyzed reaction of **112** to incorporate other carbon-based nucleophiles are provided in Table 1.[45,54] The residual bromide in products **144** was used for further elaboration, as exemplified by the syntheses of *arabino* sugar **145** and the deoxy derivative **146**.



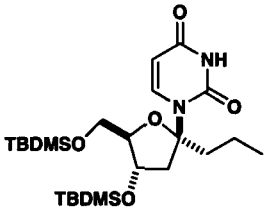
112 **144**

Table 1. Reaction of anomeric pivalates with carbon-based nucleophiles

Reagent	R	Yield (%)
allyltrimethylsilane	allyl	65
$PhC(OTMS)CH_2$	CH_2COPh	69
$CH_3C(OTMS)CH_2$	CH_2COCH_3	30
Me_3Al	Me	73
TMSCCAlEtCl	CCTMS	76



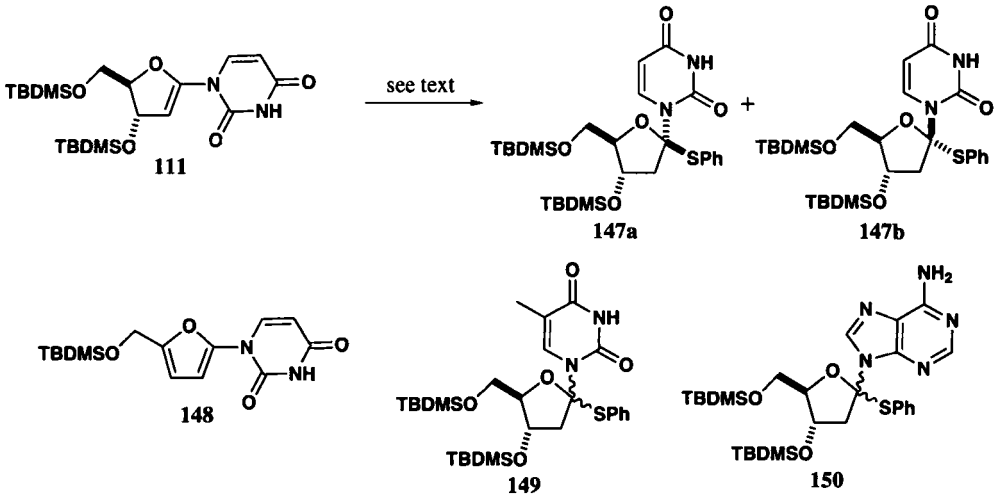
145



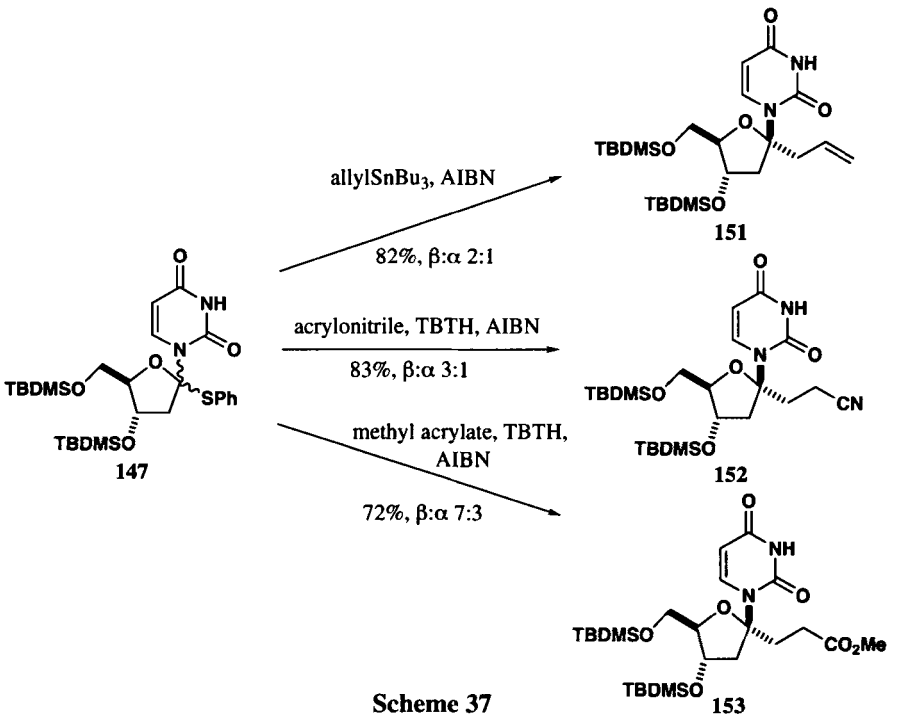
146

In another paper from the same group, the direct generation of an anomeric radical was achieved by C-S bond homolysis.[55] Starting from uracil derivative **111**, addition of thiophenol to give a mixture of anomers **147a** and **147b** (3:1) was complicated by competing formation of the

corresponding furan **148**. The addition of triethylamine to the reaction mixture, however, overcame this problem and gave the same products in 94% yield in a 1:5.7 ratio. The C1'-thiophenoxy-thymine **149** and -adenine **150** intermediates were prepared in the same way.



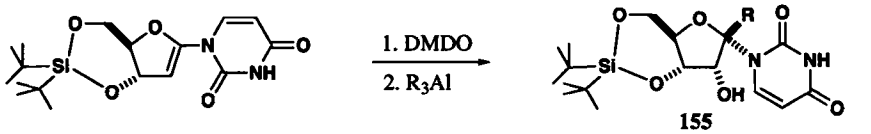
The mixture of anomers **147a** and **147b** underwent radical allylation under a variety of conditions to give predominantly the β-anomer **151** (β:α, 2:1 to 3:1) with the best yields (82%, β:α, 2:1) obtained with allyltributyl tin and AIBN (*Scheme 37*). Selective β-allylation was also



Scheme 37

observed for **149** and **150**. The anomeric radical from **147** also underwent addition to acrylonitrile and methyl acrylate to give β-anomers **152** and **153**, respectively, with modest selectivity (2:1 to 3:1). Careful control of the reaction conditions was required to limit the formation of unwanted spirocyclic products (see Section IV.2, *Scheme 92*).

Another approach to C1'-alkylated nucleosides used epoxidation of a glycal with dimethyldioxirane (DMDO) as a key step,[56] to give exclusively the α-epoxide which was not isolated but proved fairly stable in $CDCl_3$. Ring opening with excess (3 equiv.) organoaluminum reagents, gave *psico*-nucleosides **155** with the β-anomer predominating (*Fig. 1*).



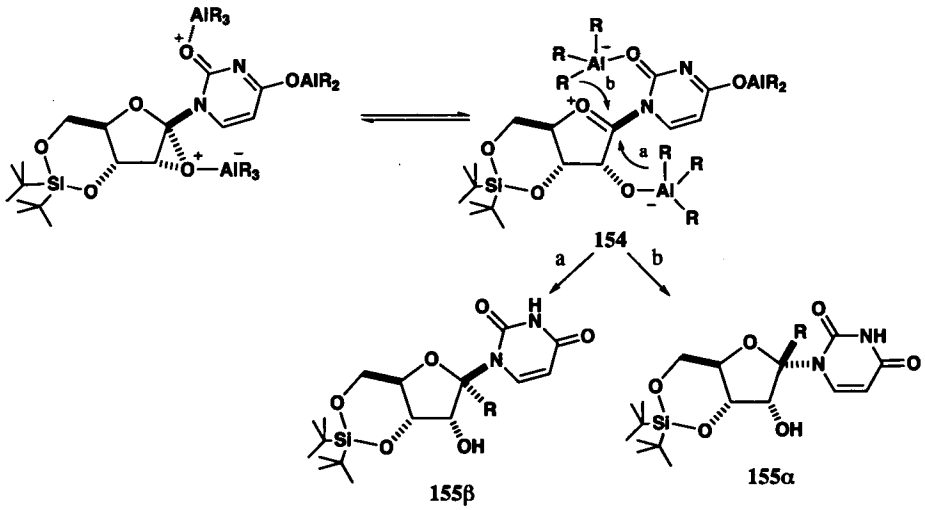
155

R_3Al	%Yield	β/α
Me_3Al	86	5/1
Et_3Al	90	4/1
i-Bu_3Al	35	9/1
$(H_2C{=}CH)_3Al$	90	32/1

C1'-Branched Nucleosides 155 *via* Ring Opening with Organoaluminum Reagents

Fig 1

It was proposed that, after initial coordination of R_3Al and oxonium ion **154** formation, two modes of nucleophilic addition were possible. Attack *via* the C2'-*O*-aluminate (pathway a, *Fig. 2*) would produce **155**β-only, while both **155**α and **155**β could arise from the attack of the pyrimidine-linked nucleophile (pathway b), depending on the rotation of the ribose-base bond.

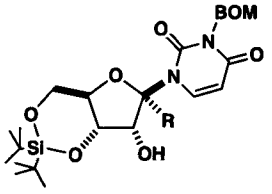


Modes for Nucleophilic Addition of Organoaluminum Reagents to 154

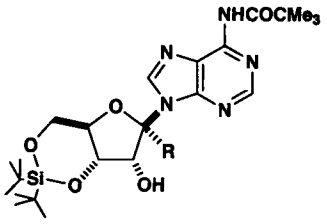
Fig 2

Measures were taken to block pathway b, directing formation to the desired β-anomer

exclusively. Accordingly, the N^3-position of the nucleobase was protected using the sterically demanding BOM-group. This presumably prevented coordination of the aluminum to the base, and, as expected, only the β-anomers **156** were observed. Similarly, β-adenine analogs **157** were synthesized, and oxidative cleavage of the alkene and desilylation of **157c** gave N^6-pivaloyl angustmycin C, which was isolated as the corresponding triacetate.



156a R = Me 93%
156b R = Et 75%
156c R = *i*-Bu 39%



157a R = Me 80%
157b R = Et 59%
157c R = $CH{=}CH_2$ 68%

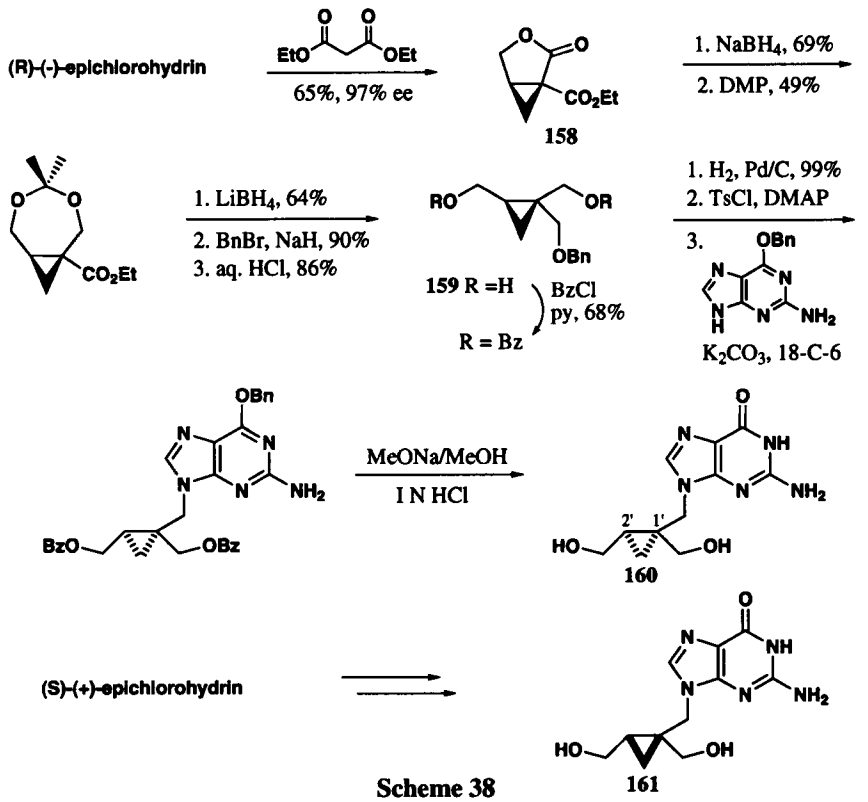
6. C1'-Branched-1'-homo-cyclopropyl Analogs

As has been illustrated, many modifications have been performed on natural nucleosides in order to enhance their activity or selectivity or to improve bioavailability. Resistance towards enzymatic hydrolysis constitutes another of the incentives in designing nucleoside analogs. Hence, analogs in which a methylene group is inserted between the base and sugar would be expected to be more hydrolytically stable. Such compounds have been synthesized in the *psico*-nucleoside analog category and are termed C2'-homo-*psico*-nucleosides.

Tsuji and coworkers had evaluated epoxide-based homo-*psico*-nucleosides **58** and **59**.[24] Because of stability issues, a cyclopropyl moiety was substituted for the epoxide, and cyclopropyl-homo-*psico*-nucleoside **160** and its enantiomer **161** were prepared.

The synthesis of **160** was initiated with lactone **158**, obtained in >97% ee from (*R*)-(-)-epichlorohydrin and diethyl malonate (*Scheme 38*). Selective reduction of the lactone and protection of the resulting diol, followed by reduction of the ester, benzylation and acetal cleavage afforded diol **159** (R=H). The diol was benzoylated, and the benzyl ether was cleaved. The resulting primary alcohol was activated as the tosylate and condensed with benzyl-protected guanine to provide, after hydrolysis, homo-*psico*-nucleoside **160**. Enantiomer **161** was prepared by the same procedure, starting from (*S*)-(+)-epichlorohydrin.

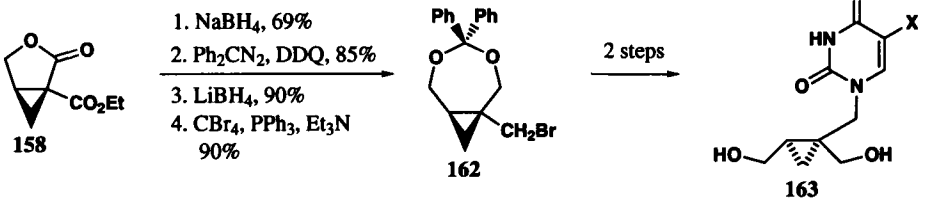
Antiherpetic (HSV) evaluation showed that the 1'S,2'R-enantiomer **160** was approximately 40 times more potent than the known antiherpetic agent, acyclovir, as measured by a quantitative CPE reduction assay. Enantiomer **161** showed weak activity, which was possibly due to its contamination with **160** (< 3%). Although inactive against HIV-1, compound **160** was shown to be ten times as potent as acyclovir against VZV. Preliminary phosphorylation studies showed that **160** was phosphorylated 7-8 times faster than acyclovir. It is worth noting that previous studies had shown that similar compounds containing no methylene group between the



Scheme 38

base and cyclopropyl ring were either inactive or weakly active against HSV possibly due to inefficient phosphorylation caused by greater steric crowding. Conformational studies using molecular mechanics revealed that **160** is sufficiently flexible to be able to adopt conformers appropriate for phosphorylation.

Tsuji and coworkers also prepared a series of uracil-containing cyclopropyl-homo-*psico*-nucleosides **163** (*Scheme 39*).[57] Starting again from **158**, reduction, followed by protection



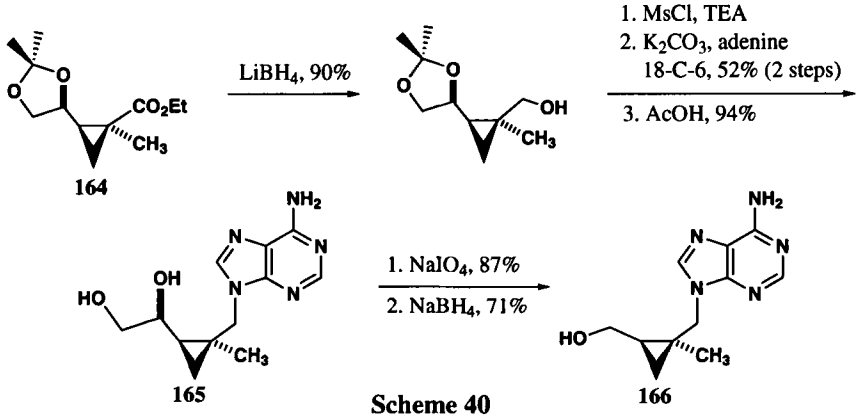
X = H, F, Cl, Br, I, Me, (*E*)-2-chloroethenyl, (*E*)-2-bromoethenyl, (*E*)-2-iodoethenyl, ethynyl, 1-propynyl

Scheme 39

of the resulting diol as the diphenyl ketal, reduction of the ester and conversion of the free hydroxide to a bromide, provided key intermediate **162**. This was coupled with a series of uracil derivatives and deprotected to give **163**. None of the compounds shown was active against HSV;

however, **163** (X = (*E*)-2-bromoethenyl) was 100 times more potent than acyclovir against clinical isolates of VZV and showed good oral bioavailability in rats (69% at 1mmol/kg). Its enantiomer was comparable in activity to acyclovir.

Another example of a cyclopropyl-homo-*psico*-nucleoside **166** was disclosed by Ortuna and coworkers (*Scheme 40*).[39] A previously described intermediate **164**[58] was reduced using



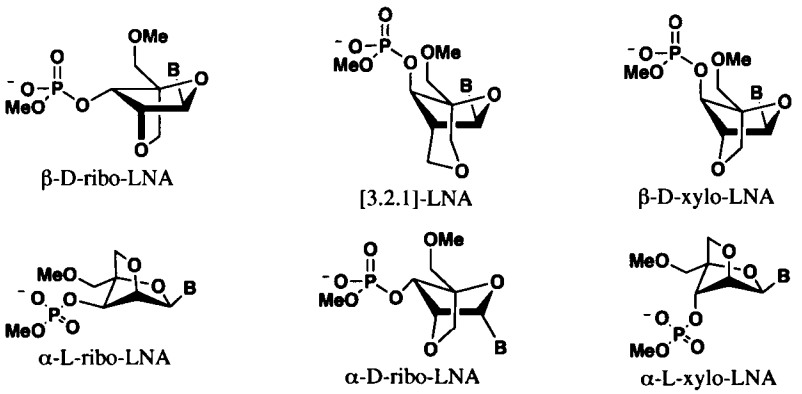
164 165 166

Scheme 40

$LiBH_4$. Mesylation, followed by *N*-alkylation with adenine and hydrolysis, gave **165**. Oxidative cleavage of diol **165**, and subsequent reduction of the resulting aldehyde provided **166** in 26% overall yield. Biological studies for this compound are said to be underway.

III. CONFORMATIONALLY LOCKED *psico*-NUCLEOSIDES

Imanishi[59] and Wengel[60] introduced locked nucleic acid (LNA), β-ribo-LNA, in 1998 (*Fig. 3*). β-ribo-LNA is a nucleic acid analog that proved capable of hybridizing with complementary DNA (*c*DNA) and RNA (*c*RNA) and producing what was the strongest duplex with

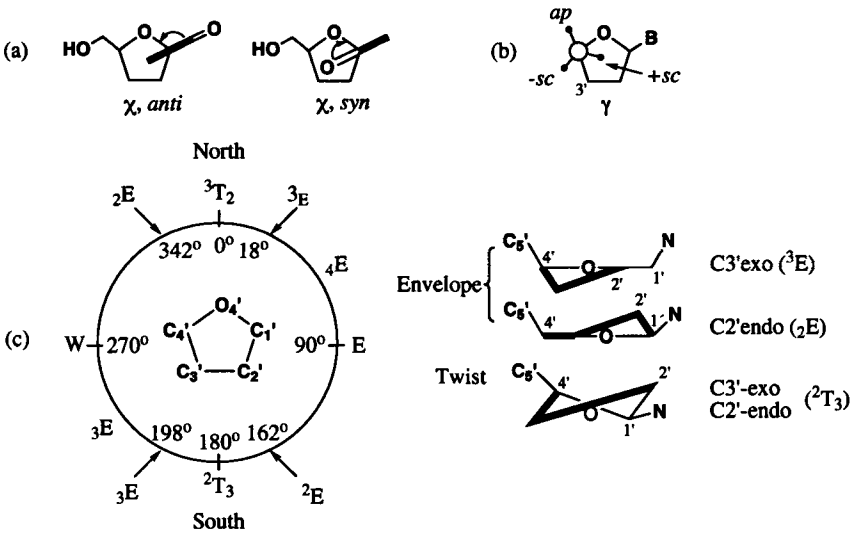


LNA Family

Figure 3

*c*RNA.[61] The LNA family has shown remarkable thermal stability and has shown no adverse reactions in rat brains. Due to the properties of LNA, and for the purpose of creating potent therapeutic agents, conformationally constrained nucleosides are of interest.

It is generally recognized that certain conformational parameters for the sugar are desired for nucleoside interaction in enzymatic processes.[62-64] Although it is likely that a single conformation is present at the various enzymatic steps, in solution there exists a rapid ring puckering equilibrium for nucleosides (*Fig. 4*). Thus, nucleoside conformational factors such as



(a) Glycosyl angle χ, (b) C4'-C5' rotational angle γ, (c) Ribose ring puckering, *P*

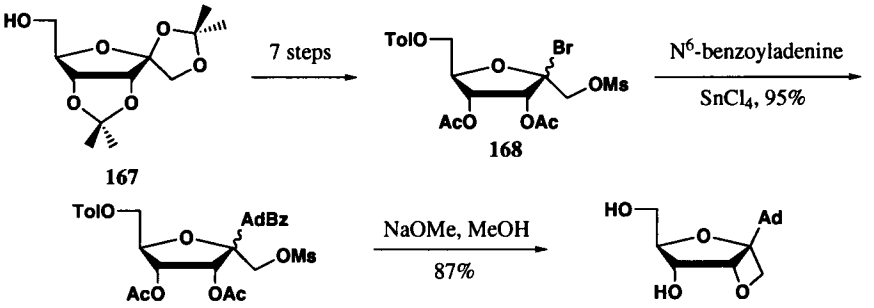
Figure 4

glycosyl torsion angle χ (the position of the nucleobase with respect to the sugar), the orientation of the 5'-OH (torsion angle γ), the position in space of the 5'-OH and carbon C3' (the main rotamers being *+sc, ap* and *-sc*), and the pseudorotation angle of the sugar (ring puckering, the sugar's deviation from planarity) are factors that may be of importance in drug design. *Fig. 4* also illustrates the ring puckering of the furanose ring in terms of phase angle of pseudorotation (*P* = 0-360°). Superscripts refer to atoms above the furanose ring while subscripts refer to the atoms below the plane. The terms *endo* and *exo* refer to atoms on the same and opposite side of C5' respectively. Some envelope and twist conformations are also illustrated in *Fig. 4.*

In attempts to control some of these conformational factors, scientists have prepared locked nucleosides having a fixed number of conformations. These conformations include low energy ones accessible in natural nucleosides and other conformations postulated to be of potential importance in enzymatic pathways. Some of these compounds fall into the category of *psico*-nucleosides as defined for this review.

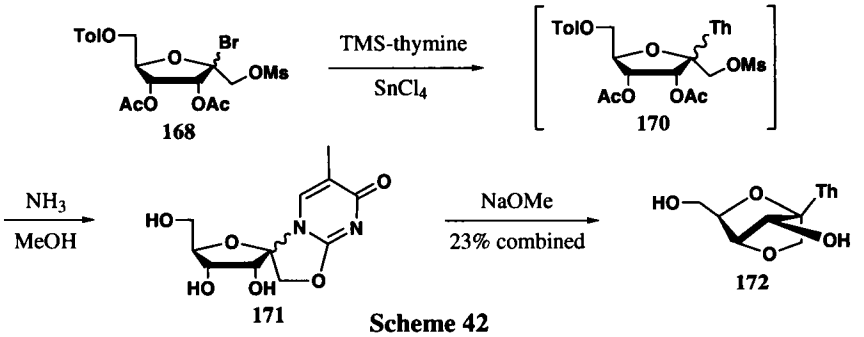
1. Anhydro-locked Nucleosides

In an effort to produce analogs which adopt the high-energy eastern conformation *O*4'-endo ($T \approx 94°$) exhibited in substrates having high affinities for RNA, compounds such as **169** were synthesized (*Scheme 41*).[65] Its preparation started from psicofuranose derivative **167** which was converted to **168** in 7 steps and then coupled with persilylated N^6-benzoyladenine in acetonitrile in 95% yield. Tandem global deprotection/oxetane ring formation occurred under mild conditions and provided 1',3'-anhydro-*psico*-nucleoside **169**. In fact, anhydronucleosides like **169** have a long history and have been made by too many groups to mention here. Prior to their role in studying the effects of conformational restriction on activity, they were targeted as a way of determining the α:β selectivity following introduction of the base.



Scheme 41

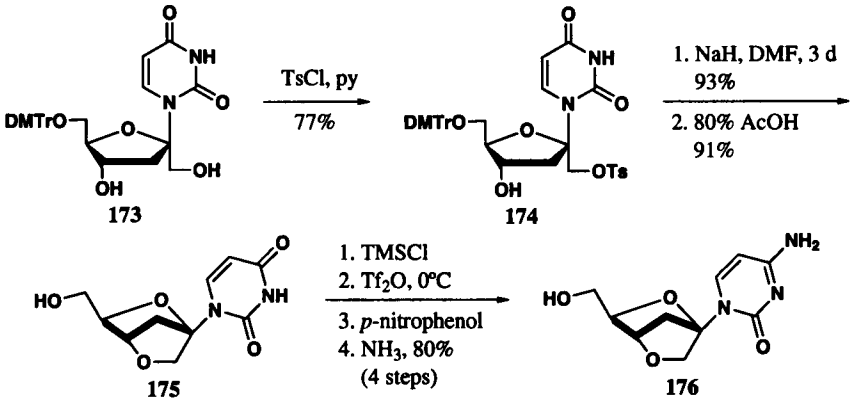
1,4'-Anhydro analog **172** was synthesized in a similar manner starting from bromide **168** (*Scheme 42*).[65] Reaction of **168** with TMS-thymine gave nucleoside **170**, which was treated with NaOMe to give **172** in 23% overall yield. Under milder conditions, NH_3/MeOH, deacylation was observed to the intermediate **171** which could be isolated but rearranged to **172** on addition of NaOMe.



Scheme 42

When investigating the conformationally locked carbocyclic nucleosides, Marquez and coworkers proposed that the extreme S-conformation ($_3$E) was needed for facile phosphorylation while the *N*-conformation ($_4$E) was required for effective reverse transcriptase interaction.[62] In

order to test this hypothesis, Kværnø and coworkers constructed southern bicyclic furanosides containing oxymethylene bridges (*Scheme 43*).[66] Tosylation of known C6'-DMTr-3'-deoxy-β-D-*psico*-furanosyluracil **173** provided the monotosylated product **174** in 77% yield. Cyclization at room temperature in the presence of NaH proceeded in high yields and deprotection resulted in 91% of the desired uracil **175**. Cytosine derivative **176** was obtained from **175** *via* temporary trimethylsilylation and triflic anhydride activation, followed by treatment with 4-nitrophenol and, finally, aqueous ammonia, according to a known four-step, two-pot procedure.[67] NOe and HMBC analysis confirmed the presence of an S-conformation in **175** and **176**. Compounds **175** and **176** lacked activity against HIV-1 using MT-4 target cells. This appeared to support Marquez's assertion of a need of sufficient flexibility between S- and N-conformations in order to interact with HIV-1 RT.



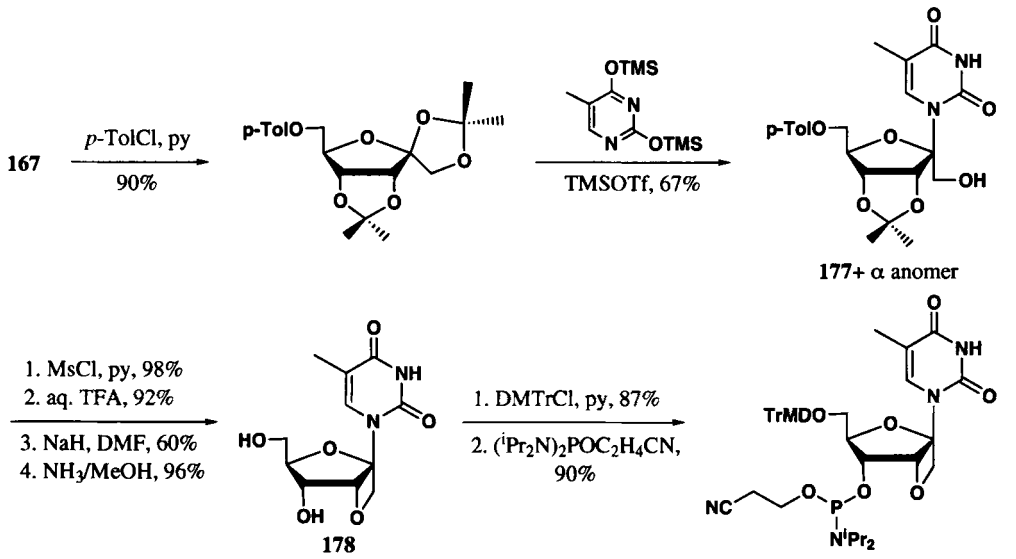
173 **174** **175** **176**

Scheme 43

2. Anhydro-locked Oligonucleotides

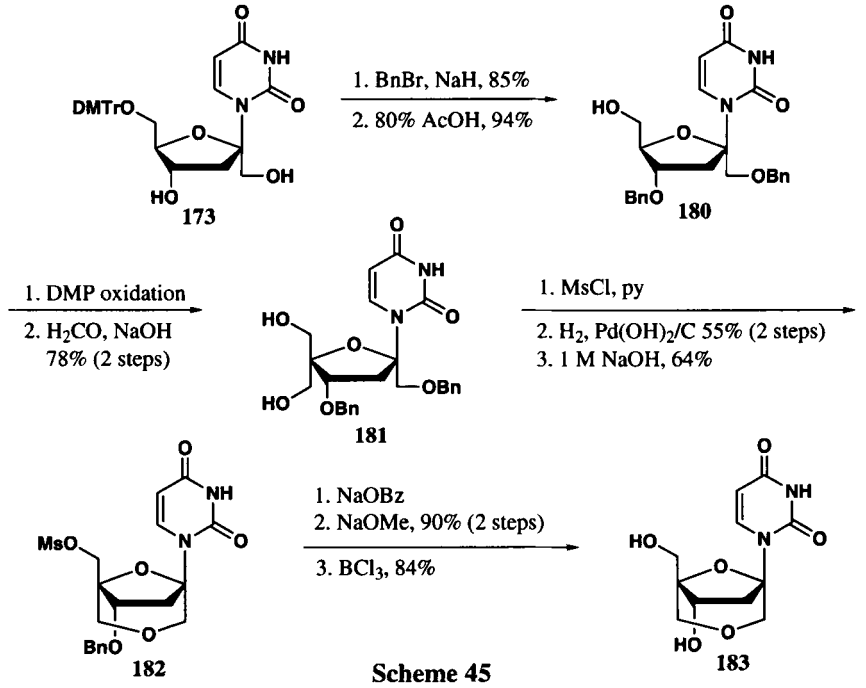
Prompted by the high affinity of N-type LNA (C3'-endo) to RNA, a group of hybrid antisense oligonucleotides (AON)/RNA, incorporating LNA **179**, has been synthesized.[68] The monomer was prepared as shown in *Scheme 44*. *p*-Toluoylation of the primary alcohol of **167**, followed by coupling with TMS-thymine, provided a 67% yield of a mixture of anomers **177**. Mesylation, acetonide deprotection and cyclization gave the C1-C3 anhydride from which the *p*-Tol group was removed using methanolic ammonia to give **178**. The primary alcohol was selectively protected and the remaining alcohol coupled with a P(III) reagent. The corresponding cytidine derivative was prepared in a similar fashion by the same group.

Properties desirable when designing antisense oligonucleotides include both increased duplex stability and ribonuclease H (RNase H) activation. RNase is an endonuclease which specifically degrades only the RNA strand in RNA/DNA heteroduplexes. It has been postulated that the high-energy O4'-endo conformation, rare in natural nucleic acids, is present in RNase H activation. Consequently analogs such as **183**, which adopt the *O*4'-endo conformation, have



Scheme 44

been prepared (*Scheme 45*).[69] The synthesis of **183** commenced with DMTr ether **173**. Benzylation of the remaining alcohols and deprotection of the DMTr group afforded **180**. Oxidation with the Dess-Martin periodinane followed by tandem aldol condensation/Cannizzaro reaction

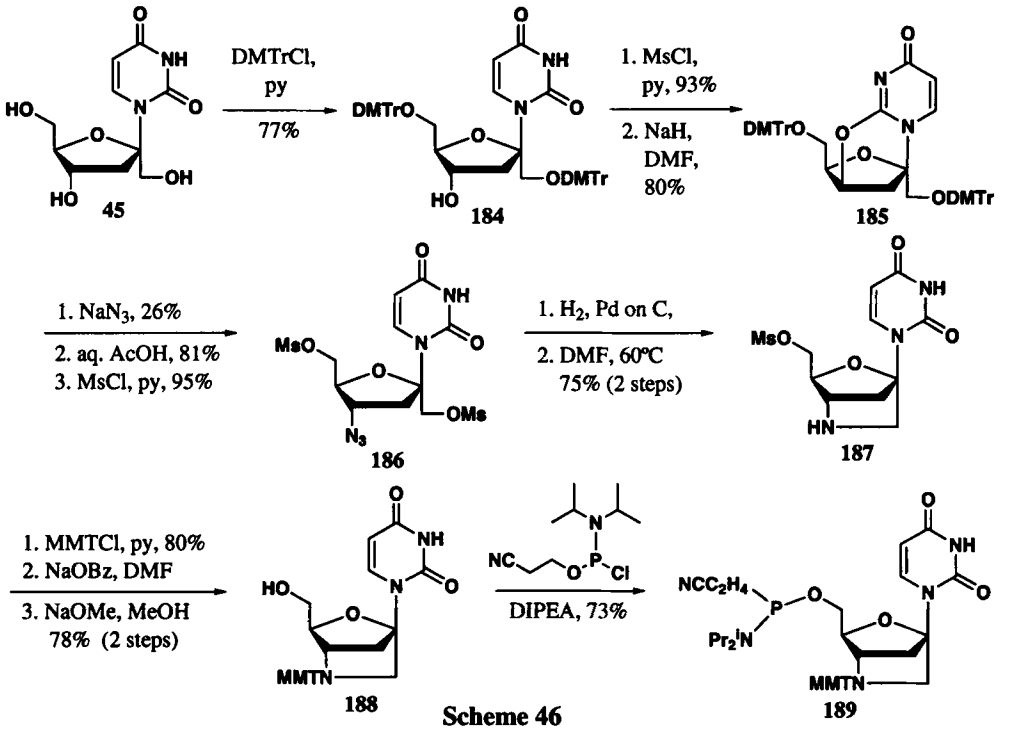


Scheme 45

provided **181** in a combined 78% yield. Double mesylation, followed by selective debenzylation of the primary alcohol and cyclization, afforded **182**. Finally, a two-step hydrolysis of the mesylate and, then, debenzylation gave **183**. When this was incorporated (up to 3 times) into a 9-mer oligonucleotide, there was a small decrease in duplex stability of 1.5 to 2.1°C/modification.

3. 3',1'-Aminomethylene Bridge

The novel system **188** possessing an aminomethylene bridge, was proposed[70] to exist in a restricted S-type furanose conformation. Its synthesis is shown in *Scheme 46*, and the starting material used was the 1-[3'-deoxy-β-D-*psico*-furanosyl]uracil (**45**). Both primary alcohols were

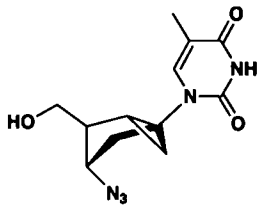


Scheme 46

converted to the DMTr-ethers, giving **184**. Mesylation of the remaining alcohol, followed by intramolecular displacement, gave **185** in 74% yield. Ring opening with inversion using NaN_3, then DMTr-deprotection and double mesylation, afforded **186**. An alternative method (not shown) for introduction of the azide required more steps but gave a higher yield. Azide reduction and cyclization yielded bicyclic **187** in 75% yield over two steps. Finally, treatment with 4-monomethoxytrityl chloride (MMT-Cl), followed by removal of the mesylate by substitution with benzoate then hydrolysis, led to desired N-MMT protected nucleoside **188**. Formation of **189** was achieved using standard procedures, and it was then introduced three times into mixed 9-mer oligonucleotide sequences, using a DNA synthesizer. Thermal denaturation analyses were then performed to *c*RNA and *c*DNA. Unfortunately, unfavorable steric and conformational interactions seemed to be at play, since the thermal stability decreased in these studies.

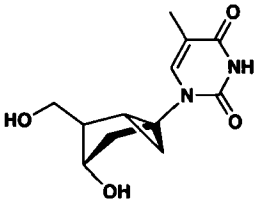
4. Locked Carbocylic Nucleoside Analogs

1',6'-Methano carbocylic thymidine *psico*-nucleosides **190** and **191** replicate the puckering of the furanose ring at its absolute south conformation (phase angle T = 162-198°, $_3E \rightarrow {}^2T_3 \rightarrow {}_3E$). The incentive for the synthesis of such compounds originates from the inhibition of HIV-1 RT by the $_2E$ north isomer **192** (as the 5'-triphosphate).[62]

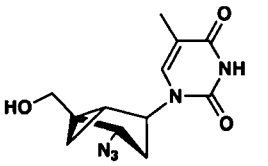


190

$_3E$, South



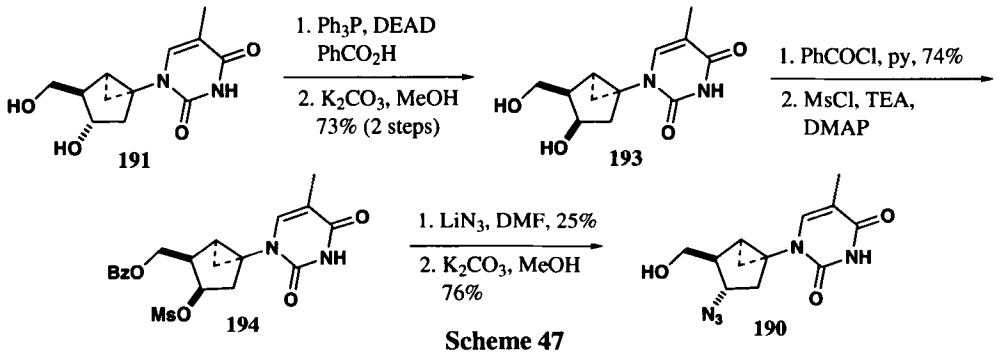
191, T = 190°



192, T = 343°

$_2E$, North

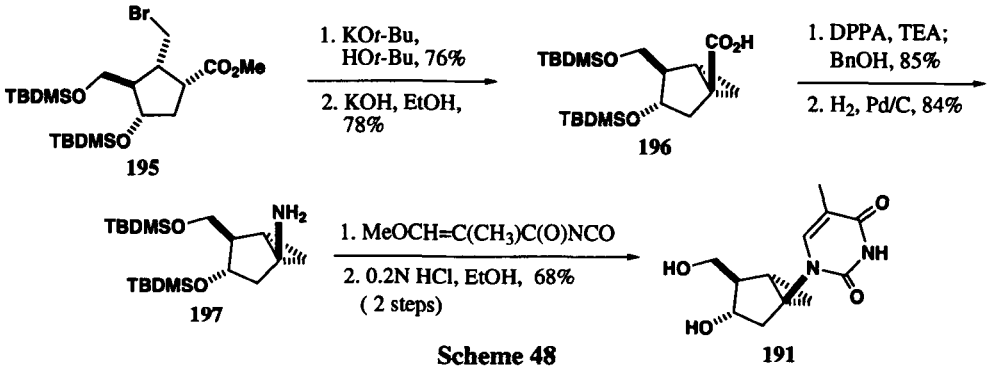
In an effort to create AZT-like locked carbocyclic analogs, compound **190** was synthesized (*Scheme 47*).[62] Previously synthesized diol **191** (*Scheme 48*) was reacted under standard Mitsunobu conditions to give a dibenzoate with inversion of configuration at C3'. Double hydrolysis provided **193**. Monoprotection of the primary alcohol as the benzoate ester and mesylation of the remaining alcohol afforded **194**. Mesylate displacement by azide proceeded with inversion, and benzoate ester deprotection gave **190**. The 5'-triphosphate of **190** was prepared but did not inhibit HIV-1 RT.



191 **193** **194** **190**

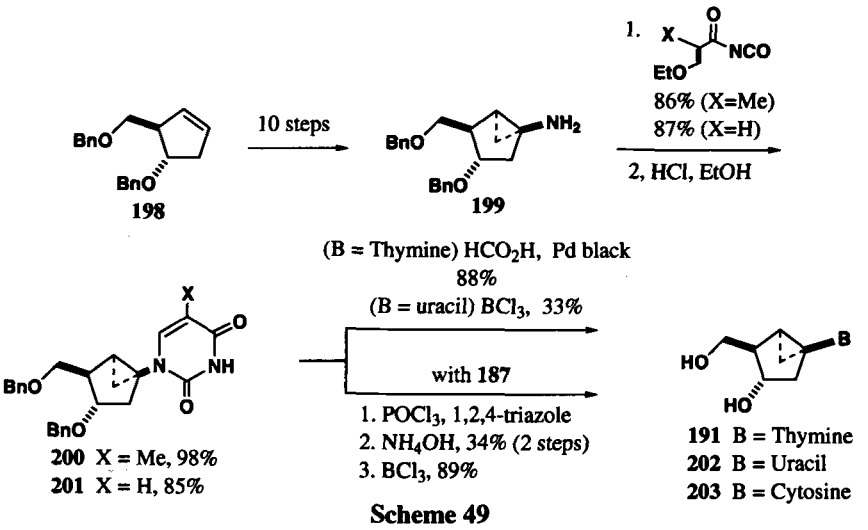
Scheme 47

Compound **191** has been synthesized by Marquez[71] and Altmann.[72] The synthesis by Altmann and coworkers exploited cyclopropane **196**, easily attained from the treatment of **195** with KO*t*-Bu, followed by hydrolysis (*Scheme 48*). Formation of the acyl azide using diphenylphosphorylazide, Curtius rearrangement with trapping of the intermediate with benzyl alcohol, and deprotection of the carbamate provided bicyclic amine **197**. Treatment of **197** with β-methoxymethacryolyl isocyanate, followed by simultaneous ring closure and deprotection under acidic conditions, gave **191** in 68% yield. Studies showed that introduction of **191** into oligonucleotides caused an undesired 1 to 1.9°C/modification reduction in the melting temperature.



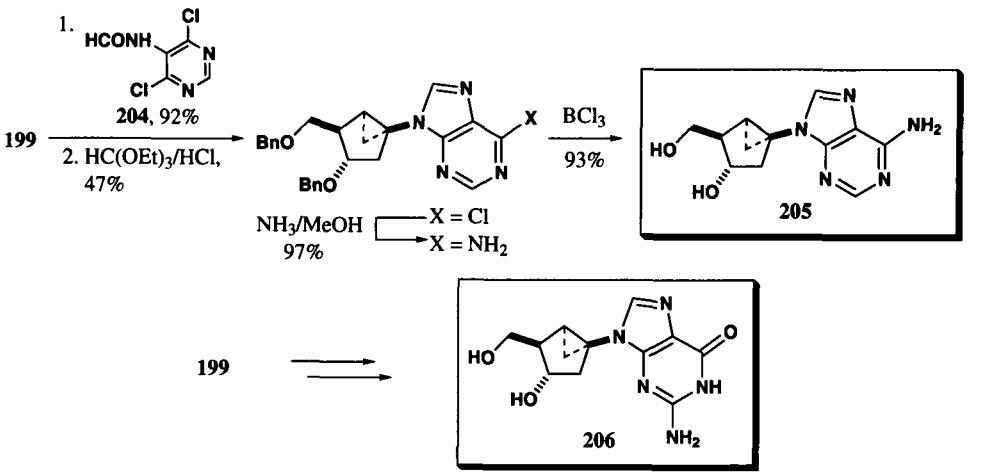
Scheme 48 **191**

Marquez and coworkers prepared **191** and other analogs **202/203** with $_3$E southern conformations (*Scheme 49*) and investigated their biological activities.[71] The syntheses began with optically pure cyclopentene **198**, which was converted in 10 steps to intermediate **199**. The heterocyclic base was then assembled providing **200** or **201**. Removal of the benzyl protecting groups in **200** (HCO_2H, Pd black) and **201** (BCl_3) afforded thymine **191** and uracil **202**, while the cytosine analog **203** was obtained from **201** *via* triazole formation, treatment with ammonia and deprotection.



Scheme 49

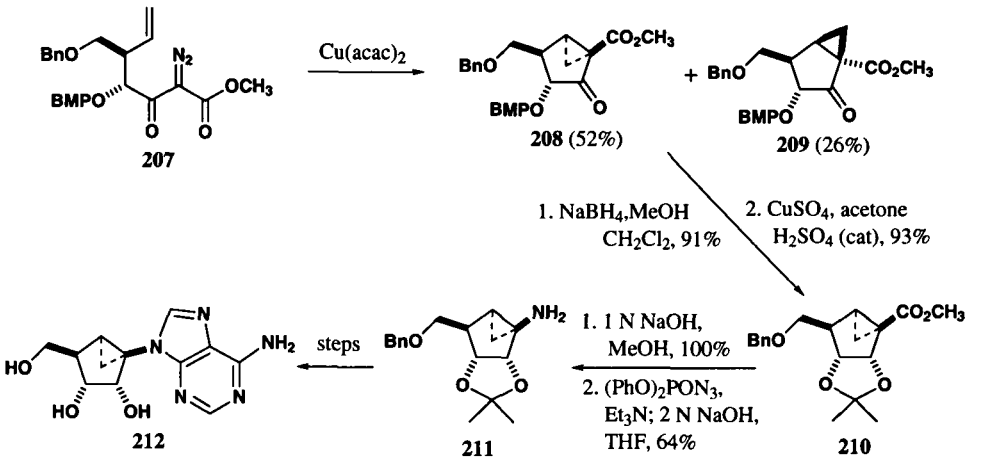
Purine locked nucleosides were also readily assembled from **199** *via* condensation with *N*-formyl pyrimidine **204**.[71] Subsequent ring closure using triethyl orthoformate under acidic conditions afforded the corresponding 6-chloropurine analog. Displacement of the chloride with ammonia and benzyl deprotection with BCl_3 gave target adenine compound **205** (*Scheme 50*). Similar methods were used for the synthesis of guanine *psico*-nucleoside **206**.



Scheme 50

Antiviral activities were then assessed on both the pyrimidine (**191**, **202**, **203**) and purine compounds (**205**, **206**), and it was determined that they were all devoid of activity, except for **205**, which exhibited anti-HCMV activity in plaque reduction assays (EC_{50}=2.4μg mL^{-1}).

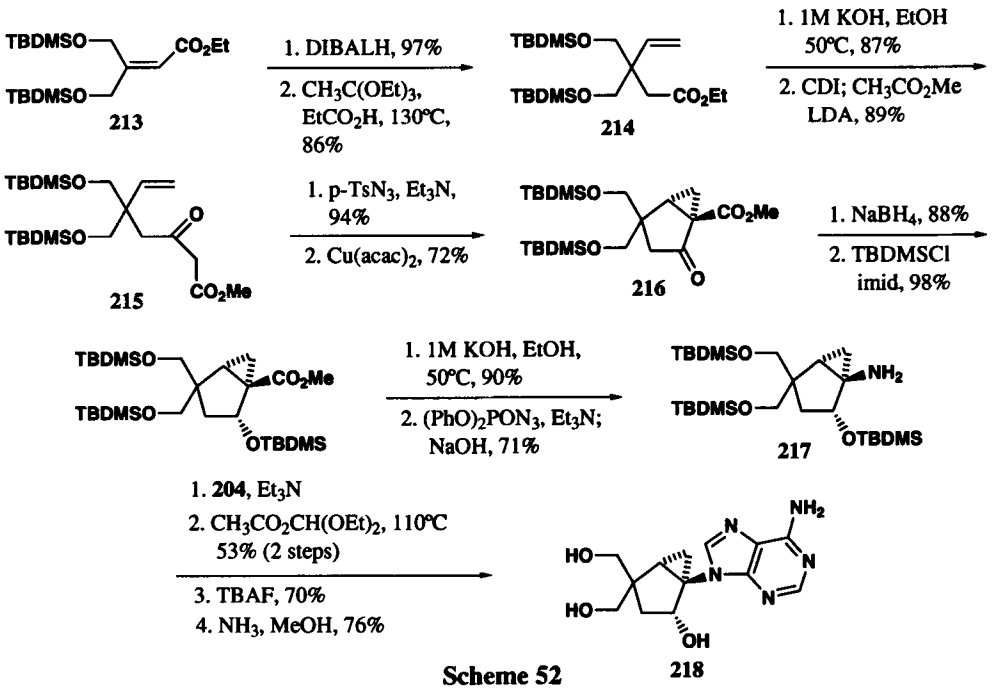
Marquez and coworkers synthesized a South ($_3$E)-ribose version **212** of **191** in racemic form (*Scheme 51*).[73] The key bicyclohexane precursor **208** was prepared by cyclization of diazo compound (±)-**207**, which was itself prepared in four steps from (*E*)-but-2-en-1,4-diol. Of the



Scheme 51

catalysts used for the intramolecular cyclopropanation, $Cu(acac)_2$ worked best to give a separable mixture of **208** and **209** in 78% yield and a 2:1 ratio. Following diastereoselective reduction of ketone **208**, simultaneous deprotection of the PMB group and acetonide formation gave **210**. Ester hydrolysis and Curtius rearrangement provided amine **211**. The adenine was appended by a similar approach to that used for the South ($_3$E)-2'-deoxyribo analog **205** in *Scheme 50*, giving **212**.

Hong prepared a related carbocyclic cyclopropyl nucleoside **218**, also in racemic form, as shown in *Scheme 52*.[74] The synthesis relied on much of the chemistry used by Marquez in the Scheme immediately above. Thus, unsaturated ester **213**, readily available from dihydroxyacetone, was reduced to the allylic alcohol and subjected to a Claisen rearrangement to give **214**.



Scheme 52

This was elaborated to the β-keto ester **215** by hydrolysis, activation as the acylimidazole and addition of the enolate derived from methyl acetate. Diazo transfer with *p*-tosyl azide, followed by cyclization with $Cu(acac)_2$, gave **216**. Reduction with $NaBH_4$ afforded the alcohol as a single isomer, which was silylated. The ester was then hydrolyzed, and a Curtius rearrangement provided amine **217**. This was converted to a diaminopyrimidine, followed by cyclization with diethoxymethyl acetate, desilylation and ammonolysis, to give target *psico*-nucleoside **218** which showed no inhibition of HIV, HSV or HCMV.

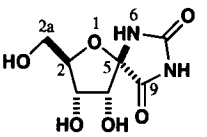
IV. SPIROCYCLIC *psico*-NUCLEOSIDES

1. Hydantocidin and Related Compounds

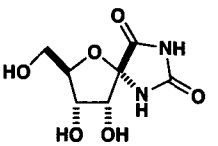
a) *Introduction*

(+)-Hydantocidin, isolated from multiple strains of *Streptomyces hygroscopicus*, was the first natural product having a spirocyclic ribofuranose identified from natural sources. It immediately attracted attention because of its potent herbicidal activity, comparable to the widely used herbicide glyphosate, against annual, biennial and perennial weeds. Equally importantly, hydantocidin has been shown to be non-toxic to microorganisms, fish and animals and not to

accumulate in soil. For a long time the mechanism of action of hydantocidin was unknown; it was eventually shown to be an adenoylsuccinate synthetase inhibitor.[75] A crystal structure of hydantocidin 2a-phosphate within the enzyme has been published.[75c,76] With the emergence of weed strains resistant to glyphosate, hydantocidin represents an alternative for the near future. However, despite the best efforts, highlighted in this section, of organic and natural product chemists, current fermentation or synthetic routes to hydantocidin are too inefficient to make the use of hydantocidin as a commercial herbicide practical. Hydantocidin has four contigious chiral centers and, therefore, 16 different isomeric forms. Although 5-*epi*-hydantocidin **219** is about 60% as potent as a herbicide as hydantocidin itself, isomers involving a change in the ribose configuration are invariably inactive, as is (-)-hydantocidin. Some modification in the base, however, is tolerated as shown later in this section.



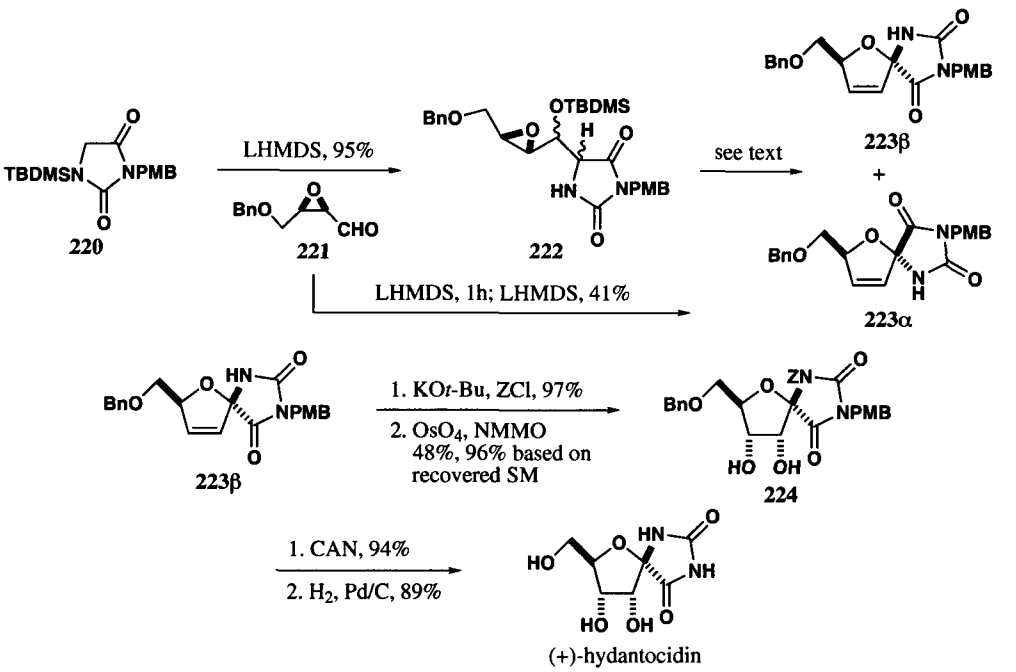
(+)-hydantocidin



219

b) *Synthesis of Hydantocidin and 5-epi-Hydantocidin*

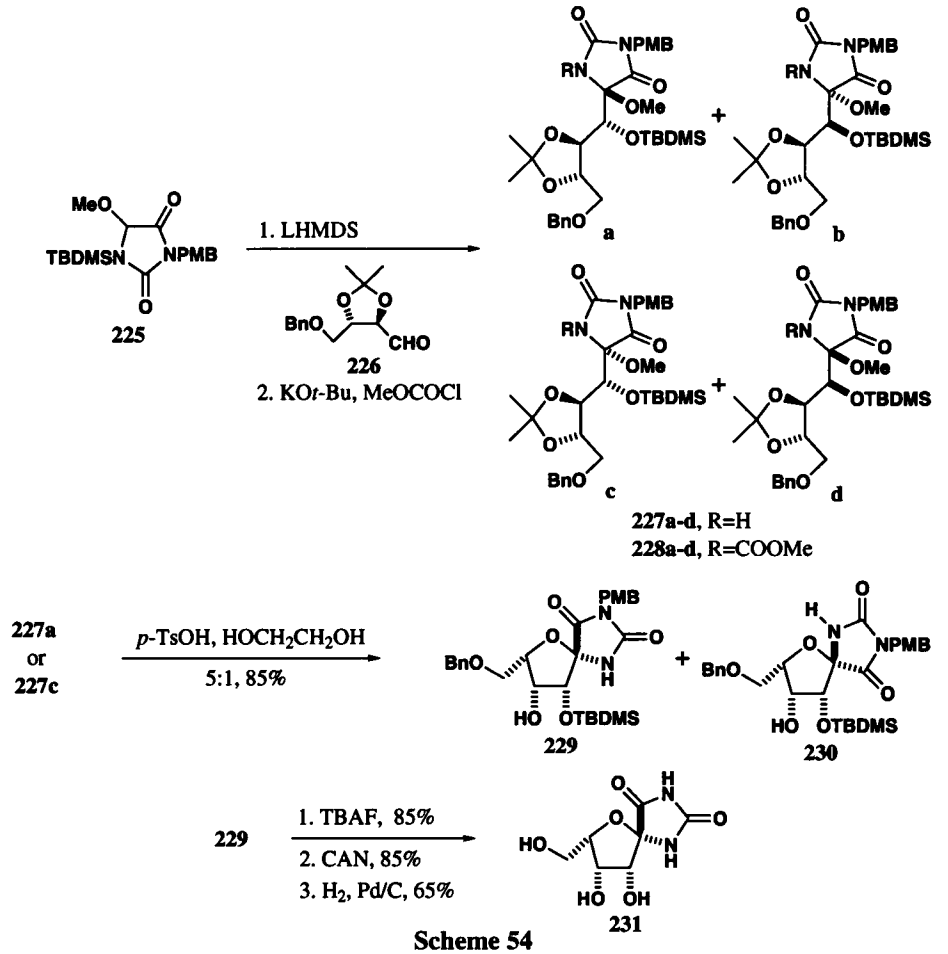
Four seminal papers by Mio and coworkers established much of the ground-work for later synthetic efforts directed towards hydantocidin, as well as divulging the first total synthesis (*Scheme 53*). In the first paper in this series,[77] the reaction of hydantoin **220** with aldehyde **221**



Scheme 53

gave all four diastereoisomers of protected hydroxyepoxides **222** in a 4.5:1:3.2:1 ratio. Cyclization then gave preferentially the undesired isomer **223α**, as well as **223β**, in a 2:1 ratio in 20-50% yield, depending on the reaction conditions. Subsequently it was found that one-pot sequential double addition of LiHMDS gave the same ratio of products in 41% yield directly from **220** and **221**. In order to get α-face selectivity during the dihydroxylation, protection of the remaining hydantoin NH was required. However, dihydroxylation was very slow. Even after 5 days only a 48% yield of **224** was obtained along with 50% recovered starting material **223β**. Removal of the two protecting groups was carried out under standard conditions, and the overall yield of (+)-hydantocidin was 33% (based on recovered **223β**).

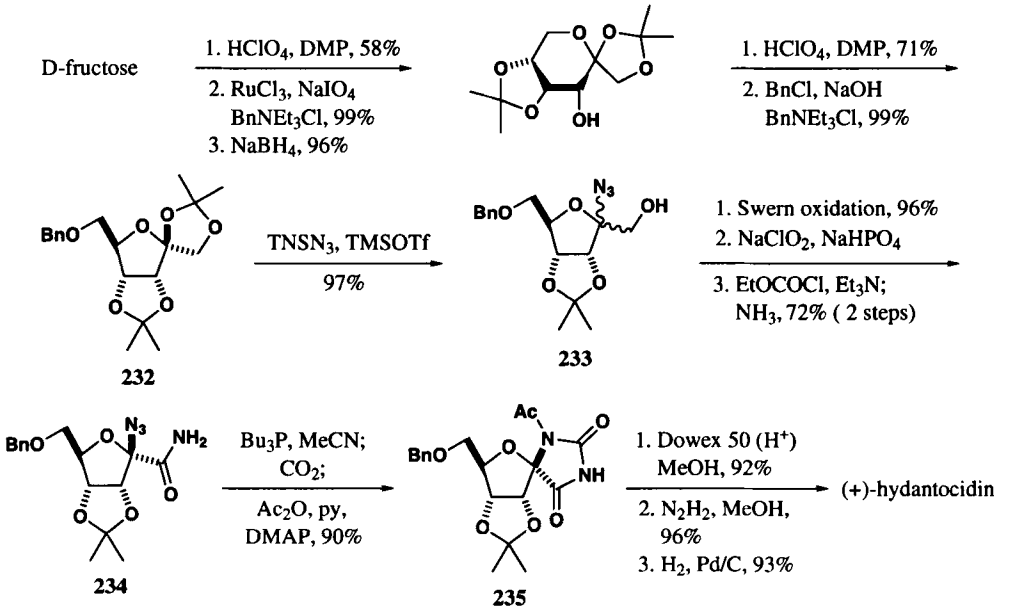
In the second paper,[78] eight stereoisomers were prepared from an aldol reaction/acid catalyzed cyclization sequence. Four were prepared from aldehyde **226**, as shown in *Scheme 54*, and the other four from its enantiomer. Thus the aldol reaction of **226** with **225** resulted in all four adducts which were separated into **227a** and **227b** (41%) and **227c** and **227d** (35%). Further



Scheme 54

separation into individual isomers **228a-c** was realized after derivatization with MeOCOCl, but the amount of **228d** was too low for isolation. Pure diastereomers **227a-c** were recovered by hydrolysis of the carbonates. Pure **227d** was obtained from epimerization of **227b** with methoxide. The isomers were then subjected to acid catalyzed deprotection/cyclization. Both **227a** and **227c** gave the same mixture of **229** and **230** (5:1, 85% total yield). Three step deprotection of **229** with TBAF, CAN and hydrogenolysis gave **231**. The other diastereomers of hydantocidin were prepared in a similar fashion.

Having established that the biological activity of hydantocidin resides only in the natural isomer, a high yielding synthesis of this compound was needed. The routes described above were not appropriate due to the mixture of compounds obtained from the aldol reactions. In the third paper,[79] a more efficient route (*Scheme 55*) was designed which formed the basis for many of the later syntheses of hydantocidin. D-Fructose was *bis*-protected and the remaining

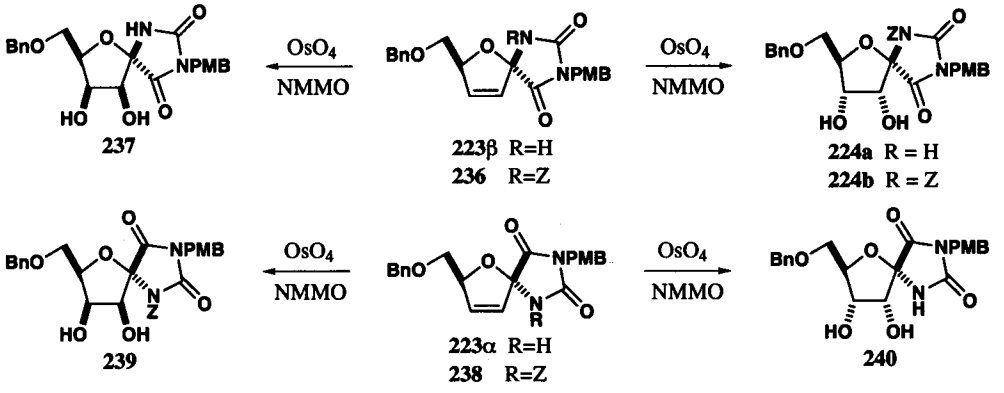


Scheme 55

hydroxyl inverted by an oxidation/reduction sequence. Pyranose to furanose conversion was followed by benzylation of the primary alcohol to give **232**. Ring opening at the anomeric position using $TMSN_3$/TMSOTf gave an inseparable mixture of the two anomers in which the desired β-anomer **233** predominated (β:α, 18:1, combined yield 97%). This was converted to **234**, isolated as a single anomer, by two step oxidation then amide formation. Reduction of the azide to the amine, followed by cyclization to the hydantoin ring under a variety of conditions, was complicated by considerable epimerization at the anomeric position. Consequently, an alter-

native method involving iminophosphorane formation was developed. After experimenting with a number of phosphorus (III) reagents and solvents, the highest yields were obtained with Bu_3P in CH_3CN. Under these conditions no trace of epimerization at the anomeric position was noted. However, epimerization did occur in the subsequent acid catalyzed removal of the acetonide, unless the product from the aza-Wittig reaction was isolated as the acetamide **235**. Removal of all three protecting groups proceeded under standard conditions to give (+)-hydantocidin in 16% overall yield.

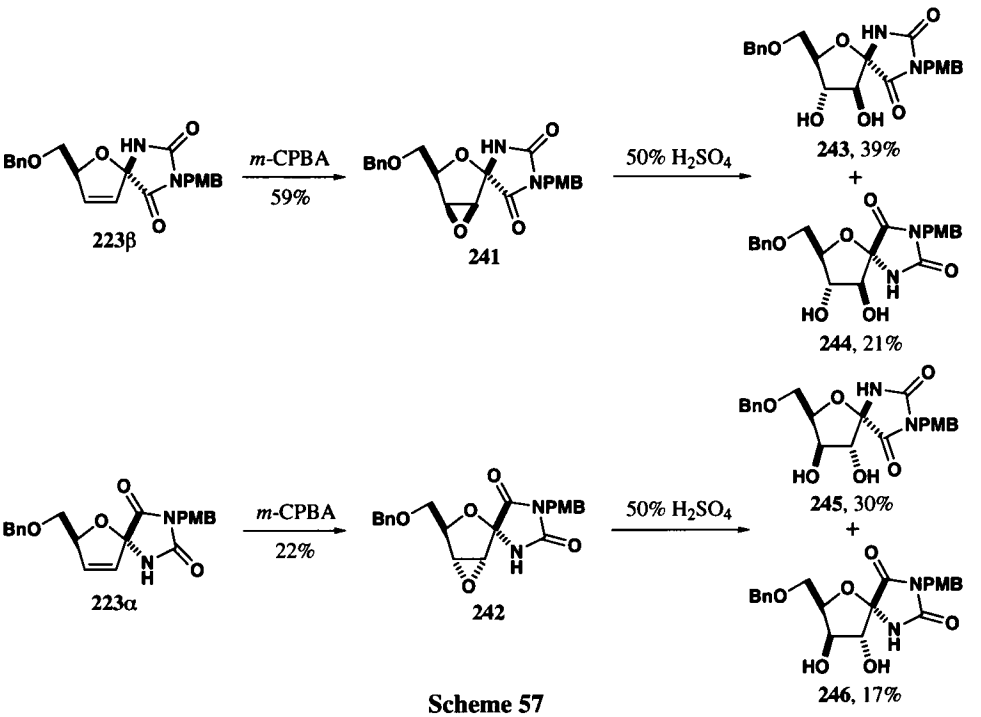
In the final paper in this series[80] a general synthetic route to all eight stereoisomers corresponding to the D-series of the sugar moiety was reported. It relied on the ability of the protecting group on the hydantoin nitrogen (c.f. **224** earlier) to control the facial selectivity in the oxidative functionalization of the alkene. Space precludes a complete discussion of all of this work, but a general outline is provided (*Scheme 56*). Thus, for the *cis*-series, **236** was converted exclusively to **224b**, while **223β** gave a mixture of **224a** and **237** (**224a**:**237**, 1:5.8). Under the same reaction conditions, **223α** afforded exclusively **240**, whereas **238** gave only **239**. Sequential deprotection of the PMB and Bn group with CAN followed by hydrogenolysis gave the target compounds.



Scheme 56

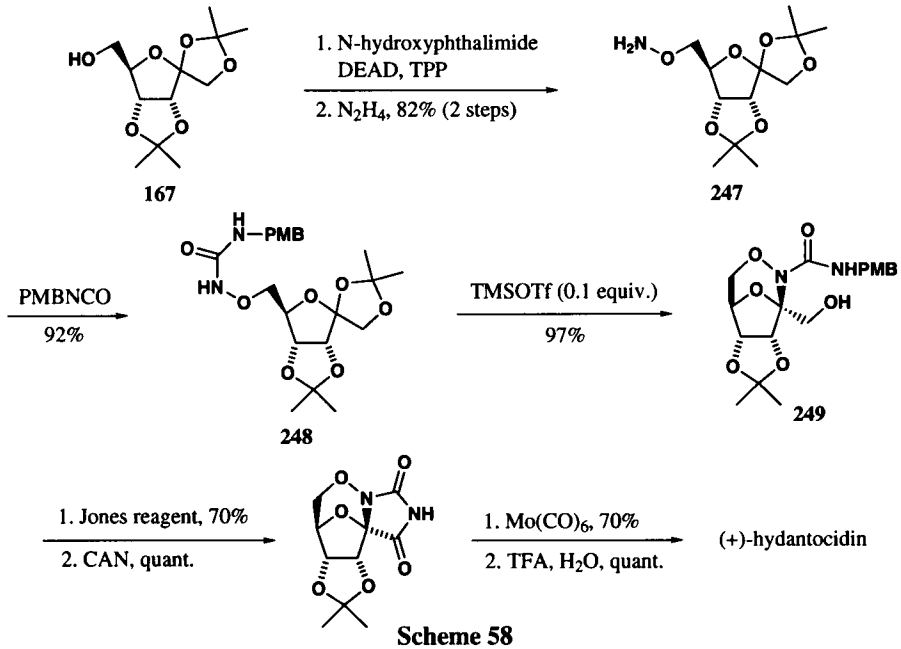
The 3,4-trans isomers **243-246** were prepared in the same paper from epoxides **241** and **242**, as shown below (*Scheme 57*). Epoxidation occurred from the face opposite to the carbonyl group at the anomeric position. Subsequent ring opening was regiospecific but gave mixtures of products due to scrambling of the stereochemistry at the anomeric center under the surprisingly drastic conditions required to effect epoxide hydrolysis.

5-*epi*-Hydantocidin **219**, which has the α-nitrogen and the β-carbonyl group, is thermodynamically more stable then the natural isomer with a β-nitrogen and an α-carbonyl group. Control of the required *cis* relationship between the hydroxymethyl and amino groups



Scheme 57

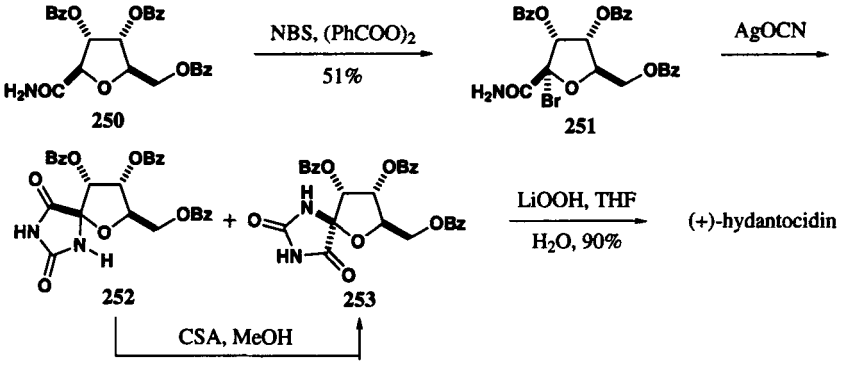
found in (+)-hydantocidin was achieved by intramolecular delivery of the nitrogen as shown in *Scheme 58*.[81] Psicofuranose **167** was converted to hydroxylamine **247** by a Mitsunobu reaction and phthalimide cleavage. Attempts to cyclize this in the presence of TMSOTf lead only to



Scheme 58

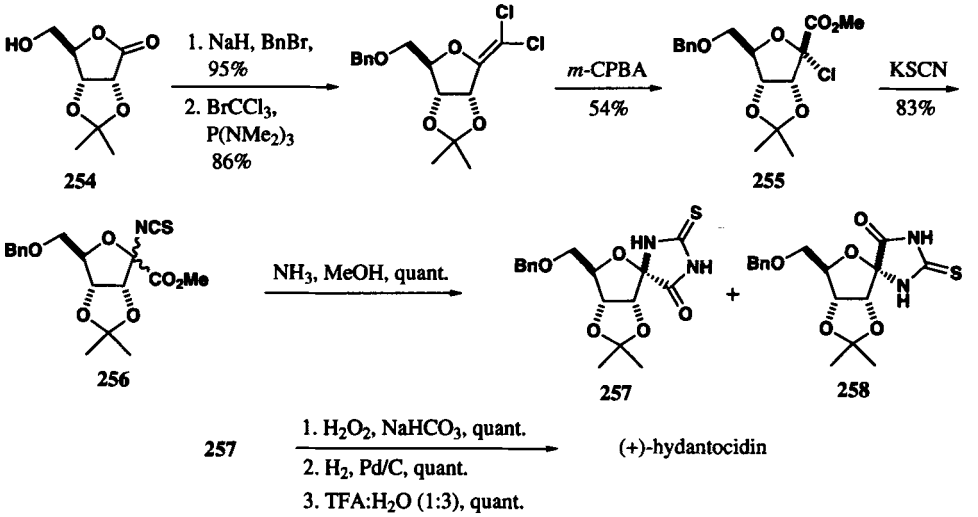
transfer of an acetone residue to the amine. To prevent this the amine was converted to PMB urea **248**. Cyclization then proceeded in excellent yield to give **249**. Oxidation with Jones reagent caused spontaneous cyclization to give the hydantoin ring, which was deprotected with CAN. Reduction of the N-O bond proved difficult but was successfully achieved with $Mo(CO)_6$. Final deprotection with aqueous TFA gave (+)-hydantocidin in 36% overall yield over eight steps.

Harrington and Jung reported a synthesis of (+)-hydantocidin in which the key step was a stereoselective anomeric radical bromination of readily available ribofuranosyl amide **250** to give **251** as a single isomer in 51% yield (*Scheme 59*).[82] Spirocyclization of this with silver cyanate gave a mixture of **252** and **253** (46%, 2:1). These were separable, and the former recycled to the latter upon treatment with acid. The benzoyl groups of **253** were removed with lithium peroxide to give (+)-hydantocidin in 90%.



Scheme 59

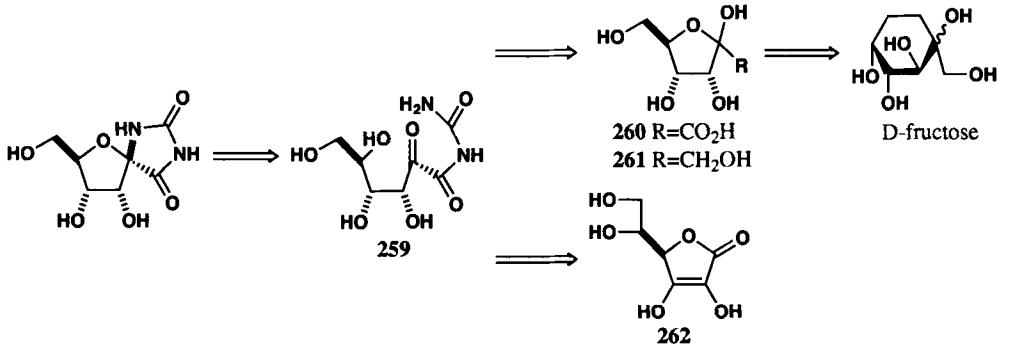
Shiozaki prepared (+)-hydantocidin by two routes from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **254**.[83] The more economical route,[83b] shown in *Scheme 60*, proceeded in 35% overall yield. Benzylation and conversion to the dichloroalkene using $BrCCl_3$, followed by oxidation



Scheme 60

with *m*-CPBA, gave α-chloroesters as a separable 4:1 mixture of anomers in favor of **255**. Reaction of **255** with KSCN gave **256**, also in a 4:1 ratio. These could not be separated but were so after conversion to the thiohydantoins **257** and **258**. Subsequent transformation of **257** to the corresponding hydantoin, hydrogenolysis and removal of the acetonide gave (+)-hydantocidin. Thiohydantoin **258** was similarly converted to 5-*epi*-hydantocidin **219**. Thiohydantoins **257** and **258** (with PMB, rather than Bn, protection on the C2a alcohol) were also transformed to C-2-thioxohydantocidin (**275**) and C-2-*epi*-thiooxohydantocidin (**276**) (Section IV. 1.c).

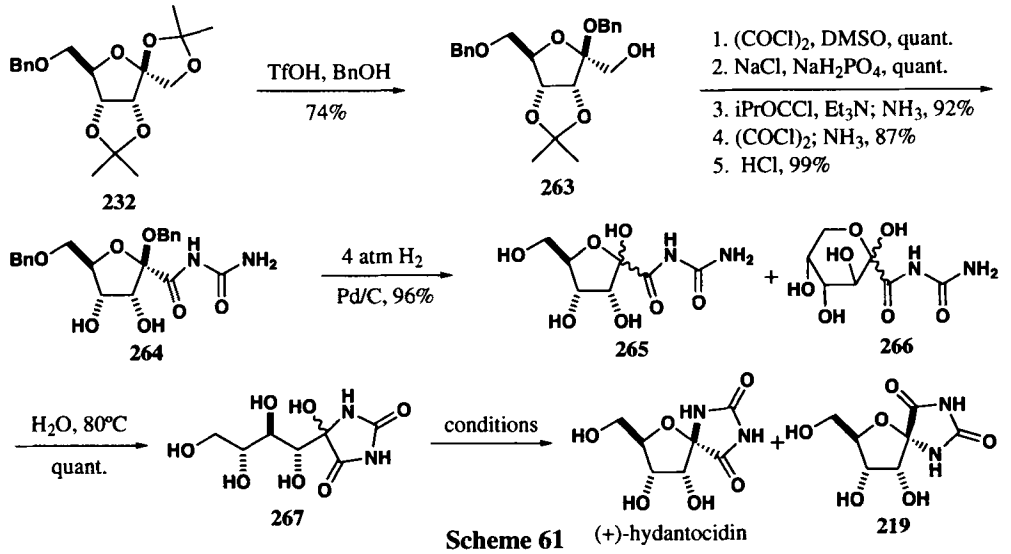
Terashima and coworkers prepared (+)-hydantocidin by a route that mimics their proposed biosynthetic pathway (*Fig. 5*).[84] Retrosynthetic analysis suggested disconnection of the N,O spiroketal to give *N*-acylurea **259**. Further analysis led either to sugar acid **260**, available from D-psicose (**261**) and, ultimately, D-fructose, or to D-isoascorbic acid (**262**).



Terashima Retrosynthesis of (+)-Hydantocidin, Based on Proposed Biosynthetic Pathway

Fig. 5

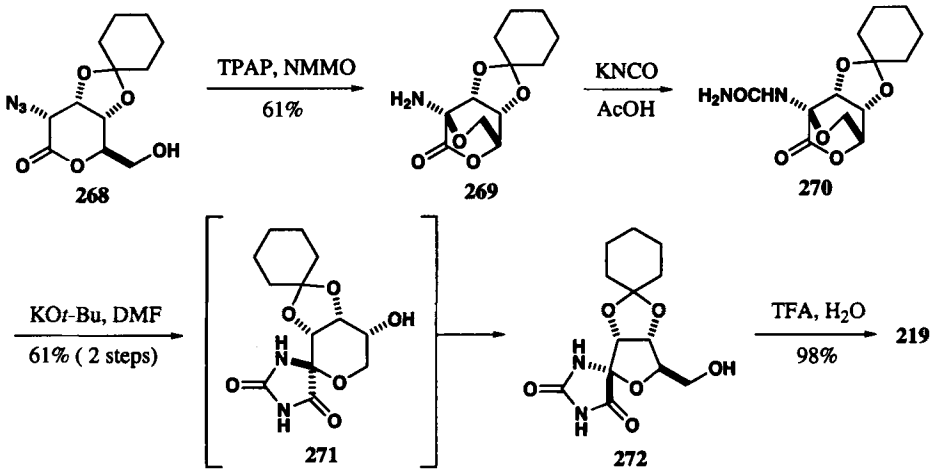
The Terashima synthesis of hydantocidin is shown in *Scheme 61*, starting from 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose (**232**). Benzyl glycoside formation using



Scheme 61

TfOH and BnOH provided β-anomer **263** stereoselectively in 74% yield. The hydroxymethyl group was converted to the acylurea **264** in five steps. Hydrogenolysis of **264** gave a 1:1 mixture of **265** and **266**, which are synthetically equivalent to **259**. Attempts to directly cyclize this mixture to (+)-hydantocidin proceeded in very low (<10%) yield. Simple heating however gave a 2:1 mixture of hydantoins **267** in a 2:1 ratio. Unfortunately, cyclization of this under many different conditions gave only a mixture of hydantocidin and the thermodynamically more stable 5-*epi*-hydantocidin (**219**) in which the latter predominated. 5-*epi*-Hydantocidin was also prepared in one step from D-isoascorbic acid and urea, although the yield was very low.[85]

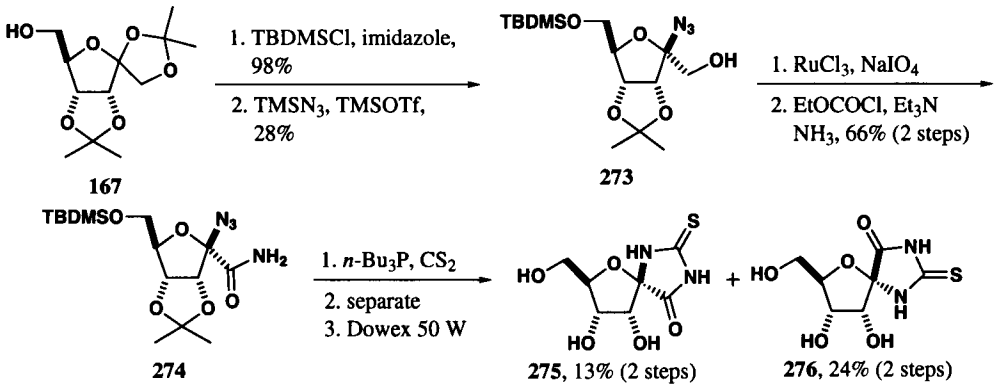
The equilibrium ratio of hydantocidin to 5-*epi*-hydantocidin (**219**) is approximately 1:4. The latter was prepared starting from an unanticipated reaction of **268** to give **269** in the presence of TPAP (*Scheme 62*).[86] With KNCO **269** was transformed to urea **270**. Treatment with KO*t*-Bu caused interconversion from the pyranose form to the thermodynamically more stable furanose **272**, presumably *via* intermediate **271**, although this was not detected. Hydrolysis gave 5-*epi*-hydantocidin (**219**). Control experiments confirmed that prolonged exposure of **219** to TFA resulted in interconversion of 5-*epi*-hydantocidin and hydantocidin with the former predominating.



Scheme 62

c) *Synthesis of Hydantocidin Analogs Modified in the Base*

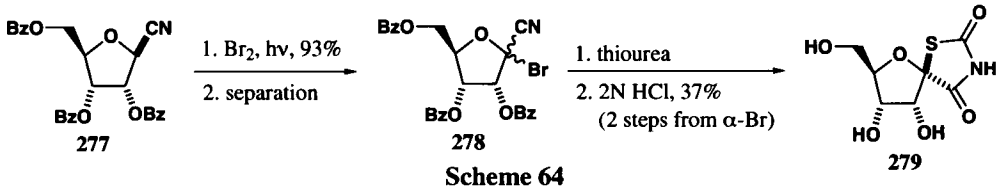
Thiooxohydantocidin was prepared as shown in *Scheme 63*,[87] starting from alcohol **167**, which was silylated and converted stereoselectively to anomeric azide **273** (βN_3:αN_3, 25:1). The low yield in the second step was due to partial loss of the TBDMS group during the azide-forming reaction. The silyl-deprotected material could be resilylated to give additional **273**. Oxidation of **273** to the carboxylic acid using *in situ* generated ruthenium tetroxide, followed by generation of the mixed anhydride and treatment with ammonia, gave amide **274**. Reaction of **274** with CS_2 and Bu_3P gave a separable mixture of thiohydantoins, which was converted to thiohydantocidin (**275**)



Scheme 63

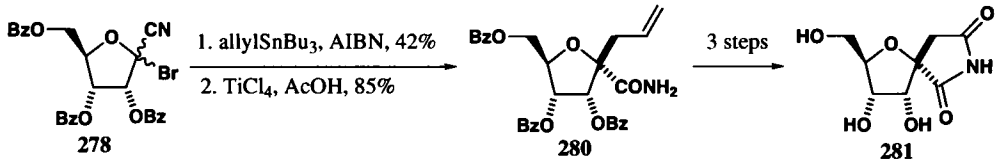
and 5-*epi*-thiohydantocidin (**276**) after removal of the isopropylidene and silyl groups. The isomerization occurred during the cyclization and not the deprotection steps and was not noted in the hydantocidin series. It and the low yield in the cyclization was explained by the poor reactivity of carbon disulphide in the aza-Wittig reaction. In an antiherbicidal assay against 10 troublesome weeds, thiooxohydantocidin **275** was equipotent to hydantocidin in 9/10 cases, but 5-*epi*-thiooxo-hydantocidin **276** was superior to 5-*epi*-hydantocidin (**219**) (8/10).

Lamberth and Blarer proposed 6-*thia*-hydantocidin (**279**) and 6-carbahydantocidin (**281**) as more stable analogs able to resist acid catalyzed epimerization. Their preparations are described in *Schemes 64* and *65*.[88] Radical bromination of nitrile **277** gave the anomeric bromides **278** in excellent yield, but in a 1:1 ratio. These were separable, and the α-Br anomer provided the desired product, 6-*thia*-hydantocidin (**279**), following addition of thiourea, acid catalyzed cyclization and deprotection (*Scheme 64*).



Scheme 64

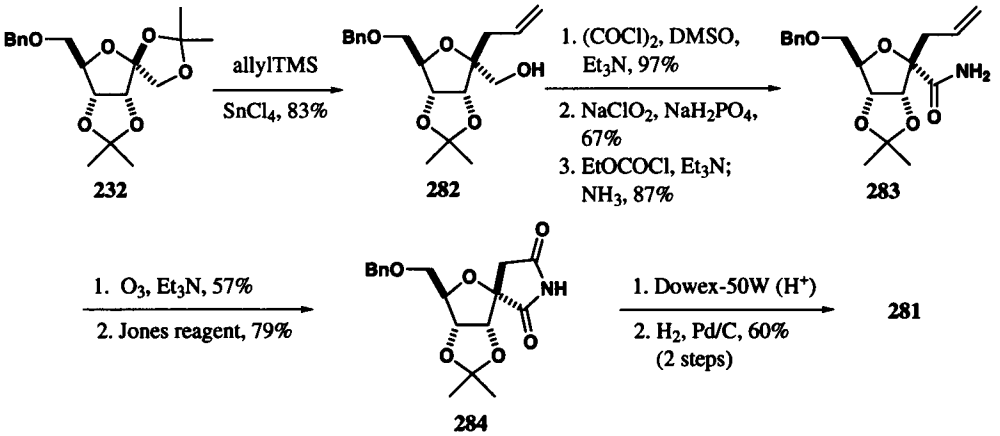
Radical allylation of the mixture of bromides **278** with allyltributylstannane gave the β-allyl adduct selectively (β:α, 5:1) in 42% yield (*Scheme 65*). Mild hydrolysis of the nitrile gave



Scheme 65

amide **280** which was converted by the approach (see *Scheme 66*) employed by Sano and coworkers[89] to 6-carbahydantocidin (**281**).

Sano and coworkers' approach to 6-carbahydantocidin (**281**) is shown in *Scheme 66*.[89] Psicofuranose **232** underwent a highly stereoselective β-allylation (β:α, 21:1) with



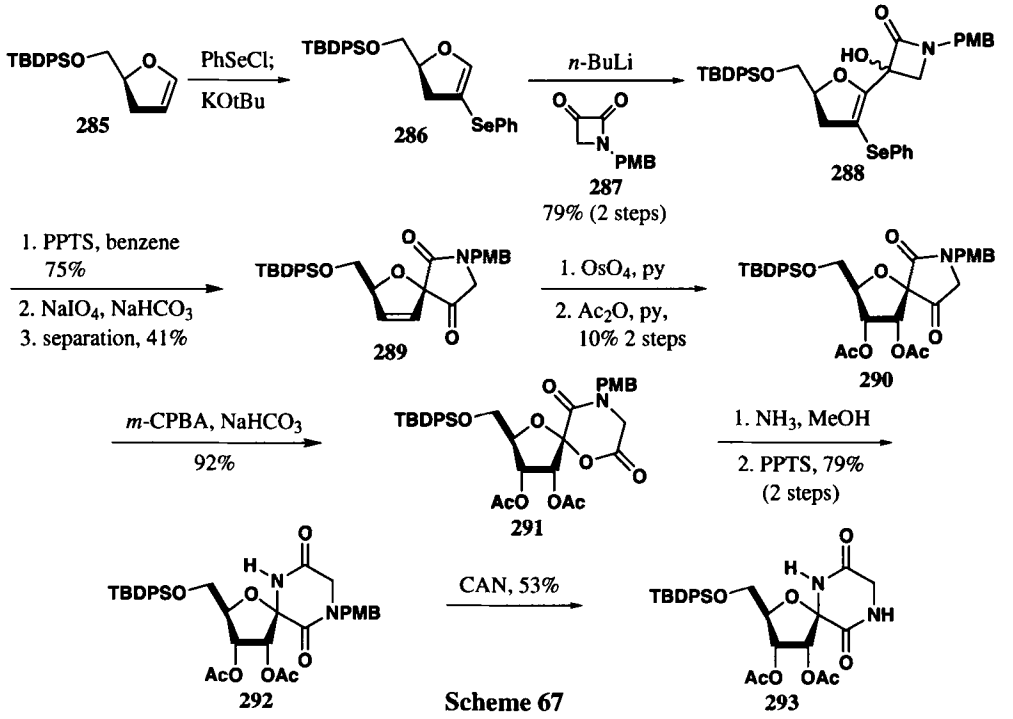
232 **282** **283** **284**

Scheme 66

allyltrimethylsilane/$SnCl_4$ to give **282** in high yield. Conversion to amide **283** proceeded under standard conditions. The succinimide ring was constructed by ozonolysis, followed by Jones oxidation of the intermediate aminal, resulting in **284**. Double deprotection gave target compound **281**. The overall yield was 13%. When tested against three common weeds, **281** was 70-90% as potent as hydantocidin at the same concentration, indicating that one of the NH groups may not be essential for activity.

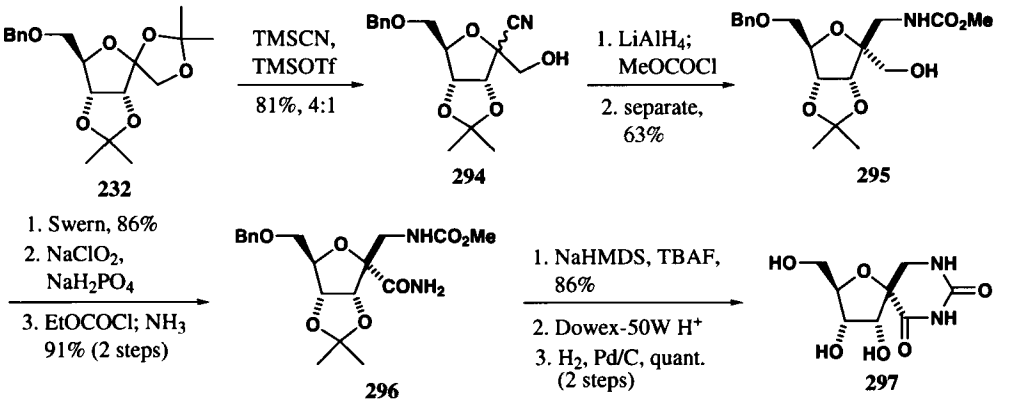
Paquette and coworkers prepared hydantocidin analogs in which the hydantoin ring was replaced by a diketopiperazine (*Scheme 67*).[90] Glycal **285** was converted to vinyl selenide **286**, which was lithiated and the vinyl anion treated with azetidinedione **287**, resulting in **288**. Rearrangement gave four isomers of a pyrrolidinedione, which were reduced to two isomers following oxidative elimination of the selenide with $NaIO_4$. Dihydroxylation of one of these, alkene **289**, proceeded with poor facial selectivity (β:α, 4:1), but the desired isomer **290** was separated upon acylation. Baeyer-Villiger oxidation provided morpholine **291**, which underwent ammonolysis to a 1:1 mixture of isomeric lactol amides that closed in the presence of acid to afford a single diketopiperazine **292**. Debenzylation gave **293**. Isomers isolated en route to **293** could be similarly treated to give diastereomeric diketopiperazines.

The dihydrouracil hydantocidin derivative **297** was prepared by Sano, Mio and coworkers as shown in *Scheme 68*.[91] Reaction of **232** with TMSCN in the presence of TMSOTf gave **294** as a mixture of anomers (81%, 4:1 ratio). The two isomers could be separated, but this was more easily done later. Consequently, the mixture was reduced and converted to the corresponding carbamates. The two isomers were then separated, and the major isomer **295** (63%)



Scheme 67

was transformed to amide **296** by known procedures. Cyclization was unsuccessful with NaHMDS, but the combination of NaHMDS and TBAF gave the dihydrouracil, which was deprotected to give **297**. Unlike hydantocidin and the succinimide derivative **281**, **297** was completely inactive as a herbicide.



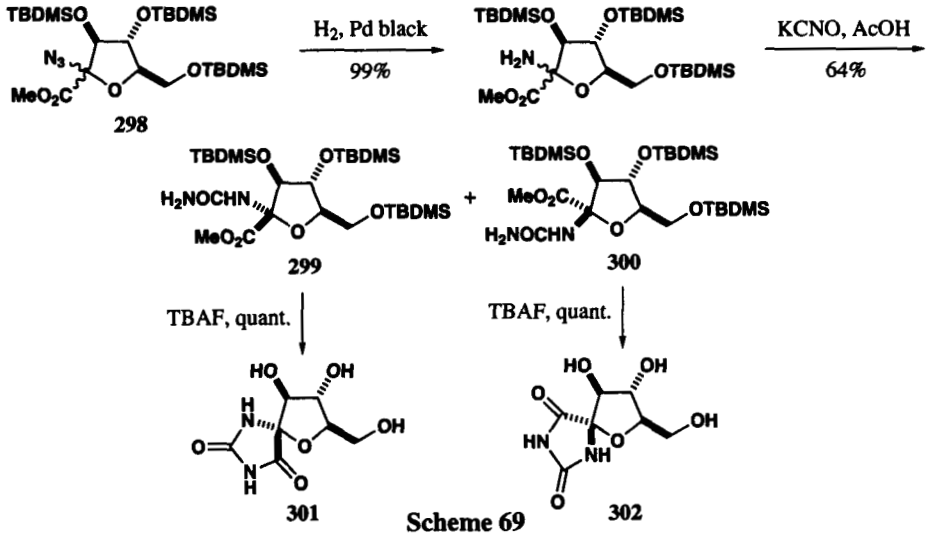
Scheme 68

d) Synthesis of Hydantocidin Analogs Modified in the Sugar

There are many analogs of hydantocidin that have been prepared that vary from the natural material in the structure of the sugar. These are outlined in the following section, but

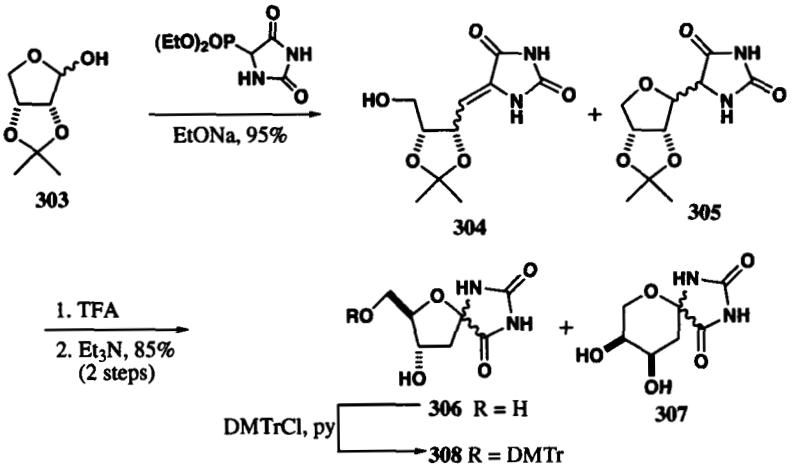
herbicidal activity for these ribose modified hydantocidin analogs has been typically poor or non-existent.

The C3-C4 *trans* diol isomers **301** and **302** of hydantocidin were prepared by Fleet and coworkers from α-azido esters **298** (*Scheme 69*).[92] Using chemistry developed in their group, **298** was prepared and reduced to a mixture of amines, which gave the corresponding ureas **299** and **300** on treatment with KNCO. These were configurationally stable under the reaction conditions and separable by chromatography. Treatment of each diastereomer with TBAF promoted hydantoin formation and deprotection, resulting in **301** and **302**.



Scheme 69

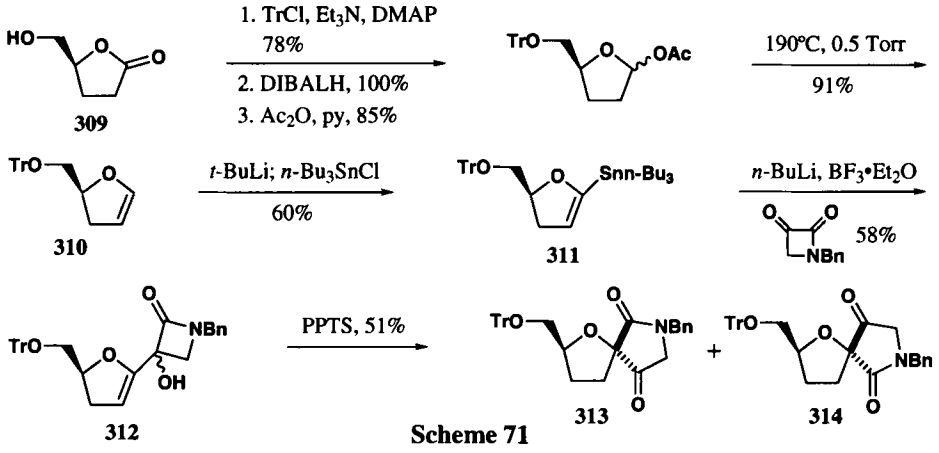
Kotera and coworkers[93] prepared 2a-DMTr-4-deoxyhydantocidin analogs **308** from lactol **303** (*Scheme 70*). Wadsworth-Horner-Emmons reaction gave a 1:1 mixture of **304** and **305**, each as a mixture of isomers. Deprotection of the acetonide, followed by cyclization with



Scheme 70

base, gave the epimeric hydantoins **306** along with their pyranose forms **307**. Selective tritylation of the primary alcohol of **306** allowed separation of **306** from **307** and of 2a-DMTr-hydantocidin (10% from **306**) from its C5 epimer (30% from **306**).

Paquette and Behrens reported the preparation of protected 3,4-dideoxyhydantocidin **313** and protected 3,4-dideoxy-*epi*-hydantocidin **314**, prepared by a 1,2 carbonyl group transposition similar to one shown earlier (*Scheme* 67).[94] As shown in *Scheme 71*, homochiral glycal

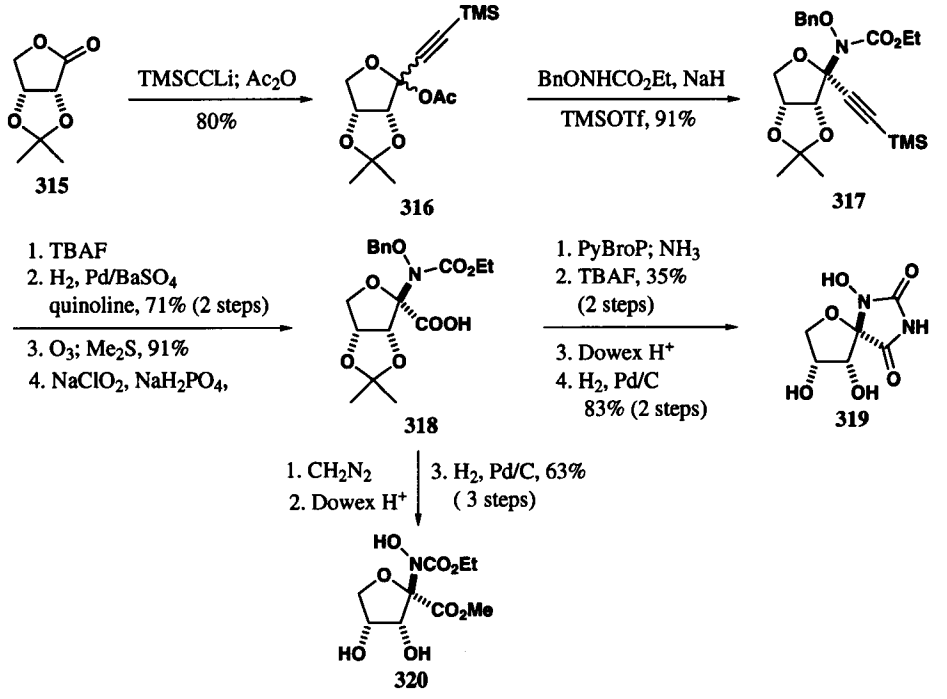


Scheme 71

310 was prepared from lactone **309** *via* a four step sequence. This was metallated at the enol ether, and the intermediate vinyl lithium was converted to stannane **311**. Remetallation with *n*-BuLi, followed by BF_3 promoted addition to an azetidinedione, gave **312** as a 1:1 mixture of isomers. Precomplexation of the Lewis acid to the azetidinone was essential to prevent its simple deprotonation by the vinyl anion. The acid catalyzed rearrangement of **312** gave a separable 1:2 mixture of **313** and **314** in a total yield of 51%.

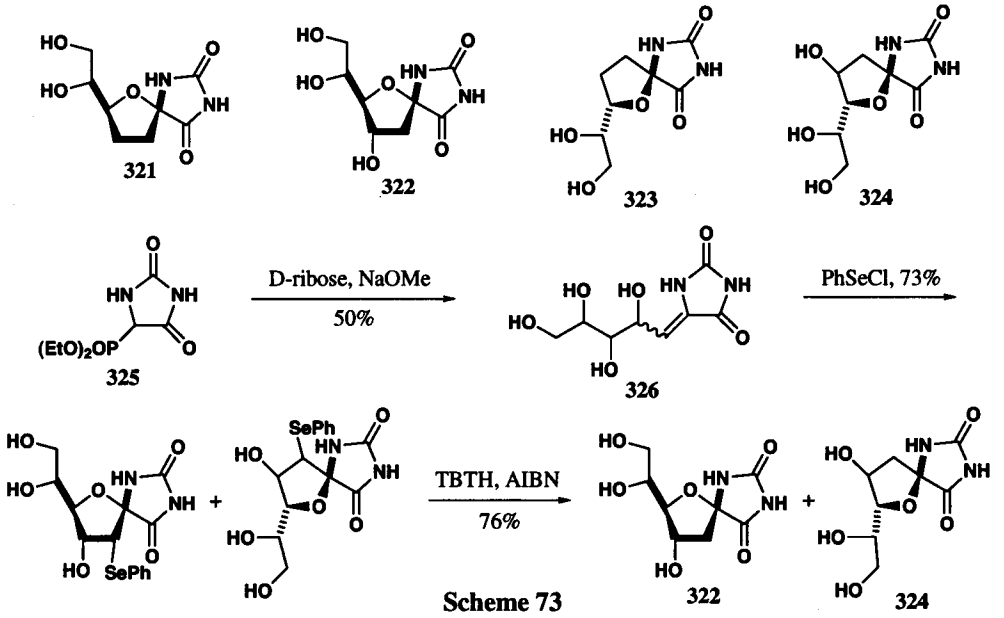
Hanessian and coworkers prepared the 2-deshydroxymethyl-*N*-hydroxyhydantocidin analog **319** and the ring opened analog **320** from 2,3-*O*-isopropylidene-D-erythronolactone **315**, as shown in *Scheme 72*.[95] Reaction with TMS acetylide, followed by acetylation, gave **316** as a mixture of anomers. This mixture was transformed to **317** as a single anomer by reaction with a protected hydroxamate in the presence of TMSOTf. Deprotection of the alkyne, reduction to the alkene and ozonolysis gave an aldehyde which was oxidized to acid **318**. This was converted to hydantocidin analog **319** by amide formation, cyclization with TBAF and double deprotection (hydrolysis followed by hydrogenolysis). Alternatively, the monocyclic analog **320** was prepared from **318** by esterification with diazomethane, followed by the same double deprotection. Both **319** and **320** lacked herbicidal activity when tested against a number of moncot and dicot plants.

Hosmane and coworkers prepared four ribose modified hydantocidin analogs **321-324**,[96] all of which were either weakly active or inactive when tested against glycogen



Scheme 72

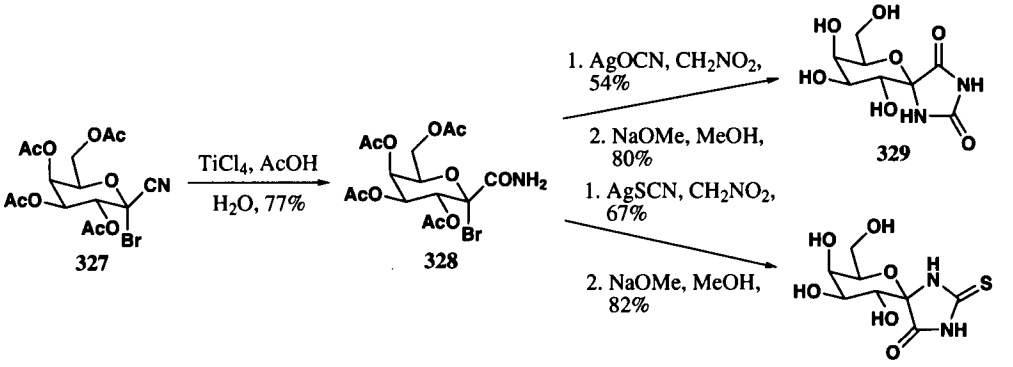
phosphorylase *b* (*vide infra*). The most potent, **322**, had a K_i of 8.2 x 10^{-3} M and was prepared as shown in *Scheme 73*. Wittig reaction of imidazolidinedione phosphonate **325** with D-ribose



Scheme 73

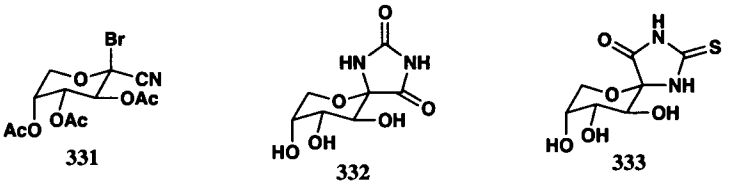
gave alkene **326** as a mixture of *E* and *Z*-isomers which was not separated. Electrophilic cyclization using PhSeCl, followed by radical removal of the selenide, gave **322** and its isomer **324** in a 2.4:1 ratio. These were separable by HPLC.

Somsak, Szilagyi and coworkers prepared four pyranoside analogs of hydantocidin and thiooxohydantocidin, as shown in *Scheme 74*.[97] Hydrolysis of (1*R*)-1-bromo-D-galactopyranosyl cyanide (**327**) under mild conditions afforded α-bromo amide **328**. Treatment of this with

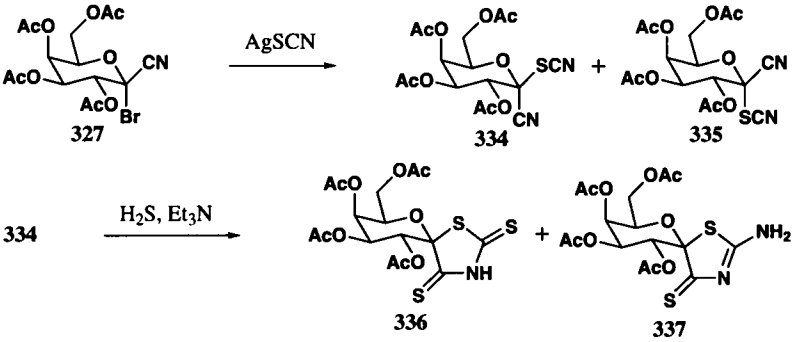


Scheme 74

silver cyanate or silver thiocyanate gave, after deprotection, the pyranose derivatives **329** of *epi*-hydantocidin and of thiooxohydantocidin **330**. The *arabino* sugar **331** gave hydantocidin analog **332** and *epi*-thiooxohydantocidin analog **333** by the same methods.

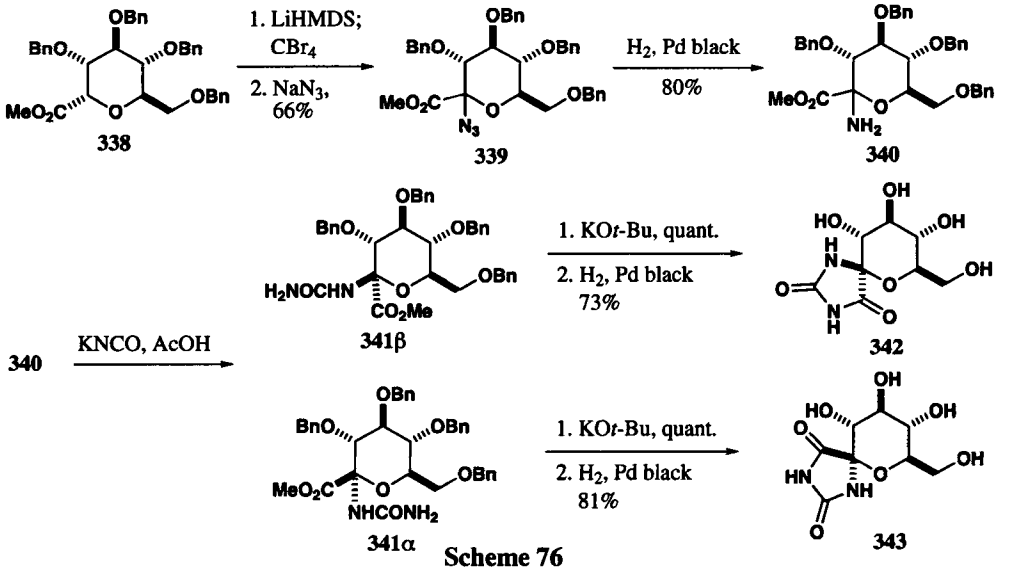


In a later paper by the same group, reaction of α-bromo nitrile **327** with thiocyanate gave a separable mixture of the two anomers **334** and **335** in a 3:2 ratio in 75% yield (*Scheme 75*).[98] Treatment of **334** with hydrogen sulphide gave **336** (58%) and **337** (12%).



Scheme 75

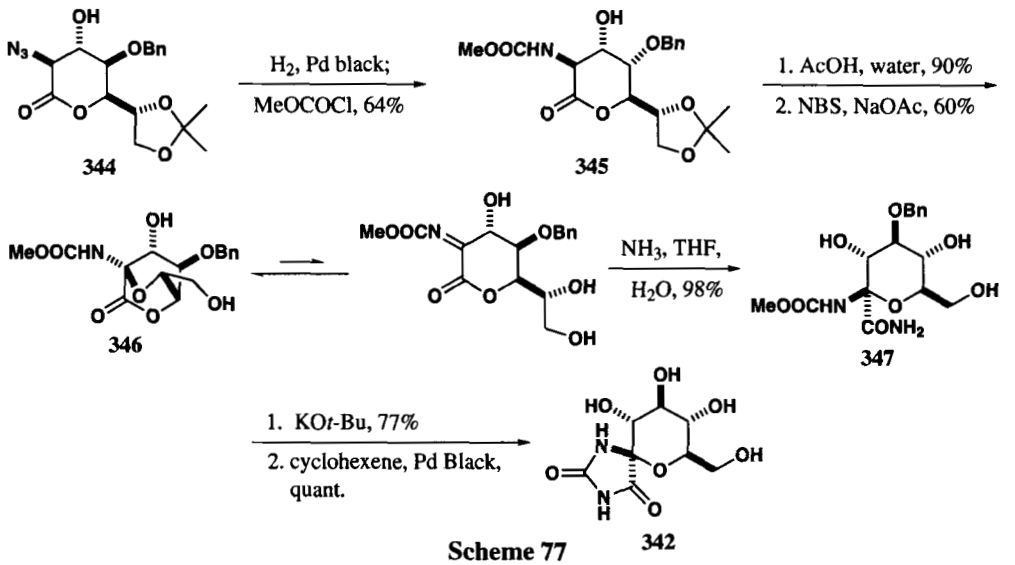
Fleet and coworkers have published extensively on the synthesis of hydantocidin analogs modified in the ribose portion. Their interest was not in compounds with herbicidal activity but rather in inhibitors of glycogen phosphorylase (Gpb) as potential therapeutic agents for the treatment of diabetes. Hydantocidin analogs **342** and **343** with the glucopyranose configuration were prepared as shown in *Scheme 76*.[99] Axial ester **338** was converted to



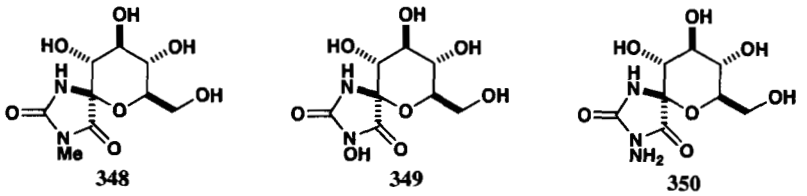
Scheme 76

the corresponding enolate which was brominated; the bromides were then converted to the corresponding azides **339**. Reduction gave a mixture of amines **340** (3:1, 86% combined), which could be separated but interconverted in solution. Therefore, the mixture was converted to ureas **341α** and **341β**. Separation gave pure **341β**, but **341α** was contaminated with about 10% **341β**. Both anomers were elaborated to the corresponding hydantoins **342** and **343** by cyclization and deprotection. When tested against Gpb, β-anomer **342** was found to be a competitive inhibitor with a $K_i = 3.1$ μM.

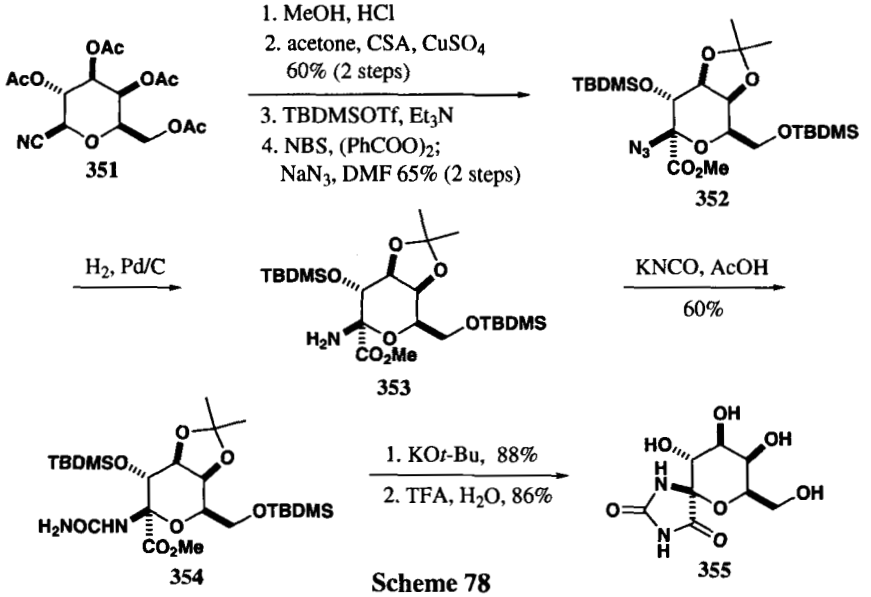
The same group later published an improved synthesis of the β-anomer (*Scheme 77*).[100] This route was β-specific and suitable for large-scale work. The starting material was β-azide **344**, which was reduced to the amine, followed by *in situ* addition of methylchloroformate. Under these conditions carbamate **345** was isolated in 64% yield. The acetonide was removed and oxidation with NBS gave an equilibrium mixture of lactones **346**. The lactone was opened with ammonia to give amide carbamate **347**. Cyclization with KO*t*-Bu, followed by deprotection, afforded **342**. Analogs **348**, **349** and **350** were also prepared using amines other than ammonia in the ring-opening step. The K_i values for **348** and **349** were 1.2 and 0.039 μM, respectively.



Scheme 77



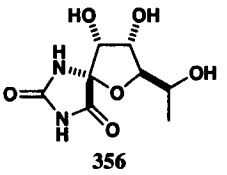
The Fleet group also reported the synthesis of a galactopyranose derivative **355** of hydantocidin.[101] This was prepared as shown in *Scheme 78* from nitrile **351**, which was transformed into α-azido ester **352** in four steps. Reduction initially afforded a single equatorial



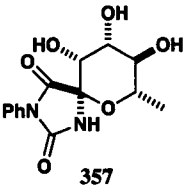
Scheme 78

amine **353**, although on standing this underwent equilibration to a mixture of anomers with the more stable axial anomer predominating. However, reaction of the mixture with potassium isocyanate, gave a single urea **354**. Presumably the axial amine was unreactive under the reaction conditions. Cyclization, followed by deprotection, proceeded as before to give **355**. Unlike the corresponding glucopyranose isomer **342**, the galactopyranose isomer **355** was completely inactive against glycogen phosphorylase.

Using similar procedures, rhamnofuranose **356**[102] and rhamnopyranose **357**[103] analogs were prepared by the same group. In the same two papers, rhamnofuranoses **361** and **362**[102] and

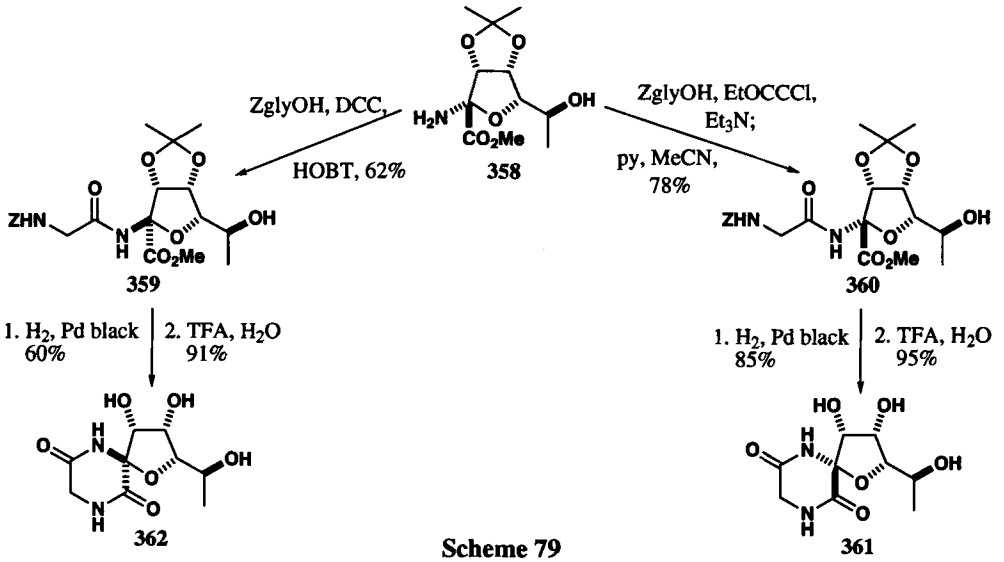


356



357

rhamnopyranose **366**[103] diketopiperazine analogs of hydantocidin were prepared. For the furanose diketopiperazines,[102] reaction of amine **358**, available from reduction of the corresponding azide, with Z-gly gave one of two products, depending on the method for activation of the acid (*Scheme 79*). Using DCC, the major product was amide **359**. The explanation for this was that

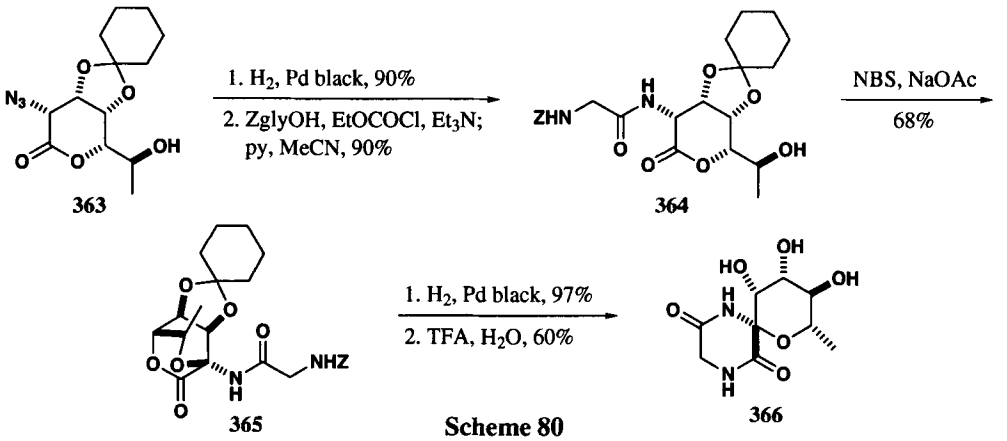


Scheme 79

the O-acyl isourea intermediate for DCC was less reactive than the mixed anhydride, and, thus, **358** equilibrated to a small amount of the more reactive, but less stable, amine epimer under the reaction conditions. Using the mixed anhydride, amide **360**, having retention of configuration at the anomeric center, was isolated. Hydrogenolysis of **360** was followed by a rapid and spontaneous cyclization to a diketopiperazine, which was fully deprotected with 50% TFA to give **361**.

Epimer **359**, however, required several days to cyclize following hydrogenolysis, and the yield was significantly lower. Deprotection gave diketopiperazine **362.**

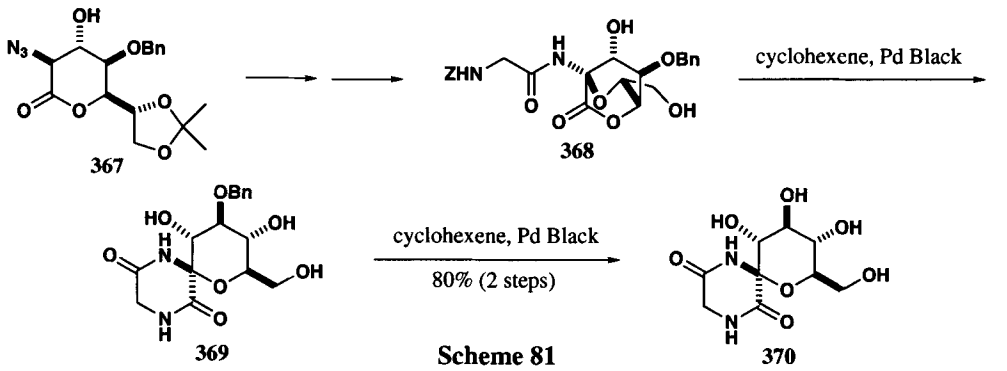
Rhamnopyranose diketopiperazine **366** was prepared as shown in *Scheme 80.*[103] Reduction of the azide in **363** provided the corresponding amine, which was acylated with ZGly. Oxidation of **364** with NBS gave bridged lactone **365** in 68% yield, based on recovered starting material. Hydrogenolysis of the carbamate gave the diketopiperazine *via* ring opening of the lactone with the free amine. Hydrolysis gave **366.**



363 **364** **365** **366**

Scheme 80

Bridged lactone **368** was used for the preparation of diketopiperazine glucopyranose **370** (*Scheme 81*).[104] Lactone **368** was prepared from azide **367** in a similar manner to the preparation of bridged lactone **365** from azide **363**. Next, sequential transfer hydrogenolysis first

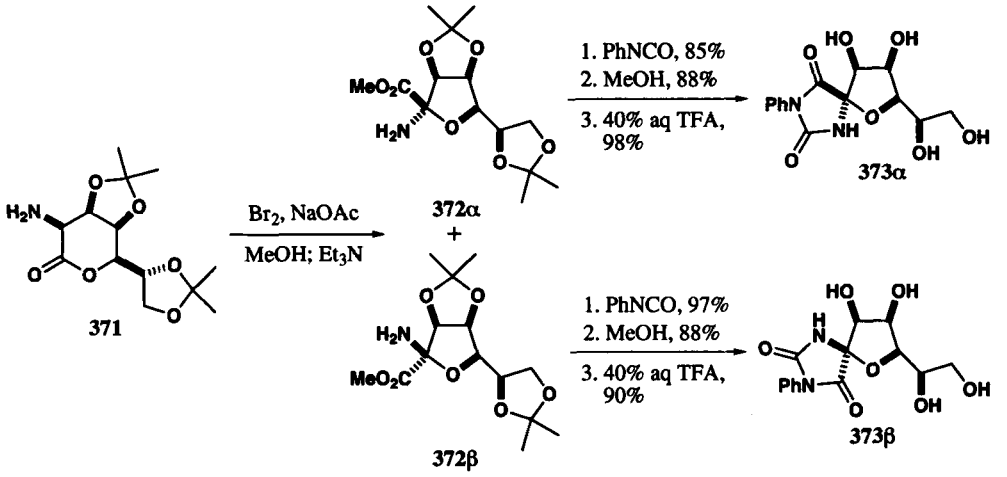


367 **368** **369** **370**

Scheme 81

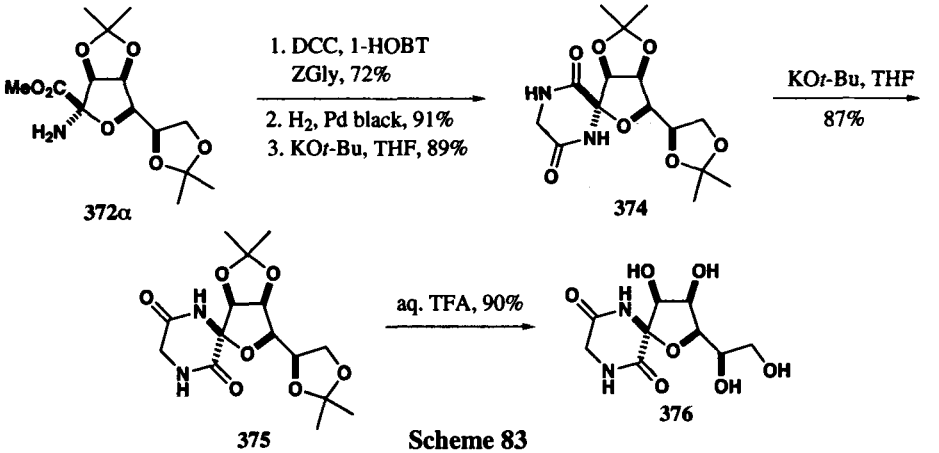
removed the carbamate protecting group. The resulting amine spontaneously cyclized to diketopiperazine **369** from which the benzyl group was cleaved in a subsequent hydrogenolysis under identical conditions. When tested against glycogen phosphorylase, spirodiketopiperazine **370** was not as potent as the spirohydantoin glucopyranose **342**; however, it did not inhibit a number of other glycosidases, indicating selectivity for glycogen phosphorylase over other sugar processing enzymes.

In the absence of an internal nucleophile a bridged lactone cannot form, and this was exploited in the route to N-Ph-hydantocidin mannofuranose isomers **373β** and **373α** (*Scheme 82*).[105] Oxidation of amine **371** with bromine in methanol, followed by the addition of Et_3N gave, presumably *via* the corresponding imine, ring contracted furanose **372β** as the major product (60%), along with epimer **372α** (17%). These were moderately stable but interconverted in solution to a 5:1 mixture (**372β** /**372α**). Addition of phenylisocyanate to **372β**, spontaneous cyclization in MeOH and deprotection completed the synthesis of **373β**. Mannofuranose isomer **373α** was prepared in the same way from **372α**. Surprisingly, unlike other hydantocidin sugar analogues, neither **373β** nor **373α** underwent equilibration in the presence of the strongly acidic conditions required for deprotection of the acetonides.



Scheme 82

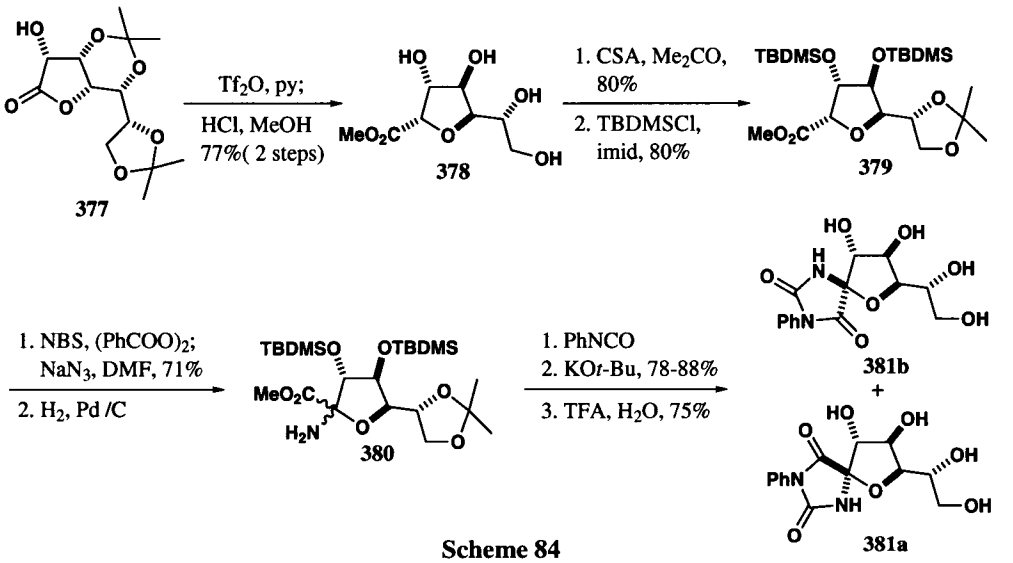
The amino sugar **372α** was also converted into diketopiperazine **374**, as shown in *Scheme 83*.[106] This was isomerized into **375** in 87% yield. Hydrolyis gave diketopiperazine mannofuranose analog **376**, again without anomeric scrambling. The explanation for this was



Scheme 83

that the thermodynamically stable form has the anomeric nitrogen and diol unit syn to each other. This is consistent with the greater stability of 5-*epi*-hydantocidin in comparison to hydantocidin.

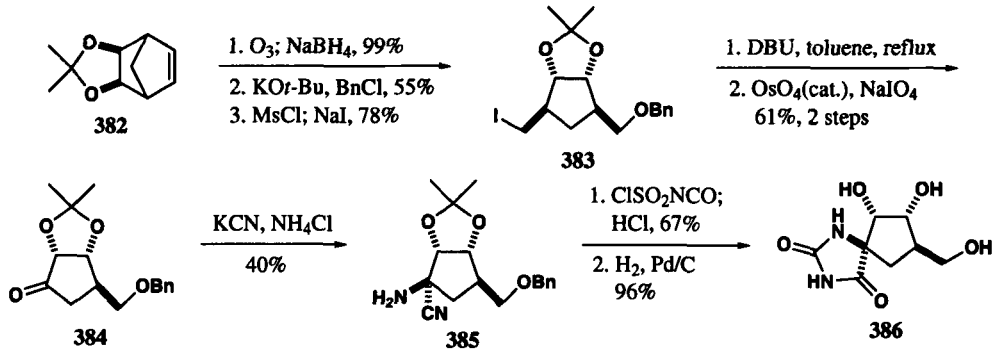
The Fleet group also reported two syntheses of a *N*-phenylglucofuranose derivative of hydantocidin. The more efficient is shown in *Scheme 84*.[107] The readily available diacetonide **377** of glucoheptonolactone was converted to the corresponding triflate. Hydrolysis of the



Scheme 84

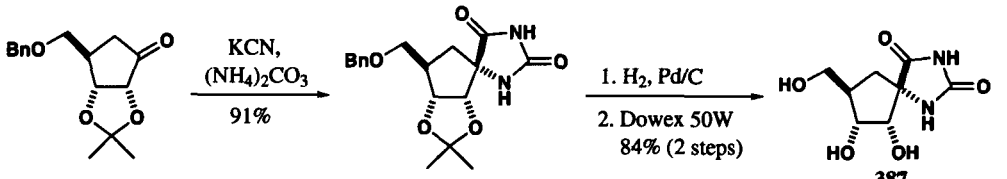
protecting groups was accompanied by a selective rearrangement to tetrahydrofuran **378** in 77% overall yield. Selective protection of the least hindered diol was followed by silylation of the remaining secondary alcohols, resulting in **379**. Radical bromination gave a mixture of relatively unstable α-bromoesters, which on addition of azide gave a separable mixture of α-azido esters (1:1, 71%). Each isomer was reduced separately but gave a mixture of α-amino esters **380** due to interconversion. The pure α-anomer gave only the α-urea on reaction with PhNCO. The β-anomer, however, gave a mixture of α- and β-ureas under the same conditions. Cyclization and deprotection gave **381β** and **381α**. During the final deprotection step a small amount of the C5-epimer was formed but this could be removed by recrystallization. Later the analogs lacking the *N*-phenyl substituent were prepared by similar procedures.[108]

As with more traditional nucleosides, the hydantocidin sugar moiety has been replaced by a carbocycle. For example, racemic hydantocidin **386** in which the ribose was replaced by a cyclopentane (carbocyclic hydantocidin) was prepared by Sano and Sugai as shown in *Scheme 85*.[109] Alkene **382**, prepared from 2,5-norbornadiene by a known procedure, was cleaved with ozone, monobenzylated and converted to iodide **383** by mesylation and displacement with sodium iodide. Elimination of HI with DBU, followed by treatment with OsO_4, gave lactone **384**. After some experimentation, reaction of **384** with KCN/NH_4Cl at 90°C provided β-amine **385** as the major product (40%) along with α-amine (15%). Hydantoin



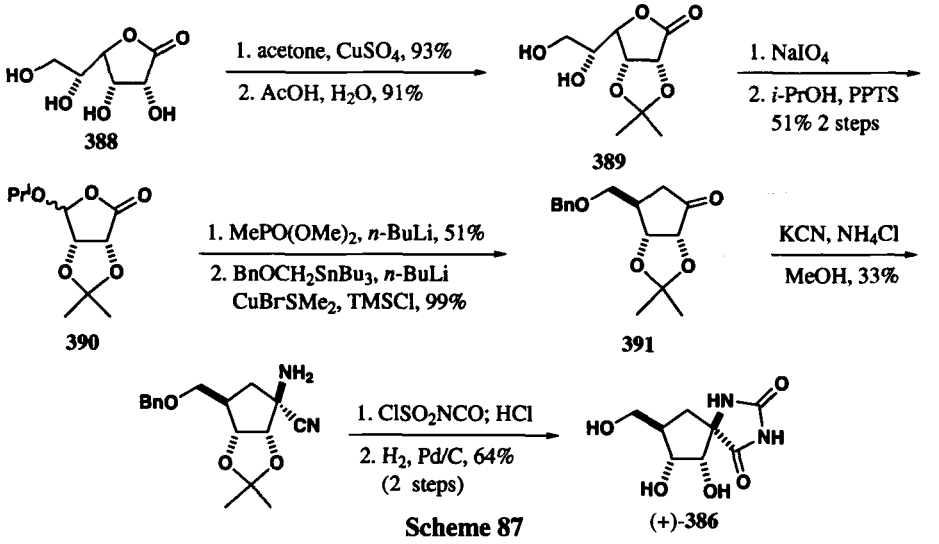
Scheme 85

formation from **385** was achieved by reaction with $ClSO_2NCO$. Acetonide cleavage with HCl, followed by hydrogenolysis, gave carbocyclic hydantocidin **386**. Similar treatment of the α-amine gave 5-*epi*-carbocyclic hydantocidin **387**. However this could be prepared more conveniently as shown in *Scheme 86*. The racemic mixture of **386** was active against three weed species whereas its C5-epimer **387** was inactive.



Scheme 86

As the biological activity of hydantocidin resides only in the (+)-enantiomer, it was assumed that the (+)-enantiomer of carbocyclic hydantocidin would also be more active. This was shown to be true by the same group. The synthesis of the (+)-enantiomer is shown in *Scheme 87*.[110]



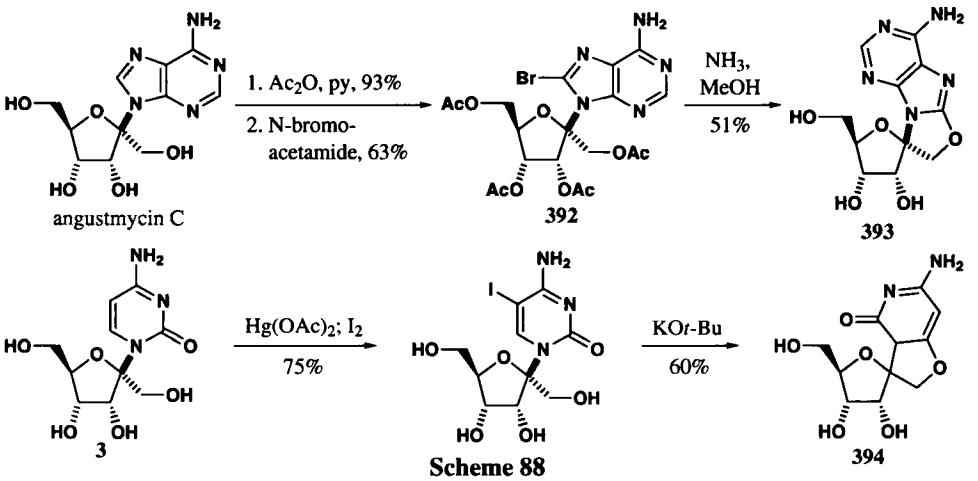
Scheme 87

D-Gulono-1,4-lactone (**388**) was converted to mono-acetonide **389** by *bis*-acetonide formation, followed by selective deprotection. The side chain was oxidatively cleaved, and the resultant compound was converted to acetal **390**. Cyclopentenone formation and subsequent stereospecific conjugate addition of the organocuprate derived from benzyloxymethyllithium gave (-)-**391** as a single isomer. Completion of the synthesis proceeded as for the racemic series, resulting in (+)-carbocyclic hydantocidin **386**.

2. Other Spirocyclic *psico*-Nucleosides

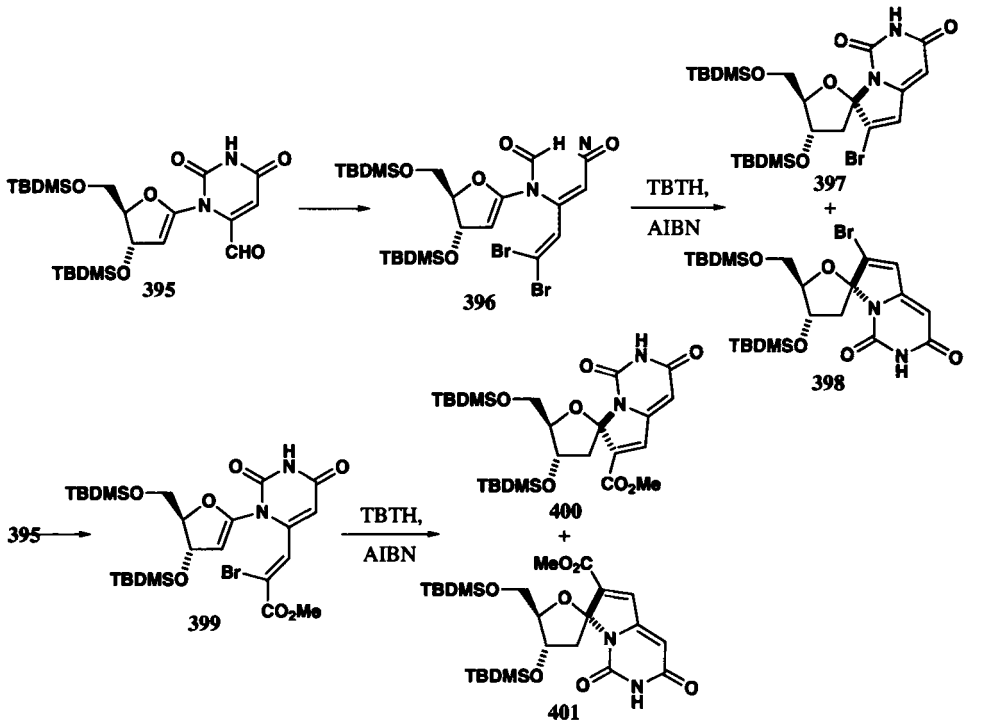
A number of spirocyclic *psico*-nucleosides have been prepared where the spiro-fusion is from the anomeric carbon to a point on the nucleobase. Again, we have covered those examples where there is a carbon-branching at the anomeric carbon and where the compounds have been specifically prepared as nucleoside analogs.

An early example of spirocyclic *psico*-nucleoside related to angustmycin C was reported in 1981 by Zavgorodny.[111] Angustmycin C was peracetylated with acetic anhydride and brominated with *N*-bromoacetamide to give **392**. Treatment with ammonia in methanol caused simultaneous cyclization and deprotection, resulting in **393**. A similar series of reactions with the non-protected cytosine angustmycin C analog **3** gave **394** (*Scheme 88*).

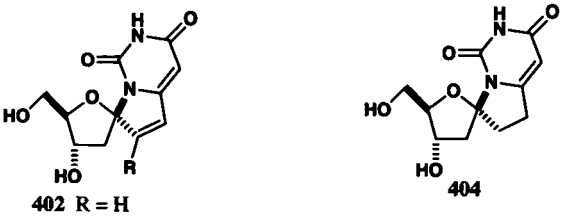


Scheme 88

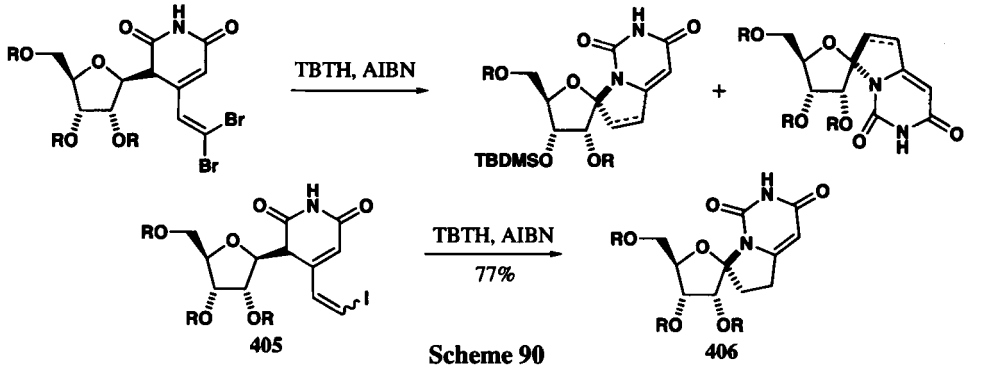
A series of spirocyclic *psico*-nucleosides was reported by Tanaka and coworkers (*Scheme 89*).[112] Aldehyde **395** underwent a Wittig reaction to give dibromoalkene **396**. Radical cyclization of this gave, after HPLC seperation, **397** (35%) and **398** (6%). These were deprotected to afford the corresponding nucleosides. A similar Wittig reaction gave **399** as the major isomer. Radical cyclization gave **400** (12%) and **401** (2%). Similar results were obtained by Gimisis and Chatgilialoglu.[113] Further transformation of the bromide or ester groups in **397** or **400** provided other modified analogs, **402**, **403** and **404**.



Scheme 89



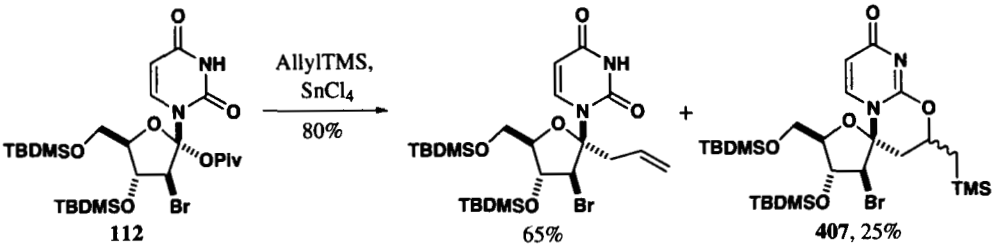
A later paper by the same group used similar procedures to prepare related products.[114] The problem with the method was that under the reaction conditions up to four products were obtained (see *Scheme 90*), and, therefore, the individual yields were often low. One exception



Scheme 90

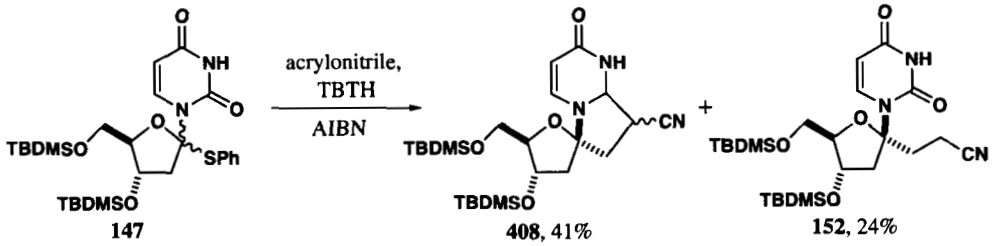
was vinyl iodide **405**, either diastereomer of which provided alkane **406** in good yield.

In the Lewis acid catalyzed reaction of **112** with allyltrimethylsilane discussed earlier, the anticipated allylated product (see *Table 1*) was acompanied with 25% of spironucleoside **407** (*Scheme 91*).[45]



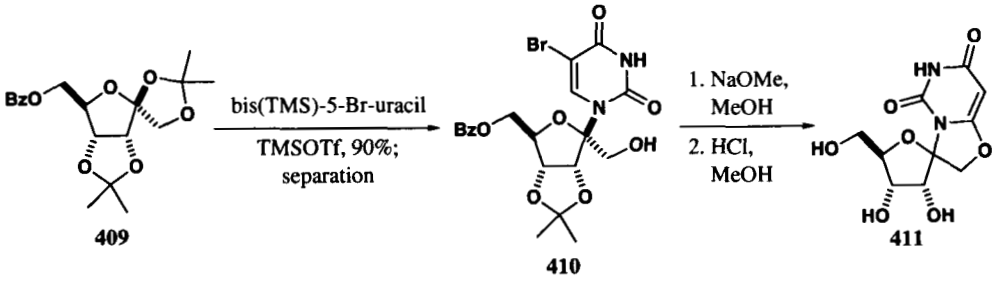
Scheme 91

In the generation and reaction of anomeric radicals described earlier (see *Scheme 37*) careful control of the reaction conditions was required to control the product distribution (*Scheme 92*).[55] Thus, when a mixture of TBTH/AIBN was added slowly to a refluxing solution of **147** and acrylonitrile, the major product (41%) was in fact the spirocyclic compound **408** along with **152** (24%).



Scheme 92

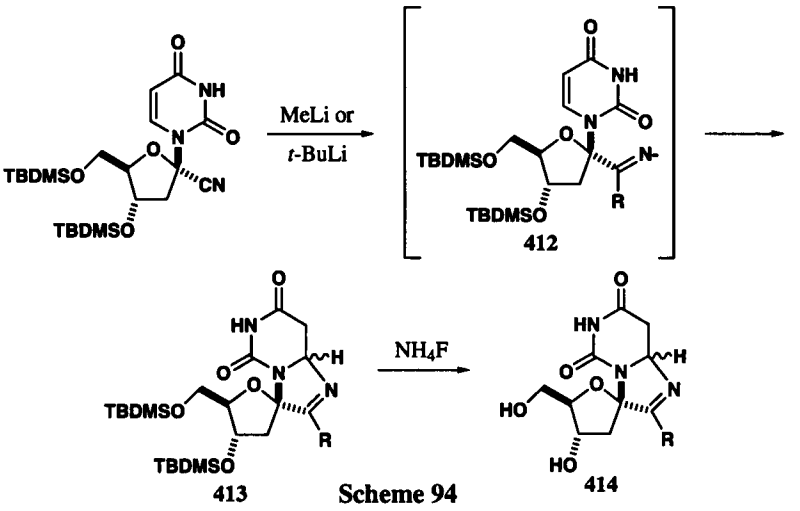
The spirocyclic uracil analog **411** has been prepared by Sarma *et al.* as shown in *Scheme 93*.[13] Benzoate **409** was coupled with bis (TMS)-5-bromouracil to give a 1:1 mixture of anomers in 90% yield. These were separable, and the β-anomer was cyclized and deprotected.



Scheme 93

The addition of organolithium reagents to previously described cyanide *psico*-nucleosides (see *Scheme 30*) can be diverted to give a spirocyclic nucleoside, as shown in *Scheme 94*,

instead of a ketone.[47] Rapid protonation/hydrolysis of the intermediate imines (*e. g.*, **412**) gave ketones (see **114**). Using a more dilute solution and allowing the reaction to proceed for a longer time allowed the imine to undergo addition to the uracil, providing **413**. Deprotection afforded spirocyclic nucleoside **414**.



Scheme 94

In summary, a fairly extensive range of *psico*-nucleosides has been described in the literature.[115] Some, such as the cyclopropyl-homo-*psico*-nucleoside **160**, have shown *in vitro* activities superior to known chemotherapeutic agents in some screens. Many others have been weakly active or inactive. Nevertheless, considering the range of nucleoside classes that has been explored, many avenues for *psico*-nucleoside synthesis remain. There are few direct comparisons of the activity of *psico*-nucleosides with the corresponding nucleosides possessing a reducing sugar. A possible role for the additional C1'-branching (traditional nucleoside numbering) in providing greater metabolic stability or additional interactions with target sites of action has not been investigated at a fundamental level. Thus, the potential importance of incorporating C1'-branching in nucleosides represents an area of research that has ample scope for continued exploration.

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