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Efficient synthesis of several methylene-expanded oxetanocin nucleoside analogues

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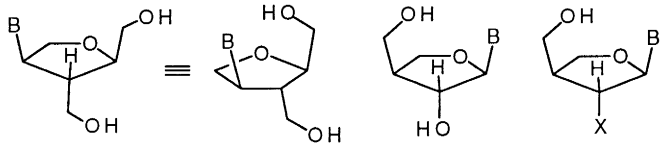
Abstract

S-Glycidol **4** has been converted by a direct route via the dihydrofuran-3-methanols **9ab** into a series of methylene-expanded oxetanocin nucleoside analogues, e.g., analogues of the normal nucleosides **2** and the known antiviral nucleosides, AZT, FdT, and ddC, **3**.

Keywords: nucleoside synthesis; anhydro nucleosides; cyclic stereocontrol; alkoxyepoxide chemistry.

Several modified nucleosides have become useful agents for the treatment of viral diseases due to their good antiviral activity.[1] In particular, nucleosides with somewhat abnormal structures, e.g., L-nucleosides or isonucleosides, have been shown to be very useful antiviral agents.[2] Recently we published a general synthesis of several 'methylene-expanded' oxetanocin isonucleosides **1** in which a methylene group was inserted between the ring oxygen and the carbon bearing the base. One of these — the thymidine analogue **1a** — showed quite good antiviral activity (TI>250).[3] We now report a very efficient synthesis of a different class of 'methylene-expanded' oxetanocin analogues **2**, in which the methylene group is inserted between the oxygen and the carbon bearing the hydroxymethyl group. In addition we report the synthesis of several modified nucleosides in this class, namely those containing azido, fluoro, or hydrido groups in place of the secondary hydroxyl, **3**. This de novo synthesis uses a novel approach, in which all of the asymmetry required is derived from the inexpensive precursor *S*-glycidol **4**.



1 (**1a** B = Th) **2** **3**

Sharpless asymmetric epoxidation of allyl alcohol using D-(+)-DIPT and cumyl hydroperoxide afforded *S*-glycidol **4** in 43% yield and >90% ee[4] (Scheme 1). This compound has been prepared in a very large scale by an industrial application of this process.[5] Treatment of the anion of **4** with 2-chloroethenyl phenyl sulfone **5** (prepared in three steps and 82% overall yield from 1,1,2-trichloroethane)[6] afforded the addition–elimination product, the 2-alkoxyvinyl sulfone **6**, in 78% yield.[6] Treatment of **6** with

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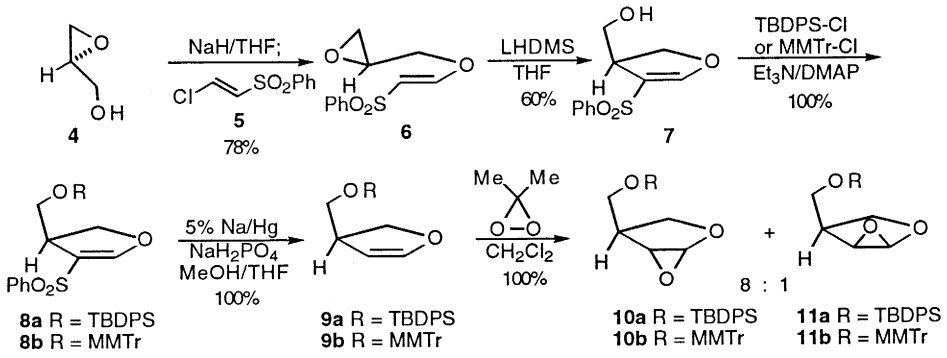
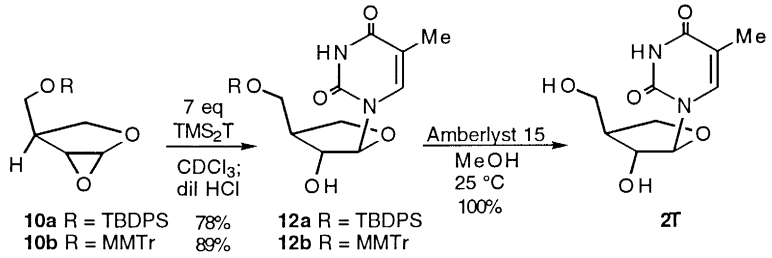


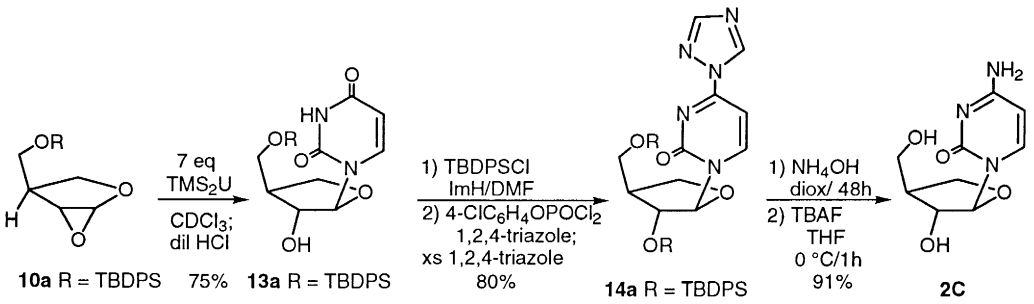
Scheme 1.

LHMDS gave in 60% yield the cyclized product **7**, the alcohol of which was protected as either the *tert*-butyldiphenylsilyl (TBDPS) or monomethoxytrityl (MMTr) ether, **8ab**, in quantitative yield. Sodium amalgam reduction gave the desired enol ethers **9ab** also in quantitative yield.

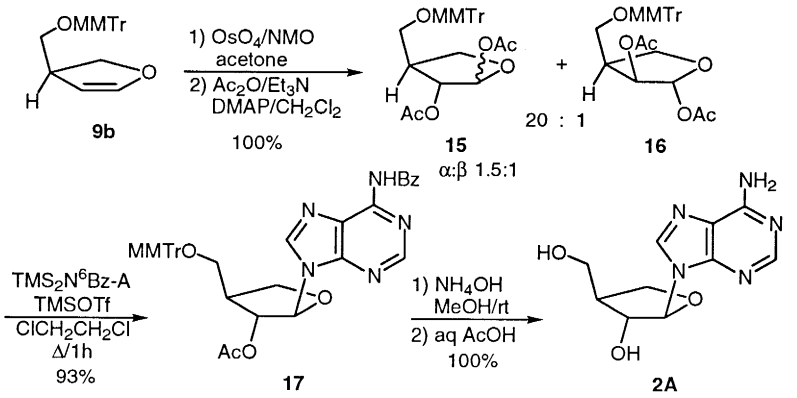


Scheme 2.

Epoxidation with dimethyl dioxirane gave the epoxides **10ab** as the major isomers as an 8:1 ratio with the opposite diastereomers **11ab** in quantitative yield. These two key compounds were then converted into the desired modified nucleosides as shown in Schemes 2–5. Both of the ethers **10ab** could be opened with excess bis-silylated thymine to give in good yields the protected nucleoside analogues **12ab**, the latter of which could be hydrolyzed to give **2T** in quantitative yield (Scheme 2). The cytidine analogue **2C** could also be prepared by treatment of the epoxide **10a** with excess bis-silylated uracil to give the protected nucleoside analogue **13a** in 75% yield (Scheme 3). Protection of the secondary alcohol as the TBDPS ether and conversion of the amide into the triazole afforded the bis-silyl ether triazole **14a** in 80% yield. Final conversion to the cytosine ring and deprotection of both silyl ethers gave the cytidine analogue **2C** in 91% yield. The purine analogues were prepared by a different route again starting with the enol ether **9b** (Scheme 4). Dihydroxylation using catalytic osmium tetroxide and NMO followed by acetylation gave a quantitative yield of a 20:1 ratio of the two isomeric diacetates **15**, as a 1.5:1 mixture of α- and β-anomers, and **16** as only the α-anomer. Reaction of this mixture with the N^6-benzoyl bis-

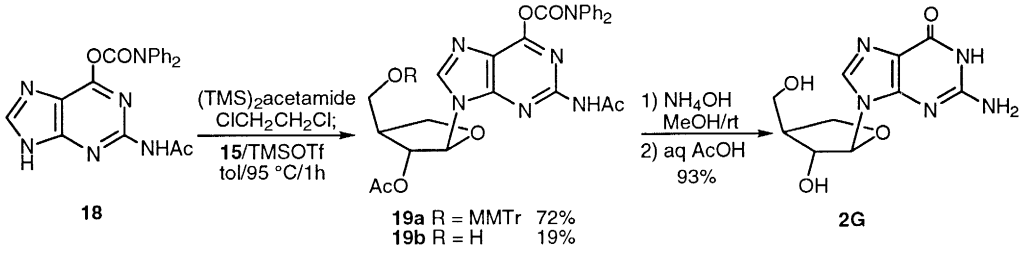


Scheme 3.



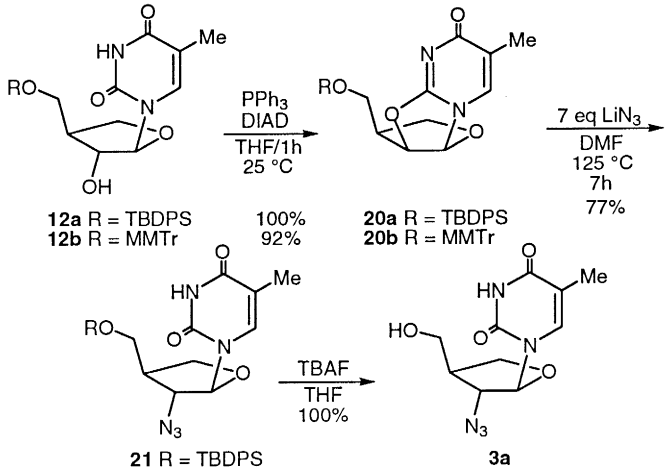
Scheme 4.

silylated adenine in the presence of trimethylsilyl triflate (TMSOTf) afforded in 93% yield the desired β-anomer **17** which was debenzoylated and then deprotected to give the adenosine analogue **2A**. Finally a similar route afforded the guanosine analogue (Scheme 5). Thus the known carbamate **18** (prepared in two steps from guanine by acetylation followed by *O*-acylation with diphenylcarbamoyl chloride)[7] was bis-silylated using bis(trimethylsilyl)acetamide and then treated with the diacetate **15** and TMSOTf to give a mixture of the MMTr ether and the alcohol **19ab** in yields of 72% and 19%, respectively. These compounds were both treated with ammonium hydroxide and then the protecting groups were removed to give the guanosine analogue **2G**.

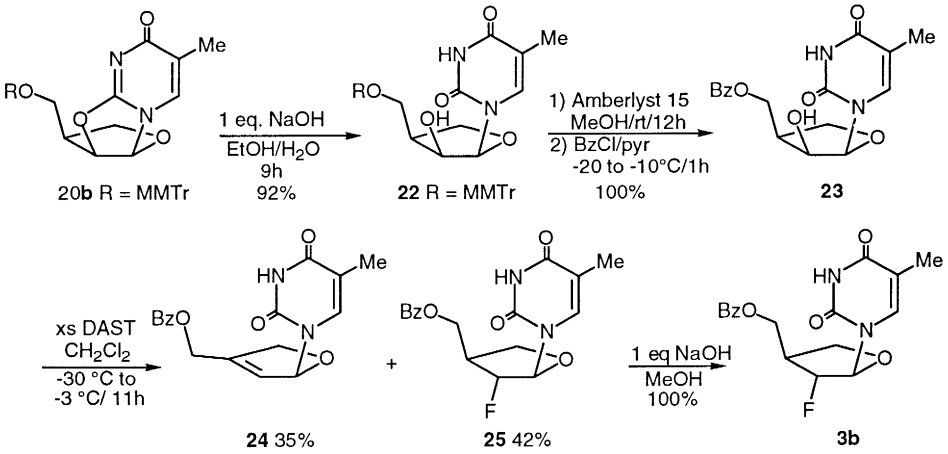


Scheme 5.

In addition to preparing the simple analogues of the natural nucleosides, we also wished to prepare several analogues which resembled more closely the well known antiviral agents, such as AZT, FdT,

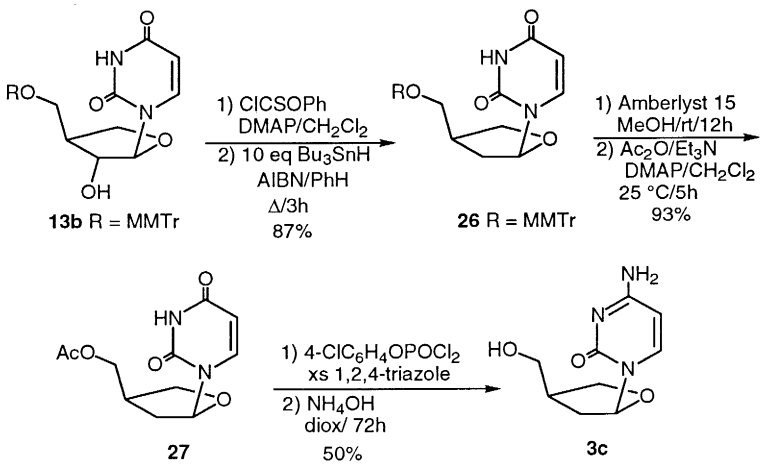


Scheme 6.



Scheme 7.

ddC, etc. Therefore we decided to prepare the three analogues, **3abc**, in which azido, fluoro, and hydrido groups replaced the secondary hydroxyl group of the appropriate nucleosides. The syntheses of these compounds are shown in Schemes 6–8. Thus, an internal Mitsunobu reaction on the two protected thymidine analogues **12ab** using diisopropyl azodicarboxylate (DIAD) afforded the 1′,2′-anhydronucleosides **20ab** in excellent yield. Opening of the silyl ether **20a** with excess lithium azide in DMF at 125°C furnished the azidothymidine **21** in 77% yield along with 17% recovered starting material. Cleavage of the TBDPS protecting group afforded the desired AZT analogue **3a** in quantitative yield. The preparation of the fluoro analogue was somewhat more difficult since we were unable to get clean opening of either 1′,2′-anhydronucleoside with fluoride ion (e.g., by using the method of Green and Blum).[8] Therefore we had to use a longer but more certain route as follows (Scheme 7). Basic hydrolysis of the anhydro nucleoside **20b** afforded the secondary alcohol of retained stereochemistry **22** in 92% yield. The protecting group on the primary alcohol was exchanged for a benzoate in two steps to give the alcohol **23**. Treatment of this alcohol **23** with excess DAST gave a 42% yield of the inverted fluoride **25** along with 33% of the elimination product **24**. The desired nucleoside analogue of FdT **3b** was then prepared in quantitative yield by basic hydrolysis of the benzoate of **25**.



Scheme 8.

The final analogue, the ddC analogue **3c**, was prepared as shown in Scheme 8. The monomethoxytrityl ether of the uridine analogue **13b** was deoxygenated by a Barton–McCombie procedure,[9] namely by formation of the phenyl thionocarbonate and treatment with excess tributylstannane to give the

deoxygenated compound **26** in 80% yield for the two steps. Exchange of the trityl protecting group for an acetate was effected in two steps and 93% yield to give the acetate **27**. Final transformation of the uridine to the cytidine via the normal triazole procedure gave the desired ddC analogue **3c** in 50% yield.

The details of the synthesis and the results of testing of some of these novel compounds will be reported in due course. The preparation of novel nucleoside analogues is currently underway in our laboratories.

Acknowledgements

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