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Conformationally Locked Bicyclo[4.3.0]nonane Carbanucleosides: Synthesis and Bio-evaluation.

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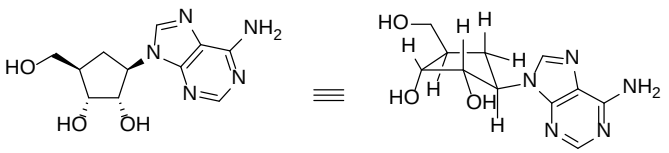
D-Ribose has been converted into 3 novel carbobicyclic nucleosides bearing a bicyclo[4.3.0]nonane framework in 16-19 steps with 5-12 % overall yields involving a Wittig olefination and an intramolecular Diels-Alder reaction as the key steps. The present synthesis also provides an efficient entry for chiral hydrindenones. The conformation studies of these carbanucleosides and their bio-evaluation as potential antiviral agents are reported.

Introduction

In recent years, carbocyclic nucleosides or carbanucleosides have warranted tremendous attention from both synthetic and medicinal chemists.[1-2] The replacement of the oxygen atom in the furanose ring by a methylene unit provides both enzymic and chemical stability, attributable to the loss of a true glycosidic linkage.[3] However, there is a significant change in the conformation due to the loss of the gauche and anomeric effects which exist in conventional nucleosides. These effects maintain the sugar moiety of the nucleoside in either a C3'-*endo* (North) or a C2'-*endo* (South) conformation.[4] In the absence of these effects, the conformation of carbocyclic nucleosides is mainly governed by the steric bulk of the nucleobase, which prefers to occupy the equatorial position and adopts an atypical C1'-*exo* conformation. The conformation of nucleosides is intriguing since any structural−activity relationship (SAR) study of antiretroviral nucleosides is complicated by the complexity of the anabolic process of activation. It involves three enzymatic steps to transform the nucleoside into its 5'-triphosphate (NTP), plus the final interaction of the NTP with the target enzyme, the reverse transcriptase (RT). Therefore, the preferences of conformation exhibited by the nucleoside, or its nucleotides, must be identified at each intervening enzymatic step. The only step which is invariant and common to all nucleoside RT inhibitors, is the final interaction of NTP with RT. The route to NTP anabolite, however, involves different kinases, all of which are highly dependent on the nature of the heterocyclic base.[5]

Aristeromycin is a representative and its conformation is illustrated in Figure 1.[6] It has been reported to be potent inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, which plays an important regulatory role in *S*-adenosyl-L-methionine (AdoMet)-dependent methylation process.[7] The methylation process is important as most plant and animal viruses require a methylated cap structure at the 5'-terminus of their mRNA for viral replication. However, their cytotoxicity precludes clinical use.[8-10]



Aristeromycin C1'-exo

Figure 1. Naturally occurring carbocyclic nucleoside Aristeromycin.

There are not many accounts on the syntheses of bicyclic carbanucleosides. In 1993, Rodriguez *et al.* pioneered the construction of dideoxyribonucleoside analogues with a bicyclo[3.1.0]hexane backbone (Figure 2) which constrains the conformation of the analogue back to the C2'-*exo* (North).[11] From then on, different kinds of conformationally restricted carbocyclic nucleosides that lock the conformation as either North or South were reported.[12]

Coxsackie B viruses[13] are single strand positive-sense RNA viruses and contain six serotypes of pathogenic enteroviruses that trigger illness ranging from gastrointestinal distress to full-

fledged pericarditis and myocarditis. They resist a wide variety of chemical treatment and to the best of our knowledge, there is still no-well accepted treatment for the Coxsackie B viruses and it is interesting to see whether our compounds could be a potential drug to treat the viruses.[14]

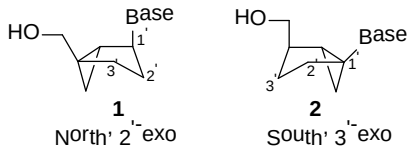


Figure 2. Conformationally locked nucleosides with a bicyclo[3.1.0]hexane system.

However, up to date, only carbobicyclic nucleosides with a bicyclo[3.1.0]hexane and a bicyclo[3.3.0]octane system were described. There is still no publication on the syntheses of carbanucleosides with a bicyclo[4.3.0]nonane system. Therefore, it is fascinating to see if they exhibit any antiviral activity. Furthermore, according to our theoretical calculation, carbanucleosides with a cyclohexane ring *cis*-fused to a cyclopentane ring should exist in either a C1'-*exo* or a C3'-*endo* conformation, which is in close agreement to the North conformer of conventional nucleosides (Figure 3) and may show RNA antiviral activity.

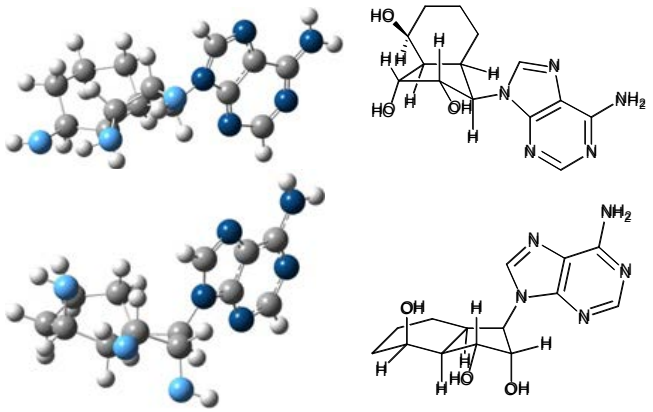


Figure 3. Conformation of bicyclic carbanucleosides calculated by DFT model: Above: C1'-*exo* conformation; Bottom: C3'-*endo* conformation.

To synthesize this class of carbobicyclic nucleosides for biological studies, we first have to synthesize the bicyclo[4.3.0]nonane core. Functionalized hydrindenones (bicyclo[4.3.0]nonenones) are versatile intermediates in complex natural product synthesis, e.g., the CD ring in steroids. It is noteworthy that syntheses of chiral functionalized hydrindenones were not an easy task via an intramolecular cycloaddition.[15] To date, only a few publications reported the intramolecular Diels-Alder (IMDA) reaction on sugars and most of these papers documented the syntheses of *trans*-decaline systems.[16] Only one report described the synthesis of a bicyclo[4.3.0]nonenone, involving a lengthy synthetic route.[17] Jarosz *et al.* reported the syntheses of chiral bicycle[4.3.0]non-2-enes from a sugar allyltin. However, the choice for protecting groups was limited as Lewis acid was employed in the preparation of the IMDA precursors.[18] In this paper, we reported a shorter route with milder conditions for the construction of chiral hydrindenone intermediates.

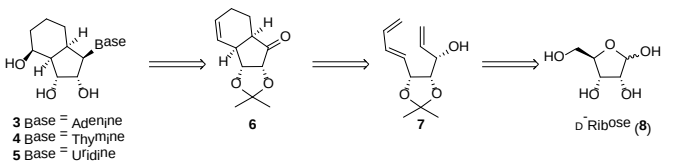
Results and Discussion

Theoretical Calculation

Gaussian 09 program package[19] was used to calculate the structures of the carbanucleosides with density functional theory (DFT) quantum chemical method. Equilibrium geometries of all molecules were fully optimized at the B3LYP/6-31G(d) level of theory.[20] Stationary points were characterized as either minima (no imaginary frequency) or transition structures (only one imaginary frequency) by calculation of the vibrational frequencies using analytical gradient procedures at the same level. Minimum energy pathways connecting the reactants and products were confirmed by intrinsic reaction coordinate (IRC) calculation.[21]

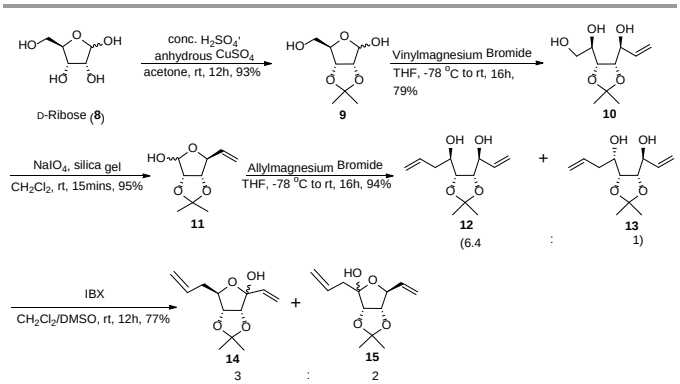
Synthesis

Retrosynthesis of the target carbanucleosides (**3**-**5**) shows that it could be synthesized from cycloadduct **6**, which would be prepared from D-(–)-ribose (**8**) via triene **7**, using an IMDA reaction as the key step (Scheme 1).

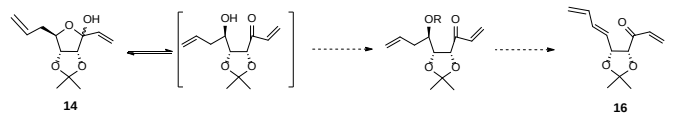


Scheme 1. Reterosynthesis of the target nucleosides.

Starting from D-(–)-ribose (**8**), the 2,3-diol in **8** was isopropylidenated to afford acetonide **9**,[22] which was then subjected to vinylation to give alkene **10** in good yield.[23] Glycol cleavage oxidation of the vicinal diol in **10** gave lactol **11**, which with allylmagnesium bromide furnished dienes **12** and **13** in a ratio of 6:1, respectively and in excellent overall yields. Aqueous indium allylation only led to decomposition of staring material. Oxidation of **12** with IBX provided a mixture of lactols **14** and **15** in a 3:2 ratio, which could not be separated by column chromatography (Scheme 2). We hoped to utilize the equilibrated open-chain form of **14** and to eliminate the homoallylic alcohol to form IMDA precursor **17** (Scheme 3). Different elimination conditions were examined, but no positive results were observed after exhaustive experimentation.

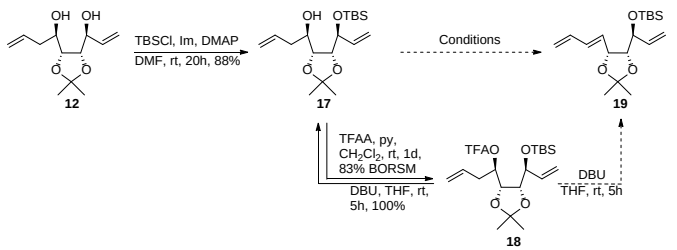


Scheme 2. Synthesis of lactol **14** and **15**.



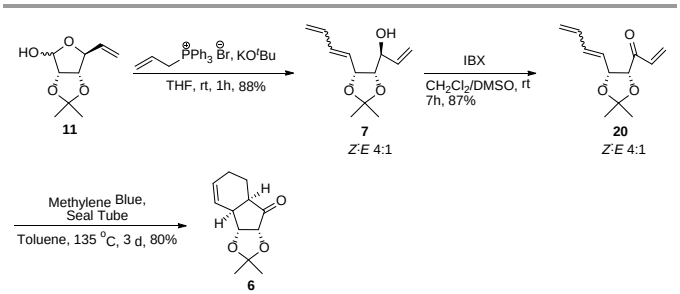
Scheme 3. Equilibrium between ring and chain form of **14**.

Since the ring opening-elimination approach failed, we changed our synthetic avenue to a protection and deprotection approach (Scheme 4). The allylic hydroxyl group in the diol **12** was protected as silyl ether **17** in good yield. The homoallylic hydroxyl group was then attempted to be eliminated. However, after trying different methods, silyl ether **17** only reacted with trifluoroacetic anhydride (TFAA) to give trifluoroacetate **18** which was then subjected to elimination in the presence of DBU. However, no triene **19** was detected, beyond recovery of alcohol **17** quantitatively. The use of other bases did not yield any desired **19**.



Scheme 4. Attempted synthesis of triene **19**.

We therefore revised our synthetic strategy and discovered that lactol **11** was a good candidate for Wittig Reaction[24] with allyltriphenylphosphonium bromide[25] to introduce the diene functionality (Scheme 5). After screening with different bases, potassium *tert*-butoxide (KO^{t}Bu) in THF gave the best yield of triene **7** in 88% with *Z* to *E* ratio in 4:1. The geometric isomers were not separable by column chromatography. In order to enhance the selectivity, Horner-Wadsworth-Emmons Olefination (HWE)[26] was tried but no reaction was observed with different kind of bases such as dimsyl sodium and *n*-butyllithium. The mixture of trienes **7** was subjected to oxidation with IBX as oxidant and furnished trienone **20** in 87% yield. Trienone **20** was highly unstable and polymerized quickly after standing in vacuum. Trienone **20** underwent IMDA reaction in toluene in the presence methylene blue in a sealed tube to give hydrindenone **6** in good yield. The structure and absolute configuration of **6** was confirmed by X-ray crystallography (Figure 4).



Scheme 5. Synthesis of **6**.

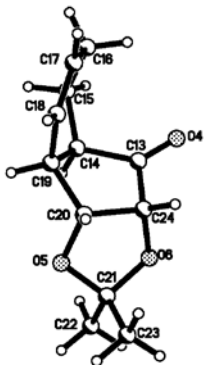


Figure 4. X-ray structure of **6**.

Initially we believed that *cis* to *trans* isomerization of the diene in **20** should precede the cycloaddition. However, theoretical calculations disagreed with this idea since the relative energy of the isomerization is surprisingly high (99 kcal/mol), which was 50 kcal/mol higher that the published value.[27] Therefore, the stereoselectivity of the cycloadduct could be explained by the proposed transition state models as shown in Figure 5. For *E*-**20**, two possible transition states, **TS-1** and **TS-2**, in the *endo* mode of cycloaddition, would lead to the formation of two thermodynamically favorable *cis*-fused cycloadducts **6** and **21**. Theoretical calculations also agreed with these results. However, the steric repulsion between the isopropylidene and the newly formed 6-memberd ring in the transition state might inhibit the formation **21**. **TS-3** might give **22** but unfortunately **22** was unable to detect. For *Z*-**20**, **TS-5** was not favorable due to the steric repulsion between the isopropylidene and the newly formed 6-memberd ring and in **TS-6**, the highly twisted conformation might inhibit the formation of the *trans*-fused cycloadduct **22**.

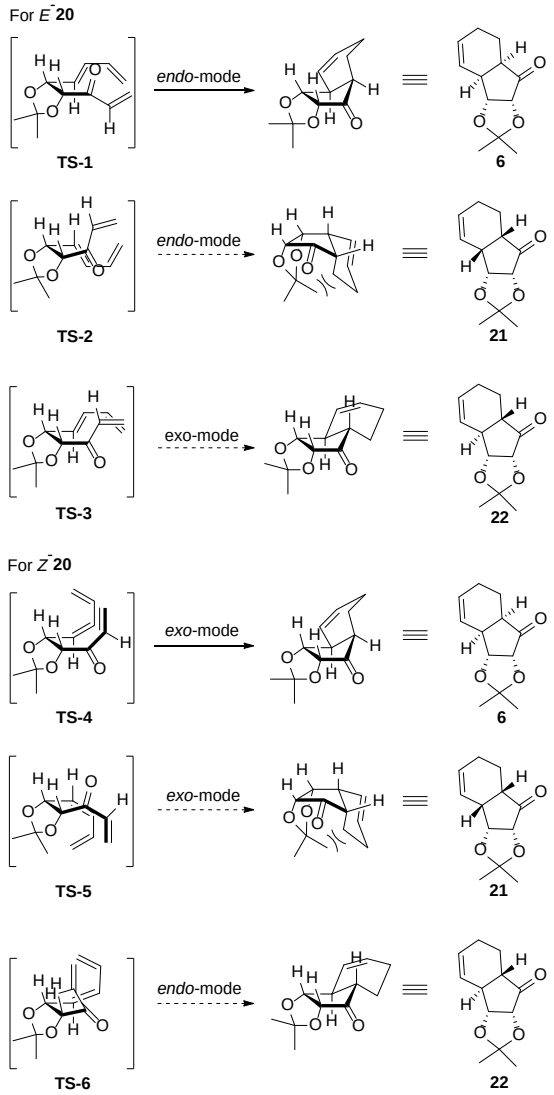
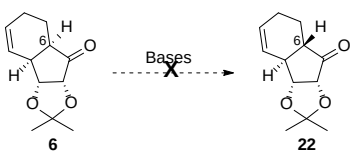


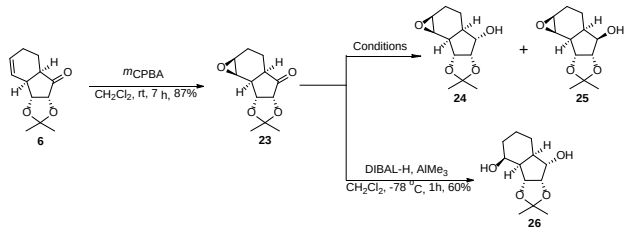
Figure 5. Proposed transition state models of the cyclization of trienone **20**.

Since there was no *trans*-fused cycloadduct **22** isolated in the previous step, epimerization was tried but failed to occur after many attempts and under a wide variety of conditions (Scheme 6).[28]



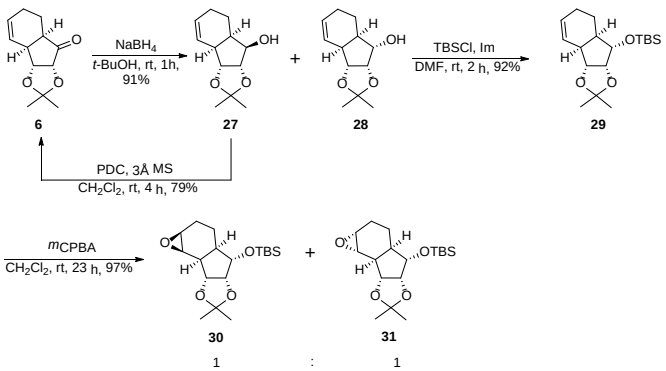
Scheme 6. Attempted epimerization of **6** to **22**.

Since epimerization was not successful, syntheses of bicyclic carbanucleosides were carried on with the *cis*-fused bicyclic carbocycle **6**. The hydrindenone **6** was epoxidized to give epoxide **23** in good yield (Scheme 7). The β-epoxide was the only isolated product and no α-epoxide was detected. The extremely high diastereoselectivity might be explained by the ketone directing effect proposed by Armstrong.[29] Reduction of epoxide was attempted with $LiBH_4$, $NaBH_4$, super hydride or $LiAlH_4$ under various conditions, but unfortunately only alcohols **24** and **25** were isolated. Interestingly, reduction with DIBAL-H in the presence of $AlMe_3$ provided the desired diol **26** in moderate yield.

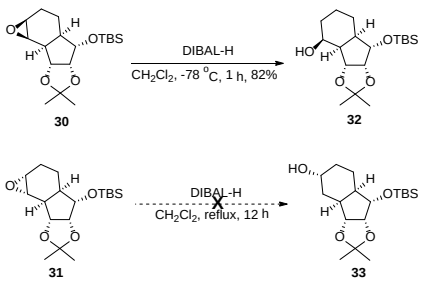


Scheme 7. Synthesis of diol **26**.

As the reduction was not as easy as expected and the yield was not satisfactory, an alternative approach was performed (Scheme 8). Hydrindenone **6** was firstly reduced with $NaBH_4$ to the corresponding alcohols **27** and **28** in an 1:4 ratio. Alcohol **27** could be oxidized back to **6** by PDC in good yield. Protection of **28** as silyl ether **29** proceeded smoothly and this was followed by epoxidation to give epoxides **30** and **31** in an 1:1 ratio. When both epoxides were subjected to reduction, only the β-epoxide **30** was susceptible to reduction, and alcohol **32** was obtained in good yield. The α-epoxide **31** was reluctant to be opened with DIBAL-H even under refluxing CH_2Cl_2 (Scheme 9).



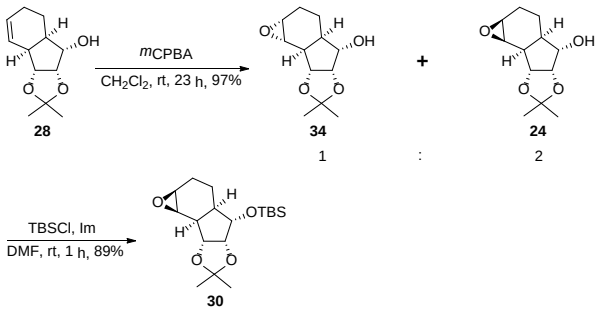
Scheme 8. Synthesis of epoxides **30** and **31**.



Scheme 9. Reduction of epoxides **32** and **33**.

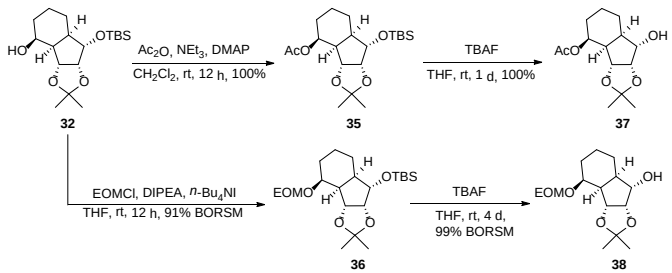
The difficulty of ring-opening in α-epoxide **33** might be attributable to the steric hindrance of the adjacent cyclopentane ring so that the hydride was unable to approach the reacting

site. To minimize the formation of α-epoxide, we chose to epoxidize alkene-alcohol **28**, and the ratio of epoxide **34** to **24** was slightly increased to 1:2 (Scheme 10). The hydroxyl group in **24** was protected as a TBS ether to furnish silyl ether **30** again.



Scheme 10. Epoxidation of **28**.

After reduction of the epoxide, the newly formed hydroxyl group in **32** was protected as acetate **35** and as ethoxy methyl (EOM) ether **36** respectively in excellent yields (Scheme 11). Removal of the silyl protecting group in both substrates proceeded smoothly to furnish alcohols **37** and **38** in excellent yields, which were the precursors for coupling with the nucleobases.

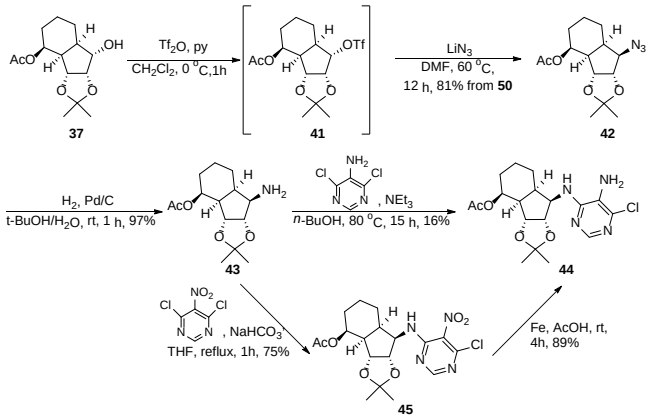


Scheme 11. Synthesis of **37** and **38**.

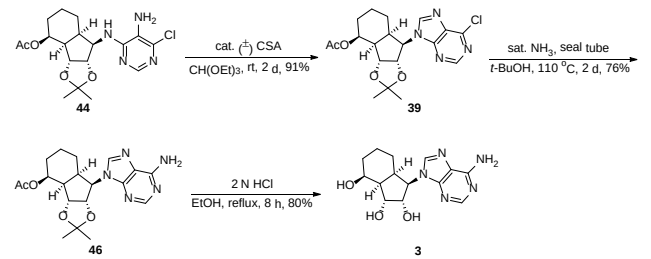
With alcohol **37** and **38** in hand, direct coupling of nucleobases with the free alcohols was examined (Scheme 12). Firstly, Mitsunobu reaction[30] was used but no desired product was isolated using either PPh_3 or PBu_3 with DIAD in refluxing toluene. Alcohols **37** and **38** were then activated by conversion into sulfonate esters (R = Ms, Tf) which were displaced with purine bases. Unfortunately, both sulfonate esters failed to form purine **39** and **40** respectively.

Scheme 12. Attempted to synthesize pyrimidine **39** and **40**.

As the convergent route failed to give any desired nucleoside, the linear approach was adopted to synthesize the target molecules. Triflate **41** was successfully converted into azide **42** in good overall yield from alcohol **37** (Scheme 13). Azide **42** was reduced to the corresponding amine **43** by catalytic hydrogenation in excellent yield. Reaction of amine **43** with 5-amino-4,6-dichloropyrimidine furnished pyrimidine **44** in miserable yield could be explained by the low electrophilicity of 5-amino-4,6-dichloropyrimidine. In order to improve the reactivity, a stronger electrophile, 5-nitro-4,6-dichloropyrimidine was used instead. Pyrimidine **45** was then obtained in good yield, and reduction of the nitro group to the amino group was achieved by using iron powder as an reductant in AcOH (Scheme 13).[31] Using standard procedure, pyrimidine **44** was transformed into the target carbanucleoside **3** (Scheme 14).

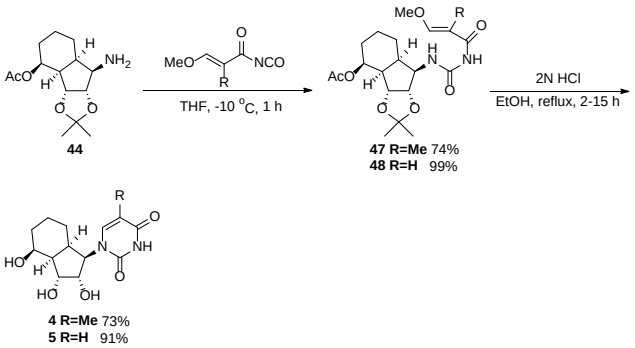


Scheme 13. Synthesis of pyrimidine **44**.



Scheme 14. Synthesis of the target adenosine analogue **3**.

The syntheses of thymidine analogue **4** and uridine analogue **5** were similar and the results are shown in Scheme 15. Amine **44** was reacted with 3-methoxymethacryloyl isocyanate[32] and 3-methoxy-2-propenoyl isocyanate[33] to produce urea **47** and **48** in 74% and 99% respectively. Both ureas **47** and **48** were then subjected to acid hydrolysis to remove all the protecting groups as well as to facilitate the cyclization. Thymidine carbanucleoside **4** was obtained in moderate yield (73%) and uridine carbanucleoside **5** was obtained in excellent yield (91%).



Scheme 15. Syntheses of thymidine analogue **4** and uridine analogue **5**.

Determination of conformation

With all the carbanucleosides in hand, the conformations of them were determined by both X-ray crystallography and NOE experiments. Disappointing results were obtained as all the carbanucleosides displayed the undesired C1'-*exo* conformation. The crystal structure of adenine **3** is shown in Figure 6. The NOE results of both nucleosides **4** and **5** also agreed with the C1'-*exo* conformation (Figure 7).

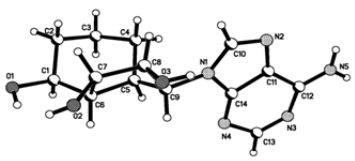


Figure 6. X-ray structure of adenosine 3

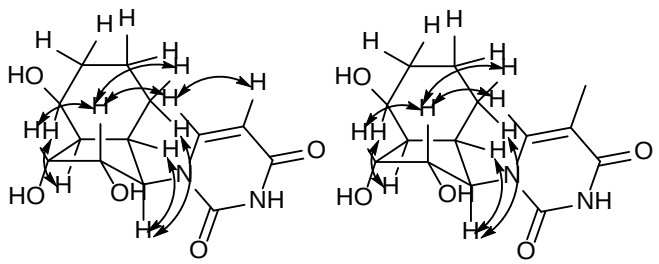


Figure 7. NOE results of nucleosides 4 and 5.

Biological Studies

Antiviral activity against enterovirus, Coxsackie B3 virus, was assessed by plaque reduction assay. Briefly, African green monkey cells (Vero) were used to cultivate virus-compound mixtures at various dilutions. After 72 hours of incubation at 37°C, infected cells were fixed and the number of plaques was counted. Percentage of reduction in number of plaques in wells with compounds was calculated. Compounds suspected to have antiviral effect were further examined for cytotoxicity by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

As a result, 3 compounds nucleosides **3**, **4** and **5** showed screening results suggestive of having weak in-vitro antiviral activity against Coxsackie B3 virus. Adenosine **3** (concentration = 1μg/mL) showed 4.9% of inhibition and thymidine **4** (concentration = 1μg/mL) showed 5.5% of inhibition and higher concentration (concentration = 100μg/mL) led to high toxicity Uridine **5** (concentration = 1μg/mL) gave the best result, which showed more 12.3% of inhibition and further structural modification is recommended.

Conclusion

To conclude, bicyclo[4.3.0]nonane carbanucleosides **3**, **4**, **5** were synthesized from D-(−)-ribose in 16 steps or 19 steps with 5%, 7% and 12 % overall yield respectively, involving a Wittig alkenation and an IMDA reaction as the keys steps. The cycloadduct **6**, a chiral functionalized hydrindenone (bicyclo[4.3.0]nonenone) should open an avenue as a versatile intermediate in complex natural product synthesis. X-ray crystallography and NOE studies of these carbanucleosides show that they display the C1'-*exo* conformation. These compounds demonstrated weak in vitro antiviral activity against Coxsackie B3 virus. It is worthwhile to modify the compounds and reassessed for a wider range of viruses. Research in this direction is in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures,characterisation data, copies of NMR spectra for all compounds, detailed DFT modelling and CIF les. CCDC. For ESI and crystallographic data in CIF or other electronic format see DOI: See DOI: 10.1039/b000000x/

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