

Controlled Inversion of 4'chiral Centre in Protected Carbasugar from D-Ribose

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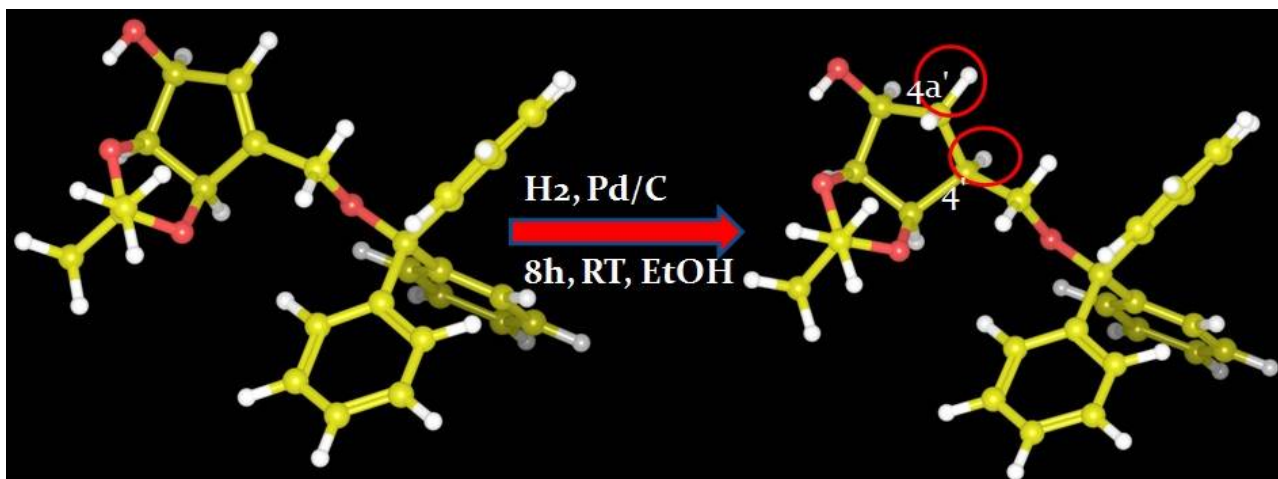
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ABSTRACT: The synthesis of 2,2-dimethyl-6-(trityloxymethyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol was started from D-Ribose. The important ring closure step was carried out by Grubbs catalyst to form pentene carbasugar where cyclopentene will be a central ring. Catalytic hydrogenation of the c=c has yielded the D-Ribose configured saturated carbasugar with excellent diastereomeric ratio (~98%). The inversion of the selective chiral center was done and the molecule 9 can be a new class of key intermediate for the synthesis of novel series of nucleoside analogs



KEYWORDS: Stereo specific Hydrogenation D-Ribose Carbasugar, Steric hindrance, carbocyclic nucleoside analogs, D-ribose configuration

I. INTRODUCTION

D-Ribose is an important counter part of de-oxy ribo nucleic acid (DNA) of many living organisms, and it generally exists in its pyranose form where bonded to its nitrogen base which is integral part of nucleoside in DNA.^{1,2} tremendous number of nucleoside analogs reported in literatures which are strong mimics of natural DNA³⁻⁵ and RNA.^{4,6-10} D-Ribose and its carbasugar analogs are important and vital bio-mimics of many new medical entities in modern medicinal chemistry research¹¹⁻¹⁴ even from long before and these have been synthesized, including iminosuars¹⁵⁻¹⁷, thiosugars¹⁵, floro,^{18,19} cloro²⁰ and bromo²¹⁻²³ carbasugars (**Fig. 1**) etc. The ability of these compounds to inhibits many viral enzymes, for example RNA dependant RNA polymerase (RdRp) of hepatitis C virus (HCV) which is responsible for the genesis of progeny RNA of the hepatitis²⁴⁻²⁶ and other viruses²⁶⁻²⁹ make D-ribose mimics interesting biological targets with potential therapeutic value.^{15,30} Carbasugars in which the ring oxygen is replaced by a methylene group can also act as glycomemetics.^{15,31} Synthesis of some carbapentofuranases^{15,32} and cabaheofuranoses^{15,33} previously reported, but direct synthesis of **9** from **8** is not reported before, we report in this letter the diastereo selective synthesis of **9** from **8** is for the first time. We designed the scheme to synthesize the diastereomer **9** from a hemiacetal of the same ring size as the desired chemical analog, a furanose hemiacetal in this case, and used ring-forming metathesis to create the carbasugar **9**.^{15-17,34-55}

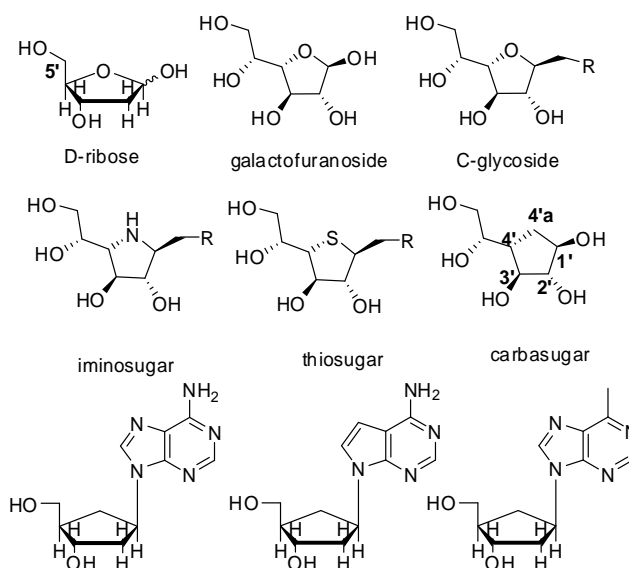


Figure 1: Few modified sugars & carbacyclic nucleosides⁵⁶

The above mentioned all (**Fig.1**) cabasugars possess the parental configuration of D-ribose. The D-ribose coupled synthetic nitrogen bases which are regular interesting nucleoside analogs in medicinal chemistry arena, which demonstrate potential antiviral properties.⁵⁶ If we alter the chiral centre in the derivatives (carbasugars) of D-ribose, the properties of the carbasugar which are part of nucleoside mimics may be different and the side effects also than regular D-ribose / carbasugars.⁵⁷⁻⁶⁰ This idea motivated us to synthesize the inverted chiral center (4') in regular carbasugar intermediate **8** to synthesize **9**.

II. MATERIALS & METHODS

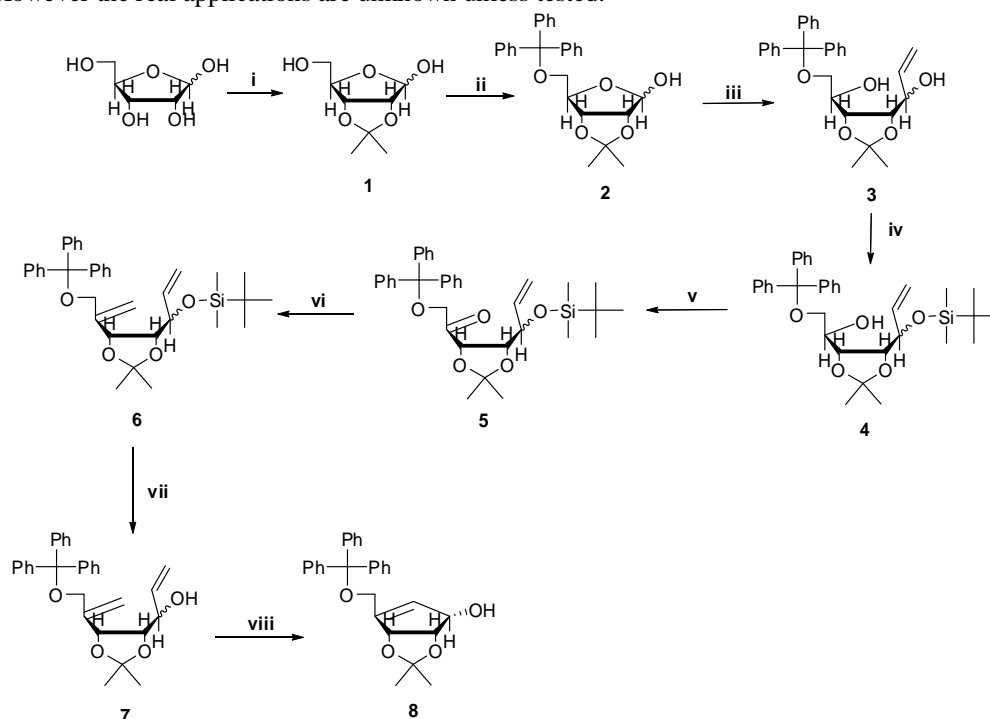
2.1 Synthesis of cyclic Carbasugar from D-ribose The modified carbasugar **8** prepared according to the previously reported method from commercially available D-ribose(scheme I),⁶¹ and **9** as per the mentioned scheme (scheme II) with improved methods and reduced purification steps. The modified step is, during TBDMSiCl protection

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the addition of TBDMSiCl was added to reaction mixture at very slow (the maximum possible slow mode (dead slow) addition, due to this implementation of this concept we selectively got only one and exclusive single and pure isomer (single spot on TLC also in NMR) where the yield was 96%. Thereafter we moved to next step (swern oxidation) without purification. Here also we observed the single spot as a reaction output and directly moved to de-protection of TBDMSiCl again without purification by column chromatography (cc) or any other method and so on we got the product of **8**. Further the intermediate **8** was subjected to hydrogenation on Pd-C (0.2mmol) to convert final product **9** with excess diastereomeric ratio (~98%). The hydrogen pressure was 55PSI units for 8h and EtOH was the solvent. The final product **9** was purified by cc and characterized by Mass and NMR spectral methods and got the pure in condition. The intermediate **9** was crystallized in CDCl_3 at room temperature and X-Ray diffraction analysis was carried out to get the structural information (**Fig. 3**). The specific rotation of the compound also recorded that is $[\alpha]_D^{20} = -9.0^\circ$. The reason for synthesizing the compound **9** is, we want to observe practically how the chiral center can be inverted on protected cabasugars and their subsequent role in nucleoside analogs and their importance in medicinal chemistry (we confirm its inversion from X-Ray structure and specific rotation, the specific rotation of **8** was 28° ⁶²). This Carbasugar can be part of novel nucleoside (new chemical entity, NCE) preparation why because general nucleosides having the configuration of C-4' is actually from D-ribose (parental configuration). The general nucleosides are reported for potentially unwanted side effects on regular medication. If we use these type inverted carbasugar (configuration of C-4' position) part in the current nucleoside analogs synthesis, It may be different from general nucleosides properties and side effects. However the real applications are unknown unless tested.



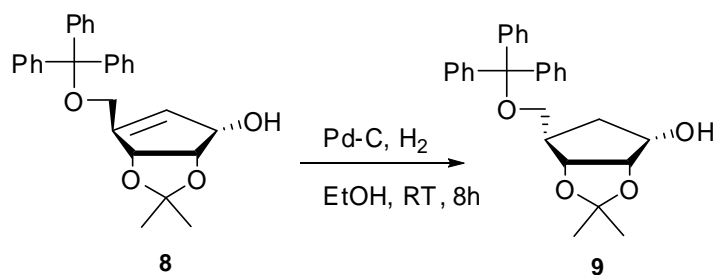
Scheme 1

Scheme 1 Reagents and conditions: (i) Acetone 2,2-dimethoxypropane, PTSA, 1h; (ii) TrCl , Et_3N , DMAP rt, 6h; (iii) Vinylmagnesium bromide, THF, -80°C , 24 h; (iv) TBDMSiCl, imidazole, DMAP, $0^\circ\text{C} - 5^\circ\text{C}$, 10 h; (v) $(\text{COCl})_2$, DMSO, DCM, Et_3N , -80°C , 10h; (vi) $\text{Ph}_3\text{PCH}_2\text{Br}$, $n\text{-BuLi}$, THF, $0^\circ\text{C} - 5^\circ\text{C}$, 10 h; (vii) TBAF, THF, rt, 12h; (viii) Grubbs II catalyst, DCM, rt, 24 h.⁶¹

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Scheme 2

2.2 Theory & Molecular modeling study of the hydrogenation of protected Carbasugar: The designed ligand (carbasugar, **8**) drawn by using maestro⁶³ software. The structure minimized by macromodel minimization^{64,65}. Force Field used OPLS_2005, solvent is water. Charges used from force field source and extended cutoff method. The minimized structure used for measuring distance between specific atoms to calculate the distance which creates steric hindrance while hydrogenation is occurring.

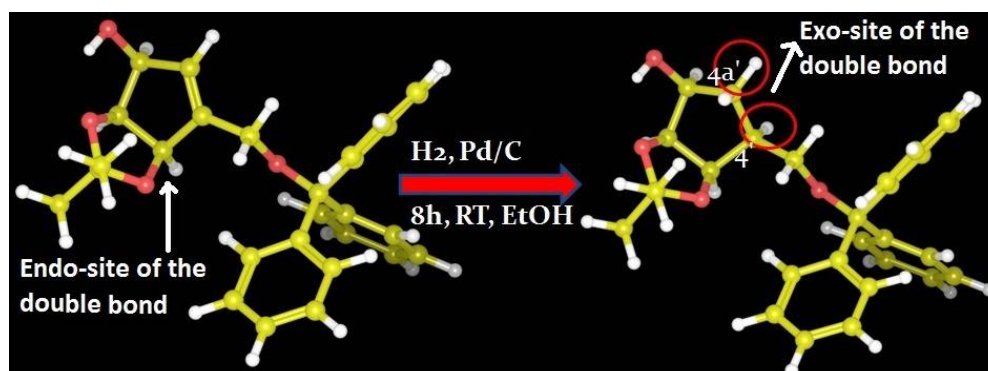


Figure 2 Pictorial demonstration of double bond site specific hydrogenation of protected cyclic pentene carbasugar to pentane carbasugar, the newly added hydrogen atoms shown in surrounded rings, those got added exclusively from Exo-site of the double bond.

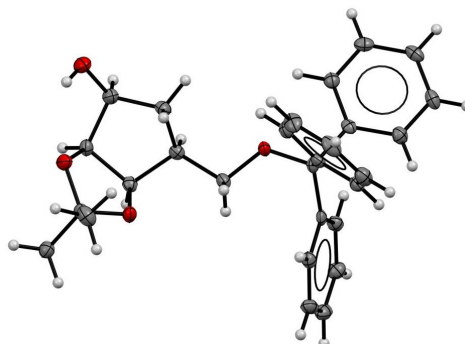


Figure 3 X-Ray structure of the Final carbasugar **9**, (Thermal ellipsoid plots for **9** at 50 % probability level)

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Table 1 Distance of double bond and the steric atoms from their position

Double bonding holding Atom	Steric Atom	Distance in Å
C-4'	H64, H65 of C-5'	2.1, 2.1
C-4', C-4'a	Acetonide Methyl Group (2' and 3' protected group)	3.8 and 3.4
C-4'a	1' OH	2.4
C-4', C-4'a	(2' and 3' Oxygen atoms)	2.4, 3.0

2.3 Observation of Steric hindrance and site direction for stereo specific hydrogenation on pentene double bond: The Endo-site of the double is having more 3D molecular hindrance compared to Exo-site of the double bond.

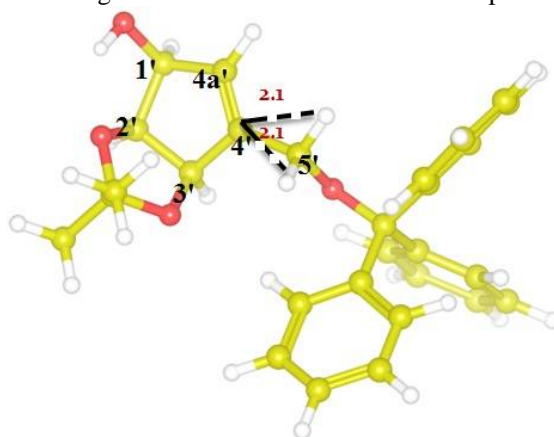


Figure 4 Describes the distance between the 4', 4'a and 5'hydrogens and the strain causing from Endo-site orientation of the double bond

The explanation has given in the following figures (Fig. 2-7). 4'C and 4'a C¹⁵ atoms which are holding the double bond having steric hindrance from the hydrogen atoms which are there on 5'C (Fig. 4), These two atoms are spatially

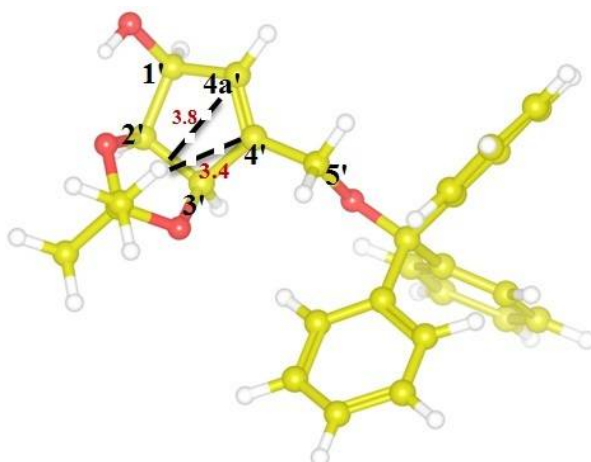


Figure 5 Describing the distance between the 4', 4'a and acetonide protected group (Methyl Group) and the strain causing from Endo-site orientation of the double bond

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oriented within the distance of 2.1\AA from the double bond because of compact distance and other factors, the addition of hydrogens takes selectively from exo-site of the double bond. Further the acetonide methyl groups (which is protected the 2',3' hydroxyl 'O' atoms of the pentene carbasugar also creating serious spatial constraint (**Fig. 5**) for the endo-site addition of the double bond.

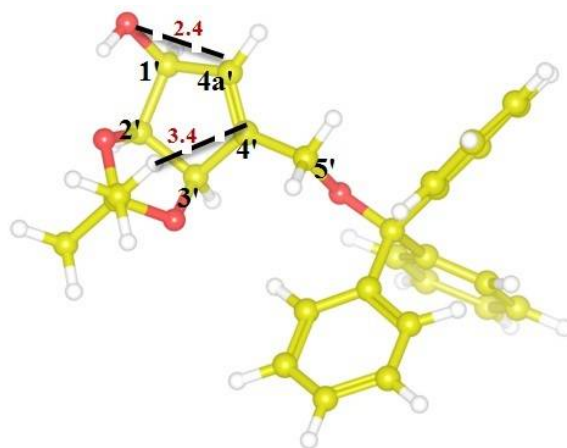


Figure 6 Describing the distance between the 4'a and 1' hydroxyl Group and the strain causing from Endo site orientation of the double bond

In addition to this, the 1'-hydroxyl group also creates the extra steric hindrance (**Fig. 6**) for the Exo-site direction of the double bond reduction. Moreover the lone pairs of electrons (**Fig. 7**) of the two oxygens (2 x 2 lone pairs on 'O' atoms) also additional strain for which the addition was forced for not to take from the Endo-site of the double bond.

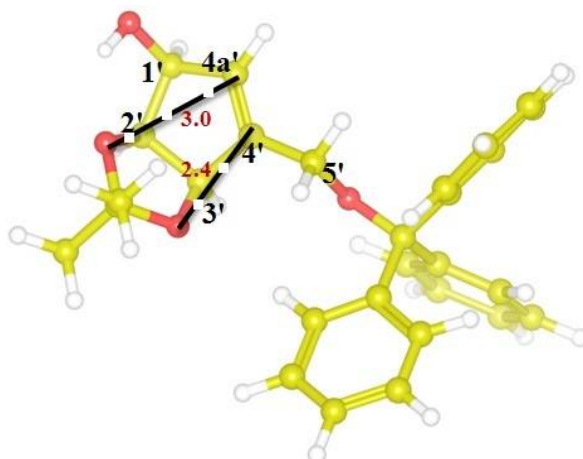


Figure 7 Describing the distance between the 4', 4'a and 2', 3' (Acetonide oxygen atoms and lone pairs of oxygen) and the strain causing from Endo site orientation of the double bond.

Fig. 2-7 are the conformation pictures of the molecule **9** drawn by using Schrodinger software and minimized structure which used for the steric distance analysis.

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2.4 Crystallization of the designed compound:

The product 9 was recrystallized from methanol and crystal grown in CDCl_3 . The crystal structure was solved using SuperNova, X-ray diffractometer with Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) and Using Olex2⁶⁶, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimisation. The crystal structures have been deposited at the Cambridge Crystallographic Data Centre 9 (Reference number CCDC 1451811). ORTEP diagram of the product 9 with thermal ellipsoids drawn at the 50% probability level (Fig. 3).

III. CONCLUSION

We first time report the site specific reduction of the double bond in a pentene ring structure without disturbing the protected groups on the carbasugar (**8**, **9**) which is very useful in carbacyclic nucleoside research and for getting newly configured chiral centre. The hydrogenation of double bond is taking over predominantly from the Exo-site (above the double bond plane of the ring which is thermodynamically favorable. The hydrogen addition cannot take place from Endo-site (below the plane of the double bond, because 2,2 dimethoxy propane protected group at 2',3' hydroxyl groups and also 1' hydroxy group at Endo-site of the double bond, are additional factors. This is also proven from modeling studies of the molecule (Fig. 2-7) which explained above. The spatial arrangements of the Endo-site of the double bond, creates effective steric hindrances to reach hydrogen atoms from Pd-C catalyst surface. The above plane of the double bond is free from steric resistance and not creating hindrance, because of this the hydrogenation preferably takes place from the exo-site of the double bond. The inverted chiral centered carbasugar is different from general nucleosides carbasugar part and their regular properties in the view of activity and side effects may also be different if, these sugar intermediates used for the preparation of new class of nucleoside analogs with respect to medicinal chemistry applications.

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Crystal data deposition:

Cambridge Crystallographic Data deposit number for the crystal structure we report (Figure 3): **CCDC 1451811**

Competing Financial Interest

The authors declare no competing financial interest.

Characterization

3aR,4R,6R,6aS)-2,2-dimethyl-6-(trityloxymethyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (*4a-carba-D-ribose 9*): White flour like powder; Yield: 95%; mp: 390 °C; IR (KBr) (ν , cm^{-1}): 3400 (-O-H stretching); MS (ESI) (m/z): 453.28 [M^+ +22]; ¹H NMR: (400 MHz, CDCl_3 -d₆): δ 1.20-1.67 (s, 6H, 2,2-dimethyl), δ 1.29 (m, 1H (s, 1H, 4'H(Tertiary proton), δ 1.64-1.65(d, 1H, $J = 5.6$ 4a' gem H), δ 1.84-1.86(d, 1H, $J = 5.6$ 4a' gem H), δ 2.87-2.91(t, $J = 1.6$, 2'H), δ 3.11-3.15(t, $J = 1.6$ 3'H), δ 3.67-3.70(m, $J = 5.6$ 1'H), δ 4.3(s, OH), δ 4.42-4.49(m, $J = 5.2$, 2 of 5'H), δ 7.21-7.38(m, $J = 7.6$, ArH),

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REFERENCES

- [1] Lindahl, T. Instability and decay of the primary structure of DNA. *Nature* **362**, 709-715 (1993).
- [2] Screaton, G. R. *et al.* Genomic structure of DNA encoding the lymphocyte homing receptor CD44 reveals at least 12 alternatively spliced exons. *Proceedings of the National Academy of Sciences* **89**, 12160-12164 (1992).
- [3] Martin, J. L., Brown, C. E., Matthews-Davis, N. & Reardon, J. E. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. *Antimicrobial Agents and Chemotherapy* **38**, 2743-2749 (1994).
- [4] Loeb, L. A. *et al.* Lethal mutagenesis of HIV with mutagenic nucleoside analogs. *Proceedings of the National Academy of Sciences* **96**, 1492-1497 (1999).
- [5] Chen, C.-H., Vazquez-Padua, M. & Cheng, Y.-C. Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. *Molecular pharmacology* **39**, 625-628 (1991).
- [6] Carroll, S. S. *et al.* Inhibition of hepatitis C virus RNA replication by 2'-modified nucleoside analogs. *Journal of Biological Chemistry* **278**, 11979-11984 (2003).
- [7] Sousa, R. Use of T7 RNA polymerase and its mutants for incorporation of nucleoside analogs into RNA. *Methods in enzymology* **317**, 65 (2000).
- [8] Crotty, S. *et al.* The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen. *Nature medicine* **6**, 1375-1379 (2000).
- [9] Strahl, C. & Blackburn, E. H. The effects of nucleoside analogs on telomerase and telomeres in Tetrahymena. *Nucleic acids research* **22**, 893-900 (1994).
- [10] Tipples, G. A. *et al.* Mutation in HBV RNA-dependent DNA polymerase confers resistance to lamivudine in vivo. *Hepatology* **24**, 714-717 (1996).
- [11] Zhu, X.-F. The latest progress in the synthesis of carbocyclic nucleosides. *Nucleosides, nucleotides & nucleic acids* **19**, 651-690 (2000).
- [12] Yin, J. *et al.* Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *Journal of Clinical Oncology*, JCO. 2012.2048. 5896 (2013).
- [13] Parker, W., Secrist 3rd, J. & Waud, W. Purine nucleoside antimetabolites in development for the treatment of cancer. *Current opinion in investigational drugs (London, England: 2000)* **5**, 592-596 (2004).
- [14] McKenzie, R. *et al.* Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *New England Journal of Medicine* **333**, 1099-1105 (1995).
- [15] Frigell, J. & Cumpstey, I. First synthesis of 4a-carba-β-d-galactofuranose. *Tetrahedron Letters* **48**, 9073-9076 (2007).
- [16] Frigell, J., Eriksson, L. & Cumpstey, I. Carbasugar analogues of galactofuranosides: β-O-linked derivatives and towards β-S-linked derivatives. *Carbohydrate research* **346**, 1277-1290 (2011).
- [17] Frigell, J., Pearce, J. A., Lowary, T. L. & Cumpstey, I. Carbasugar Analogues of Galactofuranosides: Pseudodisaccharide Mimics of Fragments of Mycobacterial Arabinogalactan. *European Journal of Organic Chemistry* **2011**, 1367-1375 (2011).
- [18] Balzarini, J., Baba, M., Pauwels, R., Herdewijn, P. & De Clercq, E. Anti-retrovirus activity of 3'-fluoro-and 3'-azido-substituted pyrimidine 2', 3'-dideoxynucleoside analogues. *Biochemical pharmacology* **37**, 2847-2856 (1988).
- [19] Watanabe, K. A., Reichman, U., Hirota, K., Lopez, C. & Fox, J. J. Nucleosides. 110. Synthesis and antiherpes virus activity of some 2'-fluoro-2'-deoxyarabinofuranosylpyrimidine nucleosides. *Journal of medicinal chemistry* **22**, 21-24 (1979).
- [20] Jacobson, K. A. *et al.* Methanocarba analogues of purine nucleosides as potent and selective adenosine receptor agonists. *Journal of medicinal chemistry* **43**, 2196-2203 (2000).
- [21] Herdewijn, P. *et al.* 3'-substituted 2', 3'-dideoxynucleoside analogs as potential anti-HIV (HTLV-III/LAV) agents. *Journal of medicinal chemistry* **30**, 1270-1278 (1987).
- [22] Watanabe, K. A. *et al.* Nucleosides. 123. Synthesis of antiviral nucleosides: 5-substituted 1-(2-deoxy-2-halogeno-. beta.-D-arabinofuranosyl) cytosines and-uracils. Some structure-activity relationships. *Journal of medicinal chemistry* **26**, 152-156 (1983).
- [23] Shealy, Y. F., O'Dell, C. A., Shannon, W. M. & Arnett, G. Carbocyclic analogs of 5-substituted uracil nucleosides. Synthesis and antiviral activity. *Journal of medicinal chemistry* **26**, 156-161 (1983).
- [24] Dhanak, D. *et al.* Identification and biological characterization of heterocyclic inhibitors of the hepatitis C virus RNA-dependent RNA polymerase. *Journal of Biological Chemistry* **277**, 38322-38327 (2002).
- [25] Wu, J. Z., Yao, N., Walker, M. & Hong, Z. Recent advances in discovery and development of promising therapeutics against hepatitis C virus NS5B RNA-dependent RNA polymerase. *Mini reviews in medicinal chemistry* **5**, 1103-1112 (2005).
- [26] Kuntzen, T. *et al.* Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-naïve patients. *Hepatology* **48**, 1769-1778 (2008).
- [27] Pawlotsky, J.-M. Hepatitis: HCV variability, the immune system and resistance to antiviral drugs. *Nature Reviews Gastroenterology and Hepatology* **6**, 383-385 (2009).
- [28] Han, H.-k. *et al.* 5'-Amino acid esters of antiviral nucleosides, acyclovir, and AZT are absorbed by the intestinal PEPT1 peptide transporter. *Pharmaceutical research* **15**, 1154-1159 (1998).
- [29] Hostetler, K. Y., Stuhmiller, L., Lenting, H., Van den Bosch, H. & Richman, D. Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides. *Journal of Biological Chemistry* **265**, 6112-6117 (1990).
- [30] Wrodnigg, T. M. & Sprenger, F. K. F. Bioactive carbohydrates and recently discovered analogues as chemotherapeutics. *Mini reviews in medicinal chemistry* **4**, 437-459 (2004).
- [31] McCasland, G., Furuta, S. & Durham, L. J. Alicyclic Carbohydrates. XXIX. 1, 2 The Synthesis of a Pseudo-Hexose (2, 3, 4, 5-Tetrahydroxycyclohexanemethanol). *The Journal of Organic Chemistry* **31**, 1516-1521 (1966).
- [32] Callam, C. S. & Lowary, T. L. Total synthesis of both methyl 4a-carba-D-arabinofuranosides. *Organic letters* **2**, 167-169 (2000).
- [33] Callam, C. S. & Lowary, T. L. Synthesis and conformational investigation of methyl 4a-carba-D-arabinofuranosides. *The Journal of Organic Chemistry* **66**, 8961-8972 (2001).

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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- [34] Seepersaud, M. & Al-Abed, Y. Studies directed toward the synthesis of carba-D-arabinofuranose. *Tetrahedron Letters* **41**, 7801-7803 (2000).
- [35] Seepersaud, M. & Al-Abed, Y. The polyhydroxy cyclopentene, a total synthesis of (-)-pentenomycin. *Tetrahedron Letters* **41**, 4291-4293 (2000).
- [36] Seepersaud, M. & Al-Abed, Y. Total synthesis of carba-D-fructofuranose via a novel metathesis reaction. *Organic letters* **1**, 1463-1465 (1999).
- [37] Seepersaud, M. & Al-Abed, Y. An enantioselective approach to trehalosin: a concise and efficient synthesis of the aminocyclopentitol core. *Tetrahedron Letters* **42**, 1471-1473 (2001).
- [38] Seepersaud, M. *et al.* Hydroformylation of cyclopentenes, novel strategy for total synthesis of carba-D-fructofuranose. *Tetrahedron Letters* **43**, 1793-1795 (2002).
- [39] Cumpstey, I. Formal synthesis of valienamine using ring-closing metathesis. *Tetrahedron Letters* **46**, 6257-6259 (2005).
- [40] Arjona, O., Gomez, A. M., López, J. C. & Plumet, J. Synthesis and conformational and biological aspects of carbasugars. *Chemical reviews* **107**, 1919-2036 (2007).
- [41] Mehta, G. & Ramesh, S. S. Polycyclitols: synthesis of novel carbasugar and conduritols as potential glycosidase inhibitors. *Tetrahedron Letters* **42**, 1987-1990 (2001).
- [42] Gómez, A. M., Danelón, G. O., Valverde, S. & López, J. C. Regio- and stereocontrolled 6-endo-trig radical cyclization of vinyl radicals: A novel entry to carbasugars from carbohydrates. *The Journal of Organic Chemistry* **63**, 9626-9627 (1998).
- [43] Mehta, G. & Ramesh, S. S. Polycyclitols. Novel conduritols and carbasugar hybrids as a new class of potent glycosidase inhibitors. *Chemical Communications*, 2429-2430 (2000).
- [44] Mehta, G., Mohal, N. & Lakshminath, S. A norbornyl route to cyclohexitols: structural diversity in fragmentation through functional group switching. Synthesis of α - and β -galactose, α -talose and α -fucopyranose carbasugars. *Tetrahedron Letters* **41**, 3505-3508 (2000).
- [45] Blériot, Y. *et al.* Synthesis of seven- and eight-membered carbasugar analogs via ring-closing metathesis and their inhibitory activities toward glycosidases. *Tetrahedron: Asymmetry* **13**, 2553-2565 (2002).
- [46] Gómez, A. M., Moreno, E., Valverde, S. n. & López, J. C. A general stereodivergent strategy for the preparation of carbasugars. Syntheses of 5a-carba- α -D-glucose, α -D-galactose, and β -D-glucose pentaacetates from D-mannose. *Tetrahedron Letters* **43**, 5559-5562 (2002).
- [47] Plumet, J., Gomez, A. M. & Lopez, J. C. Synthesis of carbasugars based on ring closing metathesis: 2000-2006. *Mini-Reviews in Organic Chemistry* **4**, 201-216 (2007).
- [48] Mehta, G., Talukdar, P. & Mohal, N. A general norbornyl based synthetic approach to carbasugars and 'confused' carbasugars. *Tetrahedron Letters* **42**, 7663-7666 (2001).
- [49] Grondal, C. & Enders, D. A direct entry to carbasugars: asymmetric synthesis of 1-epi-(+)-MK7607. *Synlett* **2006**, 3507-3509 (2006).
- [50] Yu, S.-H. & Chung, S.-K. Practical syntheses of enantiopure carbasugars: carba- β -altrose, carba- β -mannose, carba- β -idose, and carba- β -talose derivatives. *Tetrahedron: Asymmetry* **15**, 581-584 (2004).
- [51] Shan, M. & O'Doherty, G. A. Synthesis of SL0101 carbasugar analogues: carbasugars via Pd-catalyzed cyclitolization and post-cyclitolization transformations. *Organic letters* **12**, 2986-2989 (2010).
- [52] Arjona, O., Borralló, C., Iradier, F., Medel, R. & Plumet, J. One pot Michael addition, vinylsulfone isomerization and alkynyl to alkenyl triple bond reduction. Synthesis of a carbasugar related to Rancinamycin III. *Tetrahedron Letters* **39**, 1977-1980 (1998).
- [53] Mehta, G. & Reddy, D. S. Polycyclitols: Stereoselective synthesis of enantiopure polyhydroxylated hydrindanes (annulated carbasugars). *Tetrahedron Letters* **40**, 9137-9140 (1999).
- [54] Ferritto, R. & Vogel, P. Synthesis of an α -C-galactoside of a carbasugar: A new class of disaccharide mimics. *Tetrahedron Letters* **36**, 3517-3518 (1995).
- [55] Corsaro, A. *et al.* A new method for the synthesis of carba-sugar enones (gabosines) using a mercury (II)-mediated opening of 4, 5-cyclopropanated pyranosides as the key-step. *Tetrahedron Letters* **47**, 6591-6594 (2006).
- [56] Boutoureira, O., Matheu, M. I., Díaz, Y. & Castillón, S. Advances in the enantioselective synthesis of carbocyclic nucleosides. *Chemical Society Reviews* **42**, 5056-5072 (2013).
- [57] Carroll, S. & Olsen, D. Nucleoside analog inhibitors of hepatitis C virus replication. *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders)* **6**, 17-29 (2006).
- [58] Brown, N. A. Progress towards improving antiviral therapy for hepatitis C with hepatitis C virus polymerase inhibitors. Part I: Nucleoside analogues. *Expert opinion on investigational drugs* **18**, 709-725 (2009).
- [59] Jordheim, L. P., Durantel, D., Zoulim, F. & Dumontet, C. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. *Nature reviews Drug discovery* **12**, 447-464 (2013).
- [60] De Francesco, R. & Migliaccio, G. Challenges and successes in developing new therapies for hepatitis C. *Nature* **436**, 953-960 (2005).
- [61] Cho, J. H., Bernard, D. L., Sidwell, R. W., Kern, E. R. & Chu, C. K. Synthesis of cyclopentenyl carbocyclic nucleosides as potential antiviral agents against orthopoxviruses and SARS. *Journal of medicinal chemistry* **49**, 1140-1148 (2006).
- [62] Bergmeier, S. C., Cobas, A. A. & Rapoport, H. Chiroselective synthesis of (1S, 3R)-1-amino-3-(hydroxymethyl) cyclopentane, precursor for carbocyclic nucleoside synthesis. Dieckmann cyclization with an α -amino acid. *The Journal of Organic Chemistry* **58**, 2369-2376 (1993).
- [63] Schrödinger Release 2016-1: Maestro, v., Schrödinger, LLC, New York, NY, 2016.
- [64] Schrödinger Release 2016-1: MacroModel, v., Schrödinger, LLC, New York, NY, 2016.
- [65] Schrödinger Release 2016-1: LigPrep, v., Schrödinger, LLC, New York, NY, 2016.
- [66] Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. & Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *Journal of Applied Crystallography* **42**, 339-341 (2009).