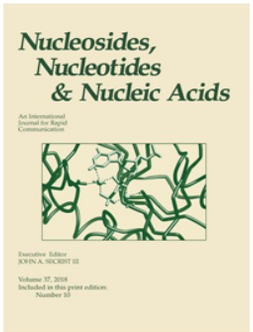

Nucleosides, Nucleotides and Nucleic Acids

ISSN: 1525-7770 (Print) 1532-2335 (Online) Journal homepage: https://www.tandfonline.com/loi/lncn20

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To cite this article: Ramakrishnamraju Samunuri, Ashok Kumar Jha & Chandralata Bal (2019): Rhodium catalyzed stereospecific reductive carbocyclization of 1,6-enynes and synthesis of 4′-methyl-6′-substituted aristeromycins, Nucleosides, Nucleotides and Nucleic Acids, DOI: 10.1080/15257770.2018.1554221

To link to this article: https://doi.org/10.1080/15257770.2018.1554221

Published online: 28 Jan 2019.

NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS
https://doi.org/10.1080/15257770.2018.1554221

Rhodium catalyzed stereospecific reductive carbocyclization of 1,6-enynes and synthesis of 4′-methyl-6′-substituted aristeromycins

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ABSTRACT

The need of long-term treatment for chronic HBV, emergence of drug-resistant viruses and inefficiency of currently approved therapies to eliminate covalently closed circular DNA (cccDNA), mandates identification of potent and selective inhibitors of HBV replication with novel mechanisms of action. Entecavir, a carbocyclic guanosine nucleoside analog, is the most potent inhibitor of HBV replication on the market. Moreover, the naturally occurring carbocyclic nucleosides aristeromycin are known for their wide range of antiviral activities.

In this research, we have utilized BINAP directed rhodium catalyzed reductive carbocyclization of 1,6-enynes (**8a–b**) through asymmetric hydrogenation which is an approach, not yet explored in carbocyclic sugar synthesis. Interestingly, we obtained exclusive *anti*-**(9a)** and *Z-anti* **(9b)** carbocyclic sugars. The new aristeromycin analogs (**10a–b**) with scaffold combination of entecavir and aristeromycin were then synthesized using the Mitsunobu reaction followed by deprotection.

ARTICLE HISTORY
Received 11 February 2018
Accepted 20 November 2018

KEYWORDS
Stereospecific reductive carbocyclization; BINAP; rhodium; aristeromycins; entecavir

1. Introduction

Chronic HBV and related death due to complications remains a major challenge for global health management. In addition, need for long-term treatment, emergence of drug-resistant viruses and inefficiency of currently approved therapies to eliminate covalently closed circular DNA (cccDNA) still mandates identification of potent and selective inhibitors of HBV replication with novel mechanism(s) of action.[1,2] Chronic patients are generally treated with entecavir, which is one of the successful anti-HBV drugs. The 6′-exo double bond seems to be an essential pharmacophore, which fits into the hydrophobic pocket at the binding site. Moreover, the anti-HBV activity of dG2 (Figure 1) is much less than entecavir.[3] However, when the 6′-exo double bond is functionalized with a fluoro group, both *E*/

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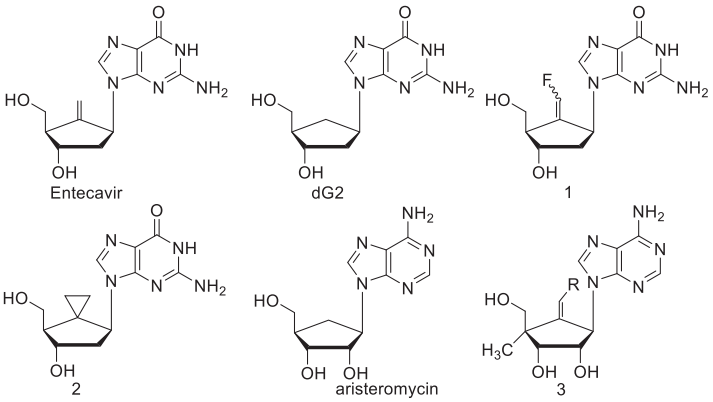


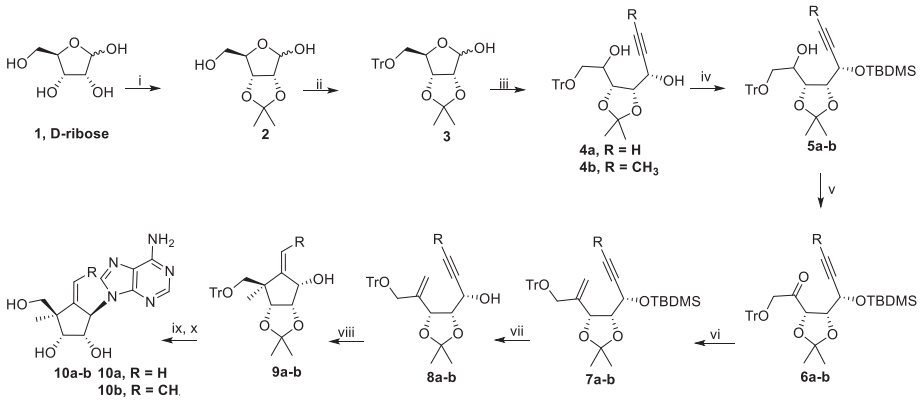
Figure 1. Chemical structures of potential carbocyclic nucleosides and target molecules.

Z isomers (**1**, Figure 1) exhibited anti-HBV activity similar to entecavir. Interestingly, the *Z* isomer was less cytotoxic compared to Entecavir.[4] The cyclopropyl-spirocarbocyclic derivative of entecavir (**2**, Figure 1) was a hundred times less potent than the parent drug,[5] which further supports the importance of the 6′-exo double bond. Naturally occurring carbocyclic nucleoside aristeromycin and its derivatives are reported to exhibit a wide range of antiviral activities.[6]

Nucleosides substituted at 4′- have attracted attention as festinavir (anti-HIV) and balapiravir (anti-HCV) reached a later phase of development.[7] However, due to limited synthetic methodologies, 4′-substituted carbocyclic nucleosides have very little representation in the literature.[8,9] Owing to the importance of aristeromycins and entecavir as antivirals, we aim to combine their features including 4′ substitution to generate new aristeromycin analogs (**3**, Figure 1)

2. Results and discussion

Kumamoto and coworkers had reported 5-*exo-dig* mode cyclization of a 5-hexynyl carbon-radical to synthesize an 5′-exomethylene carbocyclic sugar. However, this methodology yielded a mixture of four [*Z-syn*, *E-syn*, *Z-anti* and *E-anti*] isomers.[4] Herein, we report a previously unexplored key step in carbocyclic sugar synthesis involving reductive cyclization of 1,6-enynes via rhodium-catalyzed asymmetric hydrogenation[10] to exclusively generate the anti-(**9a**) and *Z-anti* isomer (**9b, Scheme 1**). The protected sugar intermediate (**3**) was synthesized from D-ribose in two steps.[11] Ring opening of **3** by reaction with a Grignard reagent produced **4a–b** with high stereoselectivity (diasteromeric ratio ~ 95:5). The compound **4a** was reported by Buchanan et al. in two previous reports[12,13] with different specific rotations and the temperature was not mentioned. However, the major diastereoisomer (**4a**) synthesized and purified, which gave specific rotation



Scheme 1. Reagents and conditions: (i) Conc.H_2SO_4, acetone, 0 °C - rt 3 hours (ii) TrCl, Et_3N, DMAP, DMF: CH_2Cl_2 (1:4 v/v), rt, 12h (iii) ethynyl/prop-1-yne magnesium bromide (0.5 M in THF), THF, −78 °C -rt, 16 hours (iv) TBDMSCl, imidazole, DMAP, DMF, 0 °C - rt, 6 hours (v) $(COCl)_2$, DMSO, DCM, Et_3N, −60 °C, 4 hour (vi) Ph_3PCH_3Br, n-BuLi (2.5 M in hexane), THF, 0 °C - rt, 2 hours (vii) TBAF (1.0 M in THF), THF, rt, 2 hours (viii) $Rh(COD)_2BF_4$, *rac*- BINAP, 1,2-dichloroethane, H_2 balloon, rt, 2 hours, (ix) N^6,N^6-Bis(tert-butoxycarbonyl)adenine, PPh_3, DIAD, THF, 10 °C - rt, 1 hour (x) TFA:H_2O (8:2 ratio), rt, 30 minutes.

+1.27 at 25 °C (c = 1.1, $CHCl_3$). The diastereomeric purity and the temperature of measurement of specific rotation may be the reason for getting different specific rotations for the same compound in the previous reports. In addition, we have confirmed the D-*allo* configuration with α-stereochemistry for the 1′-anomeric hydroxy through NOE analysis (refer SI).

The 1,6-enyne intermediates (**8a–b**) were synthesized from **4a–b** in four consecutive reaction steps; protection of 1′-OH with TBDMS, Swern oxidation, Wittig reaction followed by deprotection of TBDMS by TBAF.[11] The 1,6-enynes (**8a–b**) were subjected to BINAP directed rhodium catalyzed reductive cyclization through asymmetric hydrogenation.[10] This chemistry has significant advantage for building a substituted exocyclic double bond, which is as yet unexplored for the synthesis of carbocyclic sugars. Exposure of **8a–b** with $Rh(COD)_2BF_4$-BINAP catalyst system, H_2 at ambient temperature and pressure resulted in *anti*-**(9a)** and *Z-anti* **(9b)** carbocyclic sugars exclusively. Notably, (*R*)-BINAP, (*S*)-BINAP as well as *rac*-BINAP didnot affect the stereospecificity of the reaction. This result indicates that stereospecific product formation may be controlled by the substrate. Therefore, the role of BINAP for reaction transformation needs to be addressed. To draw any rational conclusion, reactions were conducted using $Rh(COD)_2BF_4$ only (without chiral ligand BINAP) and in another reaction $Rh(COD)_2BF_4$ with non-chiral ligand PPh_3. However, in both reactions more than 80% starting material was recovered which indicates that BINAP is necessary for the activation of the Rh-catalyst. To further understand the stereospecific control by substrate, the 3D structure of cyclization precursor **8b** (Figure 2) was generated and optimized using

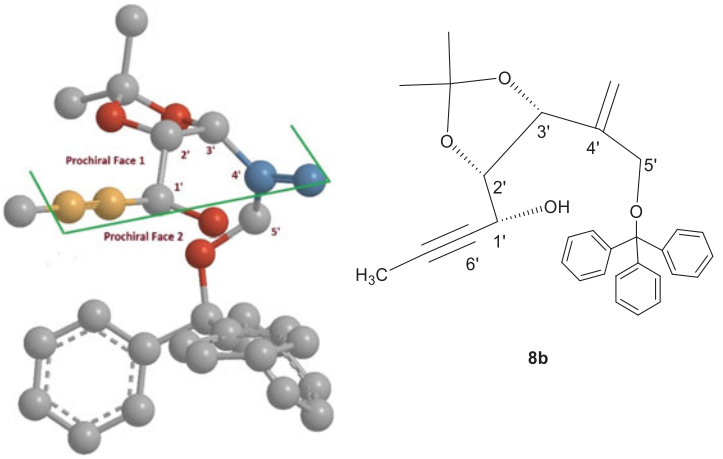


Figure 2. 3D structural pre-organization of **8b** before cyclization to show substrate controlled stereoselectivity. The Rh-catalyst system has approach only through prochiral face 1 using ligation with the acetonide followed by ligand exchange with the 1,6-enyne system. Prochiral face 2 is sterically crowded due to presence of trityl group.

Gaussian. It can be seen in the 3 D structural diagram that the reacting functional groups, ene (4′-methylene, blue) and yne (6′-alkynyl, yellow) lie in a plane (marked with green line) that creates two prochiral faces. Further, the computational modeling studies indicate that the 1′-OH is involved in intramolecular O-H … π interaction [calculated H … π (centroid) distance = 2.05Å] with the phenyl ring of the trityl group in prochiral face-**2** and in stabilizing the geometry. By that way this face will be sterically hindered for catalyst to approach the reaction precursors (alkene and alkyne groups) to initiate cyclization.

Therefore, catalyst may only approach from prochiral face-**1** consisting of the 2′, 3′-acetonide. The heterolytic activation of elemental hydrogen by the $Rh(COD)_2BF_4$-BINAP [$LnRh^I$] catalyst system forms the monohydride catalyst $LnRh^IH$. Here, we propose that the acetonide chelates with $LnRh^IH$ (**I,** Figure 3) and facilitates [2 + 2 + 1] oxidative cyclization of the1,6-enyne leading to C4′-C6' bond formation through **II** to generate a fused cyclopentane metallocyclic intermediate (**III**). During this process, most probably, C-C bond formation precedes C-H formation and determines the 7′-*Z* configuration in the product. Intramolecular hydrogen transfer from $Rh^{III}LnH$ orients the 4′-CH_3 down with opening of the 5-membered metal-centered ring (**IV**). The Rh^ILn takes up H_2 to form $Rh^{III}(H)_2Ln$ (**V**) which transfers hydrogen to the double bond to form **9b**.

The stereochemistry of **9a** and **9b** were confirmed through NOE studies separately. 5′-H of **9a** showed 1 D NOE correlation with 3′-H and 1′-H. Further, 3′-H of **9a** showed 1 D NOE correlation with 5′-H and 2′-H, however 4′-methyl didn't show any correlation with 2′-H. It confirms the

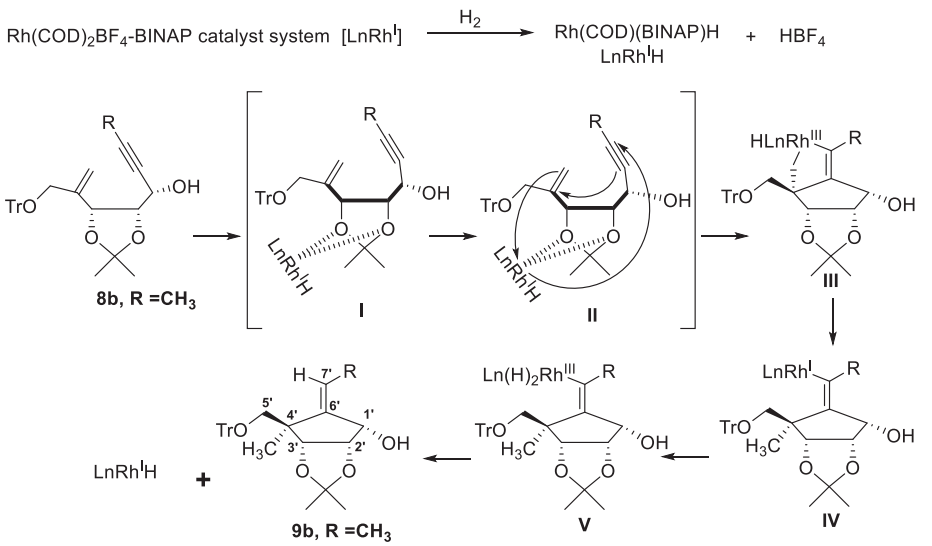


Figure 3. Proposed mechanism for stereospecific reductive cyclization of 1,6-enyne (**8b**). Transition state **I** & **II** show the Rh-ligation through the acetonide face followed by ligand exchange with the 1,6-enyne system to form Rh-complex **III**.

α-configuration of the methyl at 4′, which confirms the anti-configuration of 4′-CH_2OTr with respect to 1′-OH. Similarly, 5′-H of **9 b** showed NOE correlation with 3′-H and 1′-H. 7′-CH_3 of **9b** showed 1 D NOE with 1′-H, 1′-OH and 7′-H showed correlation with 4′-CH_3. These results confirm that the anti-**9b** exists in the *Z*-configuration. Reaction of **9a–b** with Boc-protected adenine followed by deprotection with TFA:H_2O yielded target nucleosides (**10a–b**) as single stereoisomers.

The anti-HBV assays of **10a–b** were carried out in HepG2.2.15.7 cells, however, none showed significant inhibitory activity.

3. Conclusion

In conclusion, a novel BINAP directed rhodium catalyzed stereospecific reductive carbocyclization of 1,6-enynes was established for the synthesis of 4′,6′-disubstitued carbocyclic sugars and utilized for generating aristeromycin analogs. We found that enantioselectivity of this C-C bond formation is independent of the chirality of ligand and controlled by substrate.

4. Experimental section

General procedure for alkynylation of D-ribose derivative (3): To a solution of **3** (11.56 mmol) in 50 mL anhydrous THF, ethynyl/prop-1-yne magnesium bromide (46.24 mmol, 0.5 M in THF) was added dropwise with stirring at −78 °C under argon atmosphere. After 1 hour, the temperature

was raised to rt and the reaction mixture was stirred for an additional 16 hours. The reaction mixture was cooled to 0 °C and 40 mL saturated NH_4Cl solution was added dropwise with stirring. The organic layer was separated and the aqueous layer was washed with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude **4a/4b** in ~ 95:5 diasteromeric ratio. The crude was purified on a silica gel (100–200 mesh) column chromatography, elution gradient 0–20% EtOAc in hexane and the major diastereoisomer was collected.

(1*S*)-1-((4*S*,5*R*)-5-(1-hydroxy-2-(trityloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (4a): purified yield: **71.2**%, white solid, (TLC: R_f 0.2, 20% EtOAc in hexane). $[\alpha]_D^{25:}$ +1.2 (c = 1.1, $CHCl_3$); UV(MeOH) λmax: 200.25 nm; mp: 127–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.33 (s, 3H), 2.51 (d, J = 1.8 Hz, 1H), 3.09 (d, J = 3.3 Hz, D_2O exchangeable, 1H), 3.34 (dd, J = 7.2 and 9.9 Hz, 1H), 3.52 (dd, J = 3.0 and 9.9 Hz, 1H), 3.86–3.91 (m, 1H), 4.03 (d, J = 4.8 Hz, D_2O exchangeable, 1H), 4.16 (dd, J = 5.1 and 9.6 Hz, 1H), 4.29 (dd, J = 5.4 and 8.4 Hz, 1H), 4.58–4.63 (m, 1H), 7.22–7.44 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.4, 27.7, 61.1, 64.8, 68.6, 73.6, 76.5, 79.9, 82.3, 87.1, 109.3, 127.2, 127.9, 128.5, 143.5; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{29}H_{30}O_5Na$ $[M + Na]^+$: 481.1991, found: 481.1993.

(1*S*)-1-((4*S*,5*R*)-5-(1-hydroxy-2-(trityloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (4b): purified yield: **75.1**%, white solid. (TLC: R_f 0.2, 20% EtOAc in hexane). $[\alpha]_D^{25}$: + 4.90 (c = 0.1, $CHCl_3$); UV(MeOH) λmax: 193.00 nm; mp: 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 3H), 1.33 (s, 3H), 1.88 (d, J = 1.6 Hz, 3H), 3.11 (d, J = 3.6 Hz, D_2O exchangeable, 1H), 3.32 (dd, J = 6.8 and 9.6 Hz, 1H), 3.50 (dd, J = 2.8 and 9.6 Hz, 1H), 3.89 (dd, J = 3.9 and 7.2 Hz, 1H), 3.91 (d, J = 4.4 Hz, D_2O exchangeable, 1H), 4.13 (dd, J = 5.2 and 9.6 Hz, 1H), 4.23 (dd, J = 5.2 and 8.4 Hz, 1H), 4.54–4.58 (m, 1H), 7.22–7.44 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 3.9, 25.5, 27.8, 61.3, 64.8, 68.6, 77.2, 77.7, 80.3, 81.9, 87.1, 109.1, 127.2, 127.9, 128.5, 143.6; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{30}H_{32}O_5Na$ $[M + Na]^+$: 495.2148, found: 495.2143.

General procedure for Rh-catalyzed stereospecific reductive carbocyclization of 1,6-enynes (8a-b): To a stirred solution of **8a/8b** (1.7 mmol) in 96 mL of 1,2-dichloroethane was degassed with argon gas for 30 minutes. *rac*-BINAP (0.15 mmol) and $[Rh(COD)_2]BF_4$ (0.1 mmol) were added to the above reaction mixture and stirred at rt for 2 hours under hydrogen atmosphere (1 atm). The volatiles were removed under reduced pressure and crude **9a/9b** was purified on a silica gel (100–200 mesh) column chromatography, elution gradient 0–8% EtOAc in hexane.

(3a*S*,4*S*,6*R*,6a*R*)-2,2,6-trimethyl-5-methylene-6-(trityloxymethyl)tetrahydro-3a*H*-cyclo penta[*d*][1,3]dioxol-4-ol (9a): purified yield: **70**%, white solid. (TLC: R_f 0.3, 10% EtOAc in hexane). $[\alpha]_D^{20}$: −61.7 (c = 0.5, $CHCl_3$); UV (MeOH) λmax: 212.25 nm; mp: 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.10 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 2.34 (d, J = 10.8 Hz, D_2O exchangeable, 1H), 2.90 (s, 2H), 4.27 (d, J = 5.7 Hz, 1H), 4.49 (t, J = 6.0 Hz, 1H), 4.56–4.62 (m, 1H), 5.04 (d, J = 2.4 Hz, 1H), 5.35 (d, J = 1.8 Hz, 1H), 7.20–7.39 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.8, 24.5, 26.1, 47.1, 70.6, 73.1, 77.7, 83.7, 87.0, 108.6, 110.1, 127.0, 127.8, 128.6, 143.6, 156.9; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{30}H_{32}O_4Na$ $[M + Na]^+$: 479.2198, found: 479.2197.

(3a*S*,4*S*,6*R*,6a*R*,*Z*)-5-ethylidene-2,2,6-trimethyl-6-(trityloxymethyl)tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (9b): purified yield**: 65**%, color less thick liquid. $[\alpha]_D^{25}$: −28.8 (c = 0.45, $CHCl_3$); mp =95–98 °C; UV (MeOH) λmax: 200.28 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (s, 3H), 1.24 (s, 3H), 1.35 (s, 3H), 1.83 (dd, J = 1.6 and 7.2 Hz, 1H), 2.75 (s, 2H), 4.04 (d, J = 6.4 Hz, D_2O exchangeable, 1H), 4.13 (d, J = 5.2 Hz, 1H), 4.39 (t, J = 6.4 Hz, 1H), 4.57–4.60 (m, 1H), 5.33–5.36 (m. 1H), 7.21–7.36 (m, 15H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.7, 18.0, 25.0, 26.0, 46.7, 71.2, 71.8, 78.6, 84.3, 86.3, 109.6, 121.0, 126.5, 127.0, 128.2, 143.5, 147.7; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{31}H_{34}O_4Na$ $[M + Na]^+$: 493.2355, found: 493.2353.

General procedure for synthesis of target aristeromycin analogs (10a-b): To a mixture of N^6,N^6-Bis(tert-butoxycarbonyl)adenine (0.82 mmol), **9a/9b** (0.63 mmol) and Ph_3P (1.59 mmol) in 6 mL dry THF was added DIAD (1.75 mmol) drop wise at 5–10 °C under argon atmosphere and stirring was continued at rt for 1 hour. Completion of reaction was monitored by TLC, solvent evaporated under reduced pressure and the crude was carried forward to the next step without purification. The deprotection of acetonide, Boc and trityl protecting groups was carried out by stirring in 2 ml TFA:water (8:2) for 0.5 hour at rt. After completion (monitored by TLC), the reaction mixture was neutralized by sat. $NaHCO_3$ solution and purified on a silica gel (100–200 mesh) column chromatography, elution gradient: 0–9% MeOH in CH_2Cl_2.

(1*S*,2*R*,3*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-3-methyl-4-methylene cyclopentane-1,2-diol (10a): purified yield: 60%, off white solid (TLC: R_f 0.1, 10% MeOH in CH_2Cl_2). $[\alpha]_D^{25}$: -10.4 (c = 0.25, DMSO); mp: 63–67 °C; UV (MeOH) λmax: 204.25, 216.25 and 259.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.2 (s, 3H), 3.54 (d, J = 11.2 Hz, 1H), 3.74 (d, J = 11.2 Hz, 1H), 4.03 (d, J = 4.4 Hz, 1H), 4.67 (d, J = 2.4 Hz, 1H), 4.87 (dd, J = 4.8 and 7.2 Hz, 1H), 5.14 (d, J = 3.2 Hz, 1H), 5.40–5.44 (m, 1H), 8.20 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.8, 49.6, 62.9,

69.1, 73.3, 73.7, 108.5, 118.9, 141.4, 149.4, 150.3, 154.1, 154.6; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{13}H_{17}N_5O_3$ $[M+H]^+$: 292.1401, found: 292.1394

(1*S*,2*R*,3*R*,5*R*,*Z*)-5-(6-amino-9*H*-purin-9-yl)-4-ethylidene-3-(hydroxymethyl)-3-methyl cyclopentane-1,2-diol (10b): purified yield: 55%, off white solid. (TLC: R_f 0.1, 10% MeOH in CH_2Cl_2). $[\alpha]_D^{20}$: -17.7 (c = 0.1, MeOH); mp: 138–140 °C; UV (MeOH) λmax: 204.25, 220.25 and 260.25 nm ^{1}H NMR (400 MHz, CD_3OD) δ: 1.08 (dd, J = 1.2 and 6.8 Hz, 3H), 1.14 (s, 3H), 3.58 (d, J = 11.2 Hz, 1H), 3.71 (d, J = 10.8 Hz, 1H), 4.00 (d, J = 4.0 Hz, 1H), 4.63 (dd, J = 4.8 and 7.2 Hz, 1H), 5.43 (dd, J = 2.0 and 5.2 Hz, 1H), 5.64–5.66 (m, 1H), 8.16 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 13.1, 20.1, 52.0, 63.9, 71.5, 76.7, 78.2, 120.3, 125.1, 142.8, 143.1, 150.1, 153.1, 157.5; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{20}N_5O_3$ $[M+H]^+$: 306.1566, found:306.1535.

Acknowledgements

Authors acknowledge GVK Biosciences Pvt. Ltd, Hyderabad for facilitating academic research activity. We are grateful to the Central Instruments Facility (CIF), BIT, Mesra for analytical support. We acknowledge DST FIST at Department of Chemistry, BIT, Mesra (SR/FST/CSI-242/2012) for NMR and computational chemistry facility.

References

[1] Yuen, M.-F.; Ahn, S. H.; Chen, D.-S.; Chen, P.-J.; Dusheiko, G. M.; Hou, J.-L.; Maddrey, W. C.; Mizokami, M.; Seto, W.-K.; Zoulim, F.; Lai, C.-L. Chronic Hepatitis B Virus Infection: Disease Revisit and Management Recommendations. *J. Clin. Gastroenterol.* **2016**, *50*, 286–294. DOI: 10.1097/MCG.0000000000000478.

[2] Liu, J.; Goicochea, P.; Block, T.; Brosgart, C. L.; Donaldson, E. F.; Lenz, O.; Gee Lim, S.; Marins, E. G.; Mishra, P.; Peters, M. G.; Miller, V. Advancing the Regulatory Path on Hepatitis B Virus Treatment and Curative Research: a Stakeholders Consultation. *J. Virus Eradic.* **2017**, *3*, 1–6.

[3] Innaimo, S. F.; Seifer, M.; Bisacchi, G. S.; Standring, D. N.; Zahler, R.; Colonno, R. J. Identification of BMS-200475 as a Potent and Selective Inhibitor of Hepatitis B Virus. *Antimicrob. agents Chemother.* **1997**, *41*, 1444–1448. DOI: 10.1128/AAC.41.7.1444.

[4] Kumamoto, H.; Fukano, M.; Nakano, T.; Iwagami, K.; Takeyama, C.; Kohgo, S.; Imoto, S.; Amano, M.; Kuwata-Higashi, N.; Aoki, M.; et al. Diastereoselective Synthesis of 6 ″-(Z)-and 6 ″-(E)- Fluoro Analogues of anti-hepatitis B Virus Agent Entecavir and Its Evaluation of the Activity and Toxicity Profile of the Diastereomers. *J. Org. Chem.* **2016**, *81*, 2827–2836. DOI: 10.1021/acs.joc.6b00105.

[5] Kumamoto, H.; Fukano, M.; Imoto, S.; Kohgo, S.; Odanaka, Y.; Amano, M.; Kuwata-Higashi, N.; Mitsuya, H.; Haraguchi, K.; Fukuhara, K. A Novel Entecavir Analogue Constructing with a Spiro [2.4] heptane Core Structure in the Aglycon Moiety: Its Synthesis and Evaluation for anti- hepatitis B Virus Activity. *Nucleos. Nucl. Nucleic Acids.* **2017**, *30*, 1–11.

[6] Rawal, R. K.; Bariwal, J.; Singh, V. Chemistry and Bioactivities of Aristeromycins: An Overview. *Curr. top. med. Chem*. **2016**, *16*, 3258–3273.

[7] Betson, M.; Allanson, N.; Wainwright, P. A Review of Methods to Synthesise 4'-substituted nucleosides. *Org. Biomol. Chem*. **2014**, *12*, 9291–9306.

[8] Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. Enantio- and Diastereoselective Synthesis of 4′-α-Substituted Carbocyclic Nucleosides. *Tetrahedron: Asymmetr*. **1998**, *9*,911–914. DOI: 10.1016/S0957-4166(98)00065-2.

[9] Gumina, G.; Chong, Y.; Choi, Y.; Chu, C. K. Stereoselective Synthesis of Carbocyclic L-4'-fluoro-2',3'-dideoxyadenosine. *Org. Lett*. **2000**, *2*, 1229–1231.

[10] Jang, H.-Y.; Krische, M. J. Rhodium-Catalyzed Reductive Cyclization of 1, 6-Diynes and 1, 6- Enynes Mediated by Hydrogen: Catalytic C − C Bond Formation via Capture of Hydrogenation Intermediates. *J. Am. Chem. Soc*. **2004**, *126*, 7875–7880. DOI: 10.1021/ja048498i.

[11] Thiyagarajan, A.; Salim, M. T.; Balaraju, T.; Bal, C.; Baba, M.; Sharon, A. Structure Based Medicinal Chemistry Approach to Develop 4-methyl-7-deazaadenine Carbocyclic Nucleosides as anti-HCV Agent. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 7742–7747. DOI: 10.1016/j.bmcl.2012.09.072.

[12] Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. Reaction of Ethynylmagnesium Bromide with 2, 3-O-Isopropylidene-D-ribose and 2, 3: 5, 6-di-O-isopropylidene-D-mannofuranose: Syntheses of Glycofuranosylethynes. *Carbohydr. Res*. **1974**, *36*, C5–C7. DOI: 10.1016/S0008-6215(00)82020-0.

[13] Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. C-nucleoside Studies. Part II. Pentofuranosylethynes From 2, 3-O-isopropylidene-D-Ribose. *J. Chem. Soc, Perkin Trans*. **1975**, *1*,1191–1200. DOI: 10.1039/p19750001191.