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Authors: Sateesh Dubbu, Anirban Bardhan, Ande Chennaiah, and Yashwant D Vankar

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A Cascade of Prins Reaction and Pinacol-Type Rearrangement: Access to 2,3-Dideoxy-3C-Formyl β-*C*-Aryl/Alkyl Furanosides and 2-Deoxy-2C-Branched β-*C*-Aryl Furanoside

Sateesh Dubbu,[a] Anirban Bardhan,[a]† Ande Chennaiah[a] and Yashwant D. Vankar*[a]

Dedication ((optional))

Abstract: 2,3-Dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides were synthesized in a stereoselective manner through a cascade of Prins reaction and pinacol-type rearrangement of an –OTBDPS protected homoallylic alcohol, derived from D-mannitol, and various carbonyl compounds. Furthermore, this method was successfully applied to the synthesis of a fused-bicyclic β-*C*-aryl furanoside moiety and a 2,3-dideoxy-3C-methyl β-*C*-aryl furanoside which are found in core structures of bioactive molecules. Further, the strategy was extended to a silyl-Prins reaction for the synthesis of a 2-deoxy-2C-branched β-*C*-aryl furanoside.

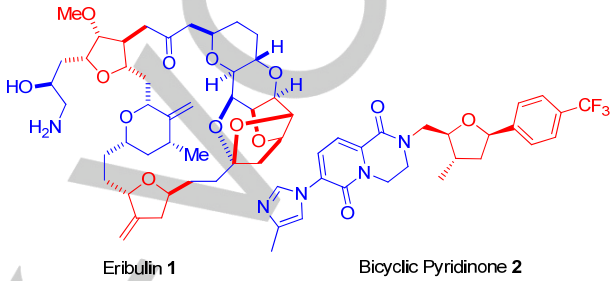

Figure 1: Biologically important tri- and tetrasubstituted *C*-furanosides.

Introduction

Carbohydrates are essential building blocks for many cellular processes in living organisms and they exist and act as physiologically important oligosaccharides in the form of glycoproteins and glycolipids.[1] Among oligosaccharides, five membered carbohydrate skeleton (furanose/tetrahydrofuran) is an important structural motif existing in a wide range of bioactive polysaccharides.[2] For example, the mycobacterial cell wall is a highly complex structure and composed of furanose ring of two lipidated polysaccharides (arabinogalactan complex and lipoarabinomannan).[2e-h] Among the five membered sugars, *C*-furanosides[3] are known to be quite stable and possess important biological properties. For instance, eribulin **1** (Figure 1) is an anticancer drug,[4] which consists of tri- and tetrasubstituted *C*-furanoside core motifs. Likewise, bicyclic pyridinone **2** (Figure 1) is a 2,3-dideoxy-3C-methyl β-*C*-aryl furanoside and known for the treatment of neurological disorders such as Alzheimer's disease and Down's syndrome.[5] Further, synthesis and study of non-natural *C*-aryl furanosides and their comparison with *C*-nucleosides is also an important area of research to study and for probing them as nucleobases.[3h-3k] Thus, owing to their fascinating structural features and inherent biological properties, construction of tri and tetra substituted β-*C*-aryl/alkyl furanosides[6] in a highly stereoselective manner is a significantly challenging task in synthetic carbohydrate chemistry.

The Prins reaction is a versatile strategy for the construction of a tetrahydropyran/furan ring systems which exist as a core structure in several natural products.[7] In this direction, we recently reported a successful utility of the Prins-pinacol-type rearrangement in carbohydrate chemistry involving C-4-*O*Bn participation on 1,2-anhydrosugar derived homoallylic alcohols in the synthesis of bridged tricyclic ketals.[8] We also synthesized 2C-branched *C*-aryl/alkyl glycosides from Perlin-aldehyde derived substrates through the Prins reaction.[9]

The importance of diversity-oriented synthesis (DOS) in the development of a small molecular library with potential biological significance through a diversity-oriented synthesis has attracted much attention.[10] In continuation of our efforts towards the synthesis of *C*-aryl/alkyl glycosides,[8,9,11] more recently we have reported on the synthesis of a molecular library of 2-deoxy-3,4-fused *C*-aryl/alkyl glycosides through the cascade Prins cyclization of a D-mannitol derived homoallylic alcohol.[12] Depending on the protection of the allylic hydroxyl group of such a D-mannitol derived homoallylic alcohol, 2-deoxy-3,4-fused sugar scaffolds namely isochroman derivatives, bicyclic vinyl halide derivatives, fluorine substituted tetrahydropyrans and furan derivatives were procured. The protecting groups used were benzyl, 1-methylnaphthyl, 2-methylnaphthyl, propargyl, allyl and substituted allyl ethers. On the other hand, when *O*-pivaloyl group was used as a protecting group, it led to a highly stereoselective formation of 2-deoxy-β-*C*-aryl/alkyl glycosides.[13] In view of such protecting group based diverse reactivity of D-mannitol derived homoallylic alcohol **3**, herein, we report the study of –OTBDPS protecting group on homoallylic alcohol **3** which led to a stereoselective synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides through the Prins-pinacol rearrangement. Additionally, the homoallylic alcohol **3** was also successfully subjected to the silyl-Prins cyclization for

[a] Prof. Dr. Yashwant. D. Vankar
Sateesh Dubbu, Anirban Bardhan, Ande Chennaiah,
Department of Chemistry, Indian Institute of Technology Kanpur,
Kanpur 208016, India
† M.Sc. research project participant (2016).
E-mail: vankar@iitk.ac.in, http://home.iitk.ac.in/~vankar/

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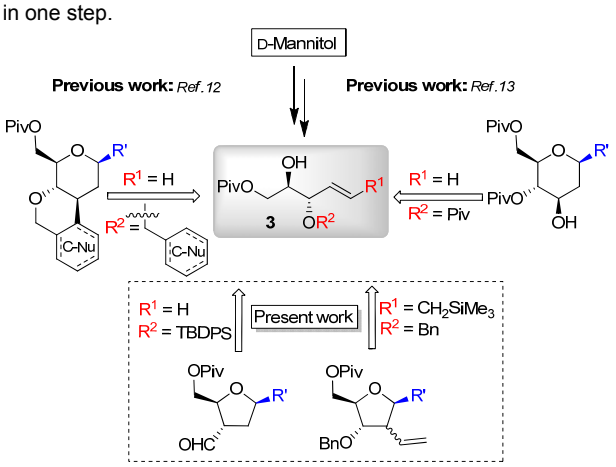
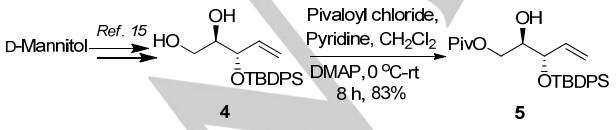
the construction of a 2-deoxy-2C-branched β-*C*-aryl furanoside in one step.



Scheme 1. Retrosynthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides and 2-deoxy-2C-branched β-*C*-aryl furanoside.

Results and Discussion

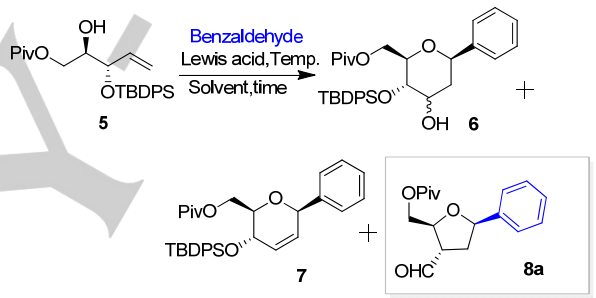
As described above, when the protecting group on the allylic alcohol part of the D-mannitol derived homoallylic alcohol **3** was benzyl or a related ether, it led to products other than the expected *C*-glycosides **6** and/**7** *via* π-participation. On the other hand, with a non-participating –*O*-pivaloyl protection, *C*-glycosides **6** were formed with high stereoselectivity. In view of these results, we decided to protect the –OH group as –OTBDPS ether in anticipation of forming products similar to **6** and/**7** as it would not involve π participation. Alternatively, we also expected the Prins-pinacol type rearrangement to occur with a C-C bond migration once the initial oxocarbenium ion was formed in a typical Prins reaction (*vide infra*). These were based on our recent experience,[8] and also along a somewhat similar report by Overman *et al*.[14] It was expected to lead to 2,3-dideoxy-3C-formyl β-*C*-phenyl furanoside **8a** (Table 1) in the reaction of **3** with benzaldehyde. The required starting material **5** was prepared from **4**, by a known strategy as shown in Scheme 2.[15] Thus, regioselective protection of the primary alcohol **4** was carried out using pivaloyl chloride and pyridine in the presence of a catalytic amount 4-dimethylaminopyridine (DMAP) to form –OTBDPS protected homoallylic alcohol **5** in 83% yield (Scheme 2).



Scheme 2. Preparation of starting material **5**.

We commenced our study by investigating the reactivity of **5** with benzaldehyde using different acid catalysts in various solvents at different temperatures. A few protic and Lewis acids such as trifluoroacetic acid (TFA), $InBr_3$ and $Sc(OTf)_3$ were screened, but these failed to initiate the reaction (Table 1, entries-1, 2 and 3). With the use of 0.2 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane as a solvent at 0 °C to room temperature we observed the formation of 2,3-dideoxy-3C-formyl β-*C*-phenyl furanoside **8a** albeit in very low yield (11%), but formation of *C*-glycosides **6** and/**7** (Table 1, entry 4) was not observed. No significant improvement was noticed in the product yield (27%) even after increasing the catalyst loading to 0.5 equiv of TMSOTf (Table 1, entry 5). However, to our delight we observed the formation of **8a** in 58% yield with 0.5 equiv of BF_3•OEt_2 at 0 °C (Table 1, entry 6). The best results were obtained by using 1.0 equiv BF_3•OEt_2 at 0 °C, 2,3-dideoxy-3C-formyl β-*C*-phenyl furanoside **8a** in 89% yield (Table 1, entry 7). Among the solvents that were used including acetonitrile, toluene and benzene (Table 1, entries-8, 9 and 10) the best results observed were with dichloromethane.

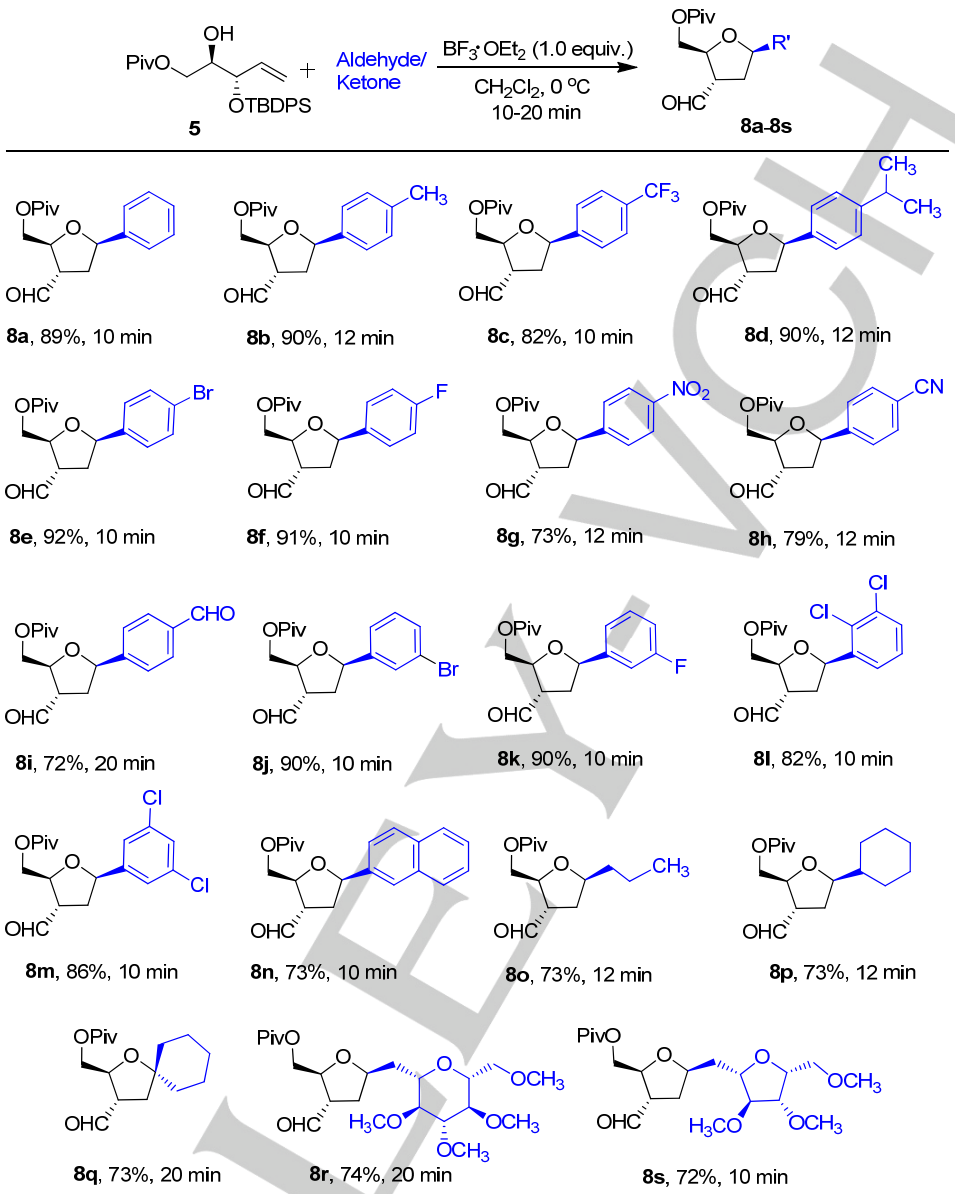
Table 1. Optimization of reaction conditions



Entry	Lewis acid	Equiv.	Solvent	Temp.(°C)	Time	8a yield(%)a
1	TFA	1.0	CH_2Cl_2	0-rt	24 h	NR
2	$InBr_3$	0.2	CH_2Cl_2	-20-rt	24 h	NR
3	$Sc(OTf)_3$	0.2	CH_2Cl_2	-20-rt	24 h	NR
4	TMSOTf	0.2	CH_2Cl_2	0-rt	1 h	11
5	TMSOTf	0.5	CH_2Cl_2	0	50 min	27
6	$BF_3{\cdot}OEt_2$	0.5	CH_2Cl_2	0	40 min	58
7	**$BF_3{\cdot}OEt_2$**	**1.0**	**CH_2Cl_2**	**0**	**12 min**	**89**
8	$BF_3{\cdot}OEt_2$	1.0	CH_3CN	0	40 h	76
9	$BF_3{\cdot}OEt_2$	1.0	toluene	0	12 h	62
10	$BF_3{\cdot}OEt_2$	1.0	C_6H_6	10-rt	40 h	46

a. Yield refers to pure product after column chromatography. NR = no reaction.

The scope of the reaction was further evaluated by using various aldehydes with diverse substitution patterns. In most cases, the products were obtained in excellent yields and high selectivity. This method is compatible with a wide range of functional groups such as nitro, aldehyde, cyano and halides (Scheme 3). The substituents present on the aromatic ring were found to have some effects on the conversion.

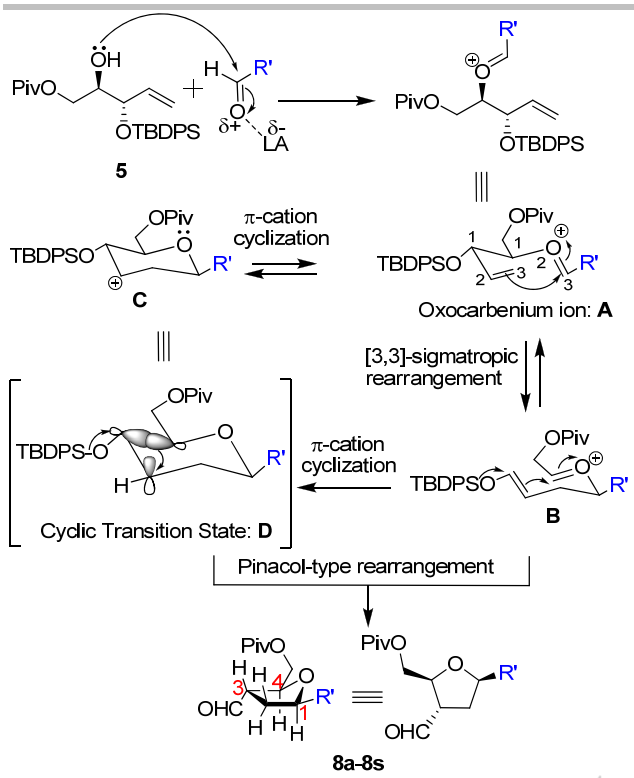


Scheme 3. Synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides **8a**-**8s**.

Aromatic aldehydes bearing an electron withdrawing substituent (Scheme 3, **8c**, **8g**,**8h** and **8i**) on an aromatic ring gave the corresponding products in relatively lower yield than with halide (**8e**, **8f** and **8j**-**8k**), and also with alkyl substituted aryl aldehydes (**8b** and **8d**). Furthermore, the reaction of –*O*TBDPS protected homoallylic alcohol **5** with the *p*-phthalaldehyde selectively gave product **8i** in 72% yield. This reaction is also quite successful with cyclohexanone leading to the spiro compound **8q** in 73% yield. Further, we could also procure two novel *C*-disaccharides **8r** and **8s** by applying the current protocol.

A plausible mechanism to account for the formation of such 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides is shown in Scheme 4. It is presumed that after initial formation of the Prins-type oxocarbenium ion **A** it can either undergo [3,3]-sigmatropic rearrangement to form **B**, or simply a π-cation cyclization to form **C**. Both of these intermediates will then undergo pinacol-type rearrangement *via* the transition state **D** involving the migration of C-C bond, followed by cleavage of the –*O*–$SiPh_2tBu$ bond resulting into ring contraction to form 2,3-dideoxy-3C-formyl β-*C*-aryl furanosides (**8a**-**8s**). Alternatively, the intermediate **B** may directly give the products **8a-8s**,as shown.

The structure of **8a** was confirmed by spectral studies and the stereochemistry of the newly generated stereocenters was



Scheme 4. Mechanism for the formation of 2,3-dideoxy-3C-formyl β-*C*-aryl furanosides **8a**-**8s.**

established based on COSY followed by NOE studies.[16] Thus, NOE studies of compound **8a** revealed that (Figure 2), irradiation of the H-4 proton at δ 4.56 resulted in an enhancement of the H-1 proton at δ 4.91–4.90. Also, irradiation of the H-1 proton at δ 4.91–4.90 resulted in an enhancement of the H-4 proton at δ 4.57–4.56 and did not show the enhancement of the H-3 proton. It indicates that H-1 proton is in *cis* orientation to H-4 proton but *trans* to H-3 proton.

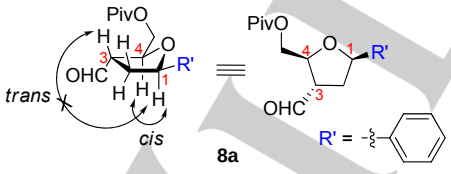
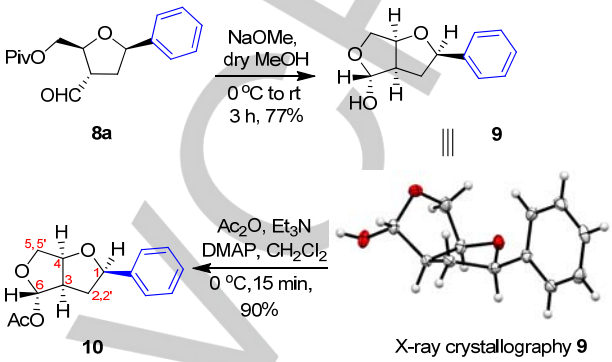


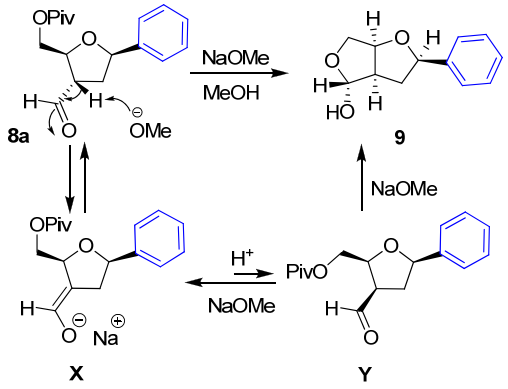
Figure 2. NOE of compound **8a**.

Apparently, the presence of an aldehyde and –*O*–pivaloyl group in the 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanoside skeleton (Scheme 3, **8a**-**8s**), makes it a useful synthetic precursor for further manipulation. Hence, to get free hydroxyl compound of **8a**, we subjected compound **8a** to hydrolysis with NaOMe in MeOH (Scheme 5). However, surprisingly, we observed the formation of a fused-bicyclic β-*C*-aryl furanoside **9** with inversion of stereocenter at C-3 position (Scheme 5). The structure of compound **9** was confirmed by spectral studies, and also X-ray crystallography (CCDC:1583906).[16] It was then protected as acetate **10** by using Ac_2O/Et_3N (Scheme 5) whose solution-state structure was established by NMR experiments including COSY, NOE and HETCOR.[16] It is worth mentioning that the molecule **10**, having fused-bicyclic β-*C*-aryl furanoside moiety, is in structural resemblance with the core structure of (+)-commiphorin, which shows antibacterial activity.[17]



Scheme 5. Synthesis of a fused-bicyclic β-*C*-aryl furanoside **10**.

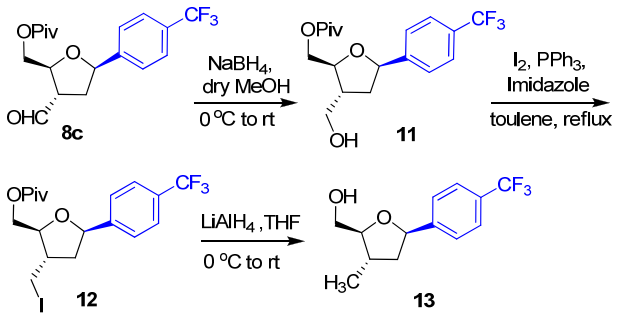
Formation of fused-bicyclic β-*C*-aryl furanoside **9**, can be explained as shown in Scheme 6. Compound **8a** may undergo a base catalyzed equilibration with enolate **X** upon proton abstraction from "α" carbon of the aldehyde. This intermediate **X** could have another equilibration with **Y** *via* inversion of the stereochemistry at C3 position, perhaps to some extent since **Y** is sterically more hindered than **8a**. Subsequently, basic hydrolysis of pivaloyl ester in **Y** with NaOMe in MeOH followed by cyclization could lead to **9**.



Scheme 6. A plausible mechanism for the formation of fused-bicyclic β-*C*-aryl furanoside **9**.

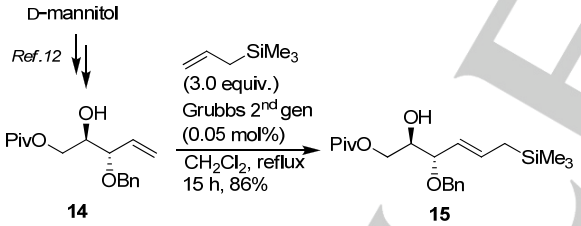
2,3-Dideoxy *C*-furanosides with a methyl group at C-3 position are important scaffolds and are present in several natural products as a core motifs such as mandelalide A,[18] gymnodimine,[19] bicyclic pyridinone[5] etc. We therefore thought of synthesizing a core structure of 2,3-dideoxy-3C-methyl β-*C*-aryl furanoside **13** (bicyclic pyridinone) by using this methodology. Toward this, 2,3-dideoxy-3C-formyl β-*C*-aryl

furanoside **8c** was first reduced with $NaBH_4$ to the corresponding primary alcohol **11** which was then converted to the final molecule **13** *via* Appel reaction followed by $LiAlH_4$ reduction of the iodide **12** (Scheme 7). Thus, the present route provides an easy alternative route to obtain 2,3-dideoxy C-3 methyl *C*-furanosides.



Scheme 7. Synthesis of core moiety of bicyclic pyridinone **13**.

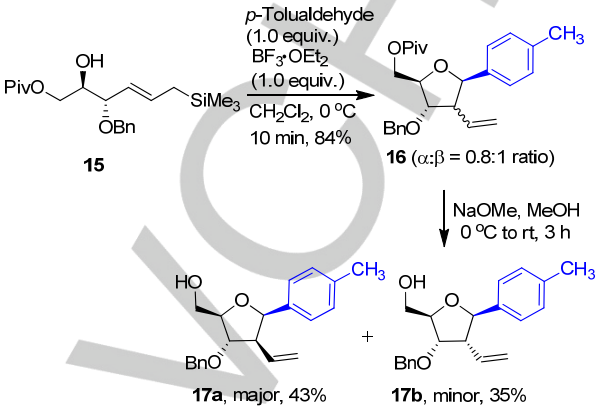
Having demonstrated the use of –OTBDPS protected homoallylic alcohol **5**, we turned our attention to extend the chain of the homoallylic alcohol of type **3** to form an allylsilane **15** and then check its feasibility in silyl-Prins cyclization. The requisite precursor **15** was prepared from –OBn protected homoallylic alcohol **14**, obtained from D-mannitol,[12] upon cross metathesis reaction with allylsilane in presence of Grubbs 2nd generation catalyst (5 mol %) in CH_2Cl_2 for 15 h at reflux (Scheme 8).



Scheme 8. Synthesis of homologated allylsilane homoallylic alcohol **15**.

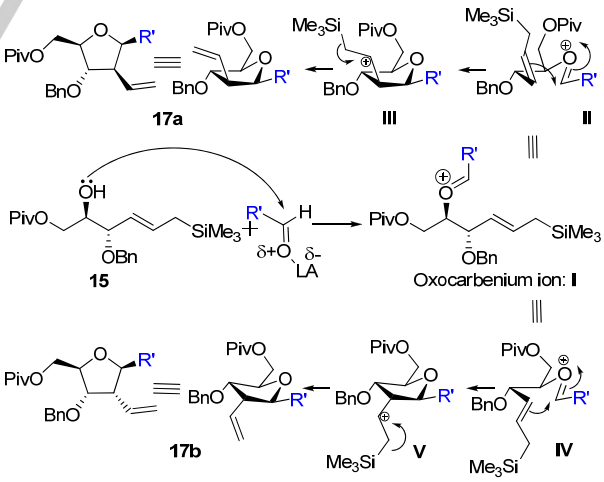
Treatment of the homologated allylsilane homoallylic alcohol **15** with *p*-tolualdehyde using 1.0 equiv BF_3•OEt_2 at 0 °C in dichloromethane (Table 1, entry 7) as a solvent gave the corresponding 2-deoxy-2C-branched β-*C*-aryl furanoside **16** in good yield (84%) as an inseparable diastereomeric mixture (α:β = 0.8:1 ratio) (Scheme 9). In order to separate the stereoisomers, compound **16** was subjected to deprotection of the –OPiv group using NaOMe/MeOH to give diastereomers **17a** and **17b** which were separated by column chromatography in 43% and 35% yield respectively. The structures of **17a** and **17b** were confirmed based on spectral studies and the stereochemistry of the newly generated stereocenters was established based on COSY followed by NOE studies.[16] Further work to explore the scope of this silyl-Prins reaction is underway and will be reported in due course of time.

A plausible reaction pathway for the silyl-Prins cyclization is shown in Scheme **10**. The reaction is likely to proceed through an oxocarbenium ion **I** formed upon reaction of the homologated allylsilane homoallylic alcohol **15** with *p*-tolualdehyde. In this reaction, BF_3•OEt_2 activates the aldehyde thus facilitating the formation of an oxocarbenium ion **I**, which is then attacked by an



Scheme 9. Synthesis of 2-deoxy-2C-branched β-*C*-aryl furanoside **17a** and **17b**.

internal olefin to generate β-silyl carbocation **III**, *via* the conformation **II**. Subsequently, the intermediate **III** hydrolytically decomposes to give corresponding products **17a**. On the other hand the formation of minor diastereomer can be explained *via* the confomation **IV** which leads product **17b** *via* β-silyl carbocation **V** followed by silyl group elimination with the help of a nucleophile present in reaction medium.



Scheme 10. Mechanism for the formation of 2-deoxy-2C-branched β-*C*-aryl furanoside **16**.

The stereochemistry of newly generated stereocenters was proved by spectral means. Thus, NOE studies[16] of compound **17a** revealed that (Figure 3), irradiation of the H-4

proton at δ 4.07 resulted in an enhancement of the H-1 proton at δ 5.25 and H-2 proton at δ 3.16. It indicates that H-4 proton is *cis* to H-1 and H-2 protons. In the NOE studies of compound **17b** (Figure 3), irradiation of the H-4 proton at δ 4.19 resulted in an enhancement of the H-1 proton at δ 4.87 and did not result in the enhancement of the H-2 proton. Further, irradiation of the H-2 proton at δ 2.71 and did not result in the enhancement of the H-4 proton. It indicates that H-4 proton is in *cis* relationship with H-1 proton, but in *trans* relationship with H-2 proton.

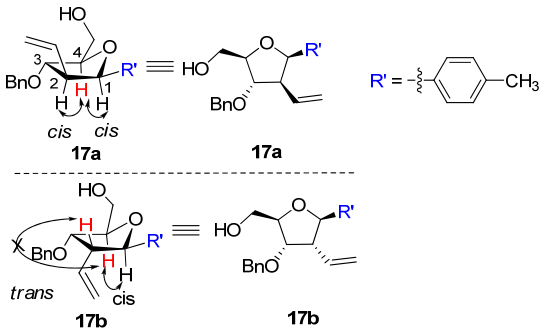


Figure 3. NOE of compound **17a** and **17b**.

Conclusions

In summary, we have developed a facile method for the stereoselective synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides through Prins-pinacol rearrangement of –*O*TBDPS protected homoallylic alcohol derived from D-mannitol. This cascade reaction is compatible with a variety of carbonyl compounds to give the corresponding 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides in good to excellent yields. Furthermore, this method was successfully applied to the synthesis of a fused-bicyclic β-*C*-aryl furanoside moiety and a 2,3-dideoxy-3C-methyl β-*C*-aryl furanoside which are found in core structures of bioactive molecules. Additionally, the strategy was extended to a silyl-Prins reaction for the synthesis of a 2-deoxy-2C-branched β-*C*-aryl furanoside whose further scope is being investigated and will form a part of future publication.

Experimental Section

General procedure:

All the dry solvents were prepared according to the standard procedures. All other reagents were used as received from either Aldrich, Spectrochem Pvt. Ltd. (Mumbai), Sd fine-chem Ltd. (Mumbai) and Lancaster chemical companies. Melting points were determined on a micro hot-stage (Yanako MP-S3). The visualization of spots on TLC plates was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100–200 Mesh) using hexane and ethyl acetate as eluents. ^1H and ^{13}C were recorded on JEOL ECX-500 (500 and 125 MHz) spectrometer or JEOL LA-400 (400 and 100 MHz) spectrometer in solution of $CDCl_3$ using tetramethylsilane as the internal standard. Coupling constants are reported and expressed in Hz; splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), m (multiplet), dt (doublet of triplet). IR spectra were recorded on Bruker FT/IR Vector 22 spectrometer and are expressed in cm^{-1}. Optical rotations were measured using a polarimeter (AUTOPOL II) at 28 °C. Mass spectra were obtained from high resolution ESI mass spectrometer using Q–TOF analyser.

General experimental procedures:

(2*R*,3*S*)-3-((*Tert*-butyldiphenylsilyl)oxy)-2-hydroxypent-4-en-1-yl pivalate (5):

Compound **4** was prepared by following a literature proecedure.[15] Compound **4** (500 mg, 1.40 mmol) was dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C. Pivaloyl chloride (0.17 mL, 1.40 mmol), pyridine (0.13 mL, 1.68 mmol) and DMAP (17 mg, 0.14 mmol) were added to this mixture and allowed to stir at room temperature for 8 h. After completion of the reaction (TLC monitoring), it was quenched with water (5 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with water (2 x 15 mL), brine (1 x 15 mL) solution, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude reaction mixture afforded **5** as a colorless thick liquid. Yield = 568 mg, 91%; R_f = 0.6 (9/1 hexane/EtOAc); $[\alpha]_D^{28}$ = +18.02° (*c* = 0.51, CH_2Cl_2); IR ($\tilde{\nu}_{max}/cm^{-1}$) 3514, 2961, 2859, 1732, 1428; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.46–7.34 (m, 6H), 5.87–5.78 (m, 1H), 5.09–5.07 (m, 1H), 4.97–4.92 (m, 1H), 4.20 (dd, *J* = 7.4, 3.9 Hz, 1H), 4.09–4.04 (m, 2H), 3.81 (dd, *J* = 10.0, 5.8 Hz, 1H), 2.34 (br s, 1H), 1.12 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.55, 136.10, 135.99, 135.54, 133.47, 133.42, 130.08, 129.92, 127.86, 127.64, 118.53, 76.30, 72.90, 64.64, 38.84, 27.24, 27.16, 19.50; HRMS calcd for $C_{26}H_{40}NO_4Si$ $[M + NH_4]^+$ 458.2727, found 458.2720.

General procedure for the synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides and 2-deoxy-2C-branched β-*C*-aryl furanoside:

To a stirred solution of homoallylic alcohol **5**/**15** (200 mg, 0.45 mmol, 1.0 equiv/200 mg, 0.57 mmol, 1.0 equiv) and aldehyde (0.54 mmol, 1.1 equiv/) in dichloromethane (3 mL) was added $BF_3{\bullet}OEt_2$ (58 µL, 0.45 mmol, 1.0 equiv) at 0 ºC. The resulting reaction mixture was stirred at same temperature until the starting material was completely consumed (TLC monitoring) (specified in Scheme 3). The reaction mixture was quenched by adding a saturated aqueous $NaHCO_3$ (3 mL) solution and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 5 mL), brine (1 x 5 mL) solution, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude reaction mixture afforded *C*-furanosides (Scheme 3 and Scheme 9).

Following the general procedure for the for the synthesis of 2,3-dideoxy-3C-formyl and 2-deoxy-2C-branched β-*C*-aryl/alkyl furanosides, compounds 8a-8s and 16 were prepared:

((2*S*,3*S*,5*R*)-3-Formyl-5-phenyltetrahydrofuran-2-yl)methyl pivalate (8a):

Colorless liquid; Yield = 117 mg, 89%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +27.14° (*c* = 0.341, CH_2Cl_2); IR ($\tilde{\nu}_{max}/cm^{-1}$) 2971, 2872, 1728, 1282, 1158; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H, –C*H*O), 7.36–7.26 (m, 5H, Ar*H*), 4.92 (dd, *J* = 9.0, 6.4 Hz, 1H, *H*-1), 4.57 (dd, *J* = 9.7, 4.8 Hz, 1H, *H*-4), 4.32 (m, *J* = 6.7 Hz, 2H, *H*-5,5'), 3.14–3.10 (m, 1H, *H*-3), 2.67–2.66 (m, 1H, *H*-2), 2.12–2.06 (m, 1H, *H*-2'), 1.22 (s, 9H, –C(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.93, 178.38, 141.12, 128.63, 127.99, 125.77, 80.95, 76.67, 65.47, 54.23, 39.02, 35.59, 27.37; HRMS calcd for $C_{17}H_{22}O_4$ $[M]^+$ 290.1518, found 290.1516.

((2*S*,3*S*,5*R*)-3-Formyl-5-(*p*-tolyl)tetrahydrofuran-2-yl)methyl pivalate (8b):

Pale yellow liquid; Yield = 125 mg, 90%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = -12.63° (*c* = 0.71, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2973, 2873, 1730, 1283, 1159; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.26–7.15 (m, 4H), 4.88 (dd, *J* = 9.1, 6.3 Hz, 1H), 4.56 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.35–4.30 (m, 2H), 3.13–3.11 (m, 1H), 2.65–2.64 (m, 1H), 2.34 (s, 3H), 2.08 (dt, *J* = 12.9, 9.5 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.05, 178.40, 138.01, 137.73, 129.28, 129.13, 125.77, 80.90, 76.51, 65.49, 54.26, 39.01, 35.57, 27.36, 21.26; HRMS calcd for $C_{18}H_{24}NaO_4$ [M + Na]$^+$ 327.1572, found 327.1570.

((2*S*,3*S*,5*R*)-3-Formyl-5-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methyl pivalate (8c):

Pale yellow liquid; Yield = 134 mg, 82%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +52.18° (*c* = 1.22, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2975, 1729, 1326, 1163, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 1.3 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 4.97 (dd, *J* = 9.1, 6.5 Hz, 1H), 4.61 (dd, *J* = 9.8, 4.5 Hz, 1H), 4.34–4.33 (m, 2H), 3.17–3.12 (m, 1H), 2.77–2.71 (m, 1H), 2.04 (dt, *J* = 12.8, 9.4 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.56, 178.37, 145.30, 125.94, 125.62, 125.59, 80.17, 76.87, 65.36, 53.98, 39.03, 35.47, 27.35; HRMS calcd for $C_{18}H_{22}F_3O_4$ [M + H]$^+$ 359.1470, found 359.1470.

((2*S*,3*S*,5*R*)-3-Formyl-5-(4-isopropylphenyl)tetrahydrofuran-2-yl)methyl pivalate (8d):

Pale yellow liquid; Yield = 137 mg, 90%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = -13.07° (*c* = 0.24, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2961, 2872, 1730, 1480, 1283; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.6 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.88 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.56 (dd, *J* = 9.9, 4.8 Hz, 1H), 4.32–4.31 (m, 2H), 3.14–3.10 (m, 1H), 2.92–2.87 (m, 1H), 2.67–2.62 (m, 1H), 2.11 (dt, *J* = 12.9, 9.5 Hz, 1H), 1.23 (s, 9H), 1.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.05, 178.37, 148.77, 138.30, 126.67, 125.90, 80.93, 76.52, 65.49, 54.29, 39.00, 35.42, 33.97, 27.36, 24.12, 24.09; HRMS calcd for $C_{20}H_{29}O_4$ [M + H]$^+$ 333.2066, found 333.2069.

((2*S*,3*S*,5*R*)-5-(4-Bromophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8e):

Pale yellow liquid; Yield = 154 mg, 92%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = -27.07° (*c* = 0.57, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2972, 2933, 1730, 1283, 1158; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.86 (dd, *J* = 9.2, 6.3 Hz, 1H), 4.57 (dd, *J* = 9.7, 4.6 Hz, 1H), 4.32–4.31 (m, 2H), 3.19–2.98 (m, 1H), 2.70–2.64 (m, 1H), 2.02 (dt, *J* = 12.9, 9.5 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.65, 178.34, 140.25, 131.73, 127.43, 121.75, 80.25, 76.74, 65.38, 54.06, 39.02, 35.49, 27.36; HRMS calcd for $C_{17}H_{21}BrNaO_4$ [M + Na]$^+$ 391.0521, found 391.0519.

((2*S*,3*S*,5*R*)-5-(4-Fluorophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8f):

Pale yellow liquid; Yield = 128 mg, 91%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +42.27° (*c* = 1.31, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2973, 1730, 1512, 1226, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.4 Hz, 1H), 7.34–7.26 (m, 2H), 7.06–7.00 (m, 2H), 4.88 (dd, *J* = 9.2, 6.2 Hz, 1H), 4.57 (dd, *J* = 9.9, 4.6 Hz, 1H), 4.33–4.31 (m, 2H), 3.14–3.11 (m, 1H), 2.66–2.63 (m, 1H), 2.04 (dt, *J* = 12.8, 9.5 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.77, 178.35, 136.83, 127.50, 127.42, 115.60, 115.39, 80.35, 76.65, 65.43, 54.15, 39.02, 35.60, 27.36; HRMS calcd for $C_{17}H_{21}FNaO_4$ [M + Na]$^+$ 331.1322, found 331.1319.

((2*S*,3*S*,5*R*)-3-Formyl-5-(4-nitrophenyl)tetrahydrofuran-2-yl)methyl pivalate (8g):

Pale yellow liquid; Yield = 112 mg, 73%; R_f = 0.5 (7/3 hexane/EtOAc); $[\alpha]_D^{28}$ = +38.18° (*c* = 0.72, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2973, 2872, 1727, 1522, 1347; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (d, *J* = 1.1 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 5.00 (dd, *J* = 9.2, 6.5 Hz, 1H), 4.65–4.62 (m, 1H), 4.35 (dd, *J* = 4.3, 2.4 Hz, 2H), 3.18–3.15 (m, 1H), 2.81–2.76 (m, 1H), 2.05–1.99 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.24, 178.30, 148.68, 147.65, 126.37, 123.92, 79.83, 77.08, 65.29, 53.87, 39.03, 35.38, 27.36; HRMS calcd for $C_{17}H_{22}NO_6$ [M + H]$^+$ 336.1447, found 336.1443.

((2*S*,3*S*,5*R*)-5-(4-Cyanophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8h):

Pale yellow liquid; Yield = 114 mg, 79%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = -21.42° (*c* = 0.32, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2964, 2874, 2229, 1730, 1282; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, *J* = 1.3 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 4.96 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.62 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.34–4.4.33 (m, 2H), 3.17–3.12 (m, 1H), 2.78–2.72 (m, 1H), 2.05–1.97 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.33, 176.39, 146.77, 132.51, 132.50, 126.32, 126.29, 80.10, 64.84, 53.88, 45.46, 39.04, 35.34, 27.35; HRMS calcd for $C_{18}H_{22}NO_4$ [M + H]$^+$ 316.1549, found 316.1543.

((2*S*,3*S*,5*R*)-3-Formyl-5-(4-formylphenyl)tetrahydrofuran-2-yl)methyl pivalate (8i):

Pale yellow liquid; Yield = 105 mg, 72%; R_f = 0.3 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +32.07° (*c* = 0.62, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2923, 2853, 1728, 1701, 1609; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.83 (d, *J* = 1.4 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 4.99 (dd, *J* = 9.1, 6.5 Hz, 1H), 4.62 (dd, *J* = 9.7, 4.5 Hz, 1H), 4.38–4.32 (m, 2H), 3.17–3.13 (m, 1H), 2.78–2.73 (m, 1H), 2.09–2.02 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.48, 191.97, 178.35, 148.19, 136.09, 130.15, 126.17, 80.31, 76.96, 65.35, 53.97, 39.03, 35.44, 27.37; HRMS calcd for $C_{18}H_{23}O_5$ [M + H]$^+$ 319.1545, found 319.1543.

((2*S*,3*S*,5*R*)-5-(3-Bromophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8j):

Pale yellow liquid; Yield = 152 mg, 90%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +17.27° (*c* = 1.75, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2972, 2873, 1729, 1480, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.4 Hz, 1H), 7.52 (s, 1H), 7.41 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.26–7.18 (m, 2H), 4.87 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.58 (dd, *J* = 9.7, 4.4 Hz, 1H), 4.36–4.29 (m, 2H), 3.15–3.10 (m, 1H), 2.71–2.26 (m, 1H), 2.04 (dt, *J* = 12.9, 9.5 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.58, 178.34, 143.61, 131.00, 130.17, 128.71, 124.38, 122.83, 80.07, 76.79, 65.35, 53.98, 39.01, 35.54, 27.37; HRMS calcd for $C_{17}H_{21}BrNaO_4$ [M + Na]$^+$ 391.0521, found 391.0519.

((2*S*,3*S*,5*R*)-5-(3-Fluorophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8k):

Pale yellow liquid; Yield = 127 mg, 90%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +7.23° (*c* = 0.47, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2960, 2926, 1731, 1283, 1158; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.3 Hz, 1H), 7.33–7.27 (m, 1H), 7.10–7.07 (m, 2H), 6.99–6.94 (m, 1H), 4.91 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.59 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.33–4.32 (m, 2H), 3.14–3.12 (m, 1H), 2.69–2.67 (m, 1H), 2.06 (dt, *J* = 12.9, 9.4 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.68, 178.40, 130.15, 121.30, 114.71, 112.73, 80.17, 76.91, 65.38, 53.98, 39.02, 35.51, 27.36; HRMS calcd for $C_{17}H_{21}FNaO_4$ [M + Na]$^+$ 331.1322, found 331.1319.

((2*S*,3*S*,5*R*)-5-(2,3-Dichlorophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8l):

Pale yellow liquid; Yield = 134 mg, 82%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +14.34° (*c* = 0.21, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2971, 1729, 1480, 1282, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, *J* = 1.6 Hz, 1H), 7.54–7.20 (m, 3H), 5.25–5.21 (m, 1H), 4.61 (dt, *J* = 6.2, 4.2 Hz, 1H), 4.42–4.32 (m, 2H), 3.12–3.07 (m, 1H), 2.98–2.92 (m, 1H), 1.99–1.91 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.49, 178.36, 141.88, 133.18, 129.54, 127.66, 124.50, 78.12, 65.08, 53.66, 39.04, 33.99, 27.37; HRMS calcd for $C_{17}H_{21}Cl_2O_4$ [M + H]$^+$ 359.0817, found 359.0810.

((2*S*,3*S*,5*R*)-5-(3,5-Dichlorophenyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8m):

Pale yellow liquid; Yield = 140 mg, 86%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +21.45° (*c* = 0.51, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2971, 2934, 1731, 1570, 1103; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.1 Hz, 1H), 7.30–7.22 (m, 3H), 4.85 (dd, *J* = 9.1, 6.4 Hz, 1H), 4.60 (dd, *J* = 9.3, 4.2 Hz, 1H), 4.37–4.28 (m, 2H), 3.17–3.12 (m, 1H), 2.73–2.68 (m, 1H), 2.02 (dt, *J* = 12.9, 9.4 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.34, 178.37, 144.87, 135.27, 128.00, 124.17, 79.52, 76.90, 65.28, 53.77, 39.02, 35.45, 27.37; HRMS calcd for $C_{17}H_{21}Cl_2O_4$ [M + H]$^+$ 359.0817, found 359.0813.

((2*S*,3*S*,5*R*)-3-Formyl-5-(naphthalen-2-yl)tetrahydrofuran-2-yl)methyl pivalate (8n):

Pale yellow liquid; Yield = 113 mg, 73%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +30.74° (*c* = 1.02, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2972, 2872, 1728,1480, 1282; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, *J* = 1.5 Hz, 1H), 7.85–7.79 (m, 4H), 7.50–7.43 (m, 3H), 5.09 (dd, *J* = 9.1, 6.3 Hz, 1H), 4.64 (dd, *J* = 10.0, 4.6 Hz, 1H), 4.39–4.37 (m, 2H), 3.18–3.15 (m, 1H), 2.74–2.73 (m, 1H), 2.17 (dt, *J* = 12.9, 9.5 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.90, 178.41, 138.52, 133.37, 133.22, 128.51, 128.07, 127.85, 126.41, 126.13, 124.57, 123.73, 81.09, 65.52, 54.29, 39.05, 35.61, 27.40; HRMS calcd for $C_{21}H_{24}O_4$ [M]$^+$ 340.1675, found 340.1670.

((2*S*,3*S*,5*S*)-3-Formyl-5-propyltetrahydrofuran-2-yl)methyl pivalate (8o):

Pale yellow liquid; Yield = 85 mg, 73%; R_f = 0.7 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +51.11° (*c* = 1.27, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2961, 2933, 1732, 1514, 1481; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.9 Hz, 1H), 4.35 (dd, *J* = 10.6, 5.0 Hz, 1H), 4.21–4.14 (m, 2H), 3.93–3.86 (m, 1H), 2.98–2.93 (m, 1H), 2.36–2.30 (m, 1H), 1.82–1.74 (m, 1H), 1.62–1.57 (m, 1H), 1.47–1.33 (m, 3H), 1.21 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.42, 178.33, 79.65, 76.14, 65.49, 54.21, 38.96, 37.74, 32.56, 27.32, 19.35, 14.21; HRMS calcd for $C_{14}H_{25}O_4$ [M + H]$^+$ 257.1753, found 257.1758.

((2*S*,3*S*,5*R*)-5-Cyclohexyl-3-formyltetrahydrofuran-2-yl)methyl pivalate (8p):

Colorless liquid; Yield = 99 mg, 73%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +4.91° (*c* = 0.23, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2926, 2853, 1730, 1283, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.8 Hz, 1H), 4.34 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.21–4.11 (m, 2H), 3.63–3.58 (m, 1H), 2.93–2.88 (m, 1H), 2.29–2.23 (m, 1H), 1.91–1.11 (m, 6H), 1.43–1.34 (m, 2H), 1.21 (s, 9H), 1.29–1.13 (m, 2H), 1.05–0.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.54, 178.34, 84.15, 75.96, 65.43, 54.15, 42.94, 38.97, 30.17, 29.72, 28.94, 27.34, 26.54, 26.07, 25.92; HRMS calcd for $C_{17}H_{29}O_4$ [M + H]$^+$ 297.2066, found 297.2064.

((2*S*,3*S*)-3-Formyl-1-oxaspiro[4.5]decan-2-yl)methyl pivalate (8q):

Pale yellow liquid; Yield = 130 mg, 73%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{28}$ = +28.11° (*c* = 0.31, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2933, 2859, 1732, 1712, 1285; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.3 Hz, 1H), 4.44–4.36 (m, 1H), 4.22–4.12 (m, 2H), 3.04–2.97 (m, 1H), 2.08–1.96 (m, 2H), 1.66–1.24 (m, 8H), 1.20 (s, 9H), 1.19–1.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.58, 178.31, 83.95, 75.46, 65.61, 54.74, 38.21, 37.87, 37.34, 27.33, 25.52, 23.74, 23.60; HRMS calcd for $C_{16}H_{26}O_4$ [M]$^+$ 282.1831, found 282.1829.

((2*S*,3*S*,5*R*)-3-Formyl-5-(((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-pyran-2-yl)methyl)tetrahydrofuran-2-yl)methyl pivalate (8r):

Pale yellow liquid; Yield = 152 mg, 74%; R_f = 0.5 (5/5 hexane/EtOAc); $[\alpha]_D^{28}$ = +27.01° (*c* = 0.47, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2935, 2829, 1730, 1283, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.8 Hz, 1H), 4.37 (dd, *J* = 10.6, 4.9 Hz, 1H), 4.18–4.13 (m, 3H), 4.08–4.01 (m, 1H), 3.60 (s, 3H), 3.55–3.53 (m, 1H), 3.52 (s, 3H), 3.49–3.44 (m, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 3.34–3.16 (m, 4H), 2.99–2.94 (m, 1H), 2.45–2.39 (m, 1H), 2.08–2.00 (m, 1H), 1.87 (dt, *J* = 12.7, 9.3 Hz, 1H), 1.76–1.70 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.11, 178.24, 83.86, 81.41, 79.70, 77.26, 76.27, 71.43, 71.40, 65.51, 60.67, 60.45, 59.28, 58.77, 54.05, 38.93, 32.26, 30.52, 27.31; HRMS calcd for $C_{22}H_{39}O_9$ [M + H]$^+$ 447.2594, found 447.2591.

((2*S*,3*S*,5*R*)-5-(((2*S*,3*R*,4*R*,5*R*)-3,4-Dimethoxy-5-(methoxymethyl)tetrahydrofuran-2-yl)methyl)-3-formyltetrahydrofuran-2-yl)methyl pivalate (8s):

Colorless liquid; Yield = 133 mg, 72%; R_f = 0.7 (5/5 hexane/EtOAc); $[\alpha]_D^{28}$ = +12.01° (*c* = 0.19, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2933, 2827, 1729, 1284, 1160; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.36 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.19–4.13 (m, 2H), 4.07–4.00 (m, 2H), 3.86 (td, *J* = 5.9, 3.7 Hz, 1H), 3.59–3.46 (m, 4H), 3.39 (s, 6H), 3.37 (s, 3H), 2.96–2.92 (m, 1H), 2.42–2.36 (m, 1H), 1.95–1.77 (m, 3H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.19, 178.22, 86.00, 85.34, 82.17, 78.78, 77.46, 76.24, 73.52, 65.49, 59.33, 57.38, 57.19, 54.18, 38.90, 34.73, 33.25, 27.29; HRMS calcd for $C_{20}H_{35}O_8$ [M + H]$^+$ 403.2332, found 403.2330.

(2*R*,3a*R*,4*R*,6a*S*)-2-Phenylhexahydrofuro[3,4-*b*]furan-4-ol (9):

Compound **8a** (300 mg, 1.45 mmol) was dissolved in dry MeOH (3 mL) and cooled to 0 °C. To this reaction mixture was added a catalytic amount of NaOMe (8 mg, 0.45 mmol) and then the mixture was stirred for 3 h at room temperature. After completion of reaction (TLC monitoring), MeOH was evaporated and the residue was diluted with water (5 mL). It was extracted with EtOAc (3 x 8 mL) and organic layer was washed with brine (1 x 5 mL). Evaporation of the organic solvent followed by purification using silica gel column chromatography gave compound **9** as a white solid; Yield = 116 mg, 77%; M.P. = 127–129 °C; R_f = 0.5 (7/3 hexane/EtOAc); $[\alpha]_D^{28}$ = +8.01° (*c* = 0.51, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3414, 2934, 1454, 1096, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 5.36 (s, 1H), 4.81–4.74 (m, 2H), 4.18–4.12 (m, 2H), 3.02–2.96 (m, 2H), 2.58–2.51 (m, 1H), 1.66–1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.50, 130.55, 128.52, 126.15, 103.66, 83.32, 82.99, 72.44, 52.20, 39.76; HRMS calcd for $C_{12}H_{14}NaO_3$ [M + Na]$^+$ 229.0841, found 229.0838.

(2*R*,3a*R*,4*S*,6a*S*)-2-Phenylhexahydrofuro[3,4-b]furan-4-yl acetate (10):

To a stirred solution of acetal **9** (100 mg, 0.47 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under nitrogen atmosphere was added Et_3N (81 μL, 0.57 mmol), followed by addition of acetic anhydride (58 μL, 0.57 mmol) and a catalytic amount of DMAP (6 mg, 0.04 mmol) at same temperature for 15 mim. On completion of the reaction (TLC monitoring), saturated $NaHCO_3$ solution (3 mL) was added and reaction mixture was stirred for 10 min.

Extraction was done with CH_2Cl_2 (3 x 8 mL), and combined organic extracts were washed with water (1 x 10 mL) and brine solution (1 x 10 mL) and then dried over Na_2SO_4. Concentration in vacuo gave crude residue which was purified by column chromatography to obtain **10** as a pale yellow liquid; Yield = 109 mg, 90%; R_f = 0.5 (5/5 hexane/EtOAc); $[\alpha]_D^{25}$ = +27.01° (*c* = 0.47, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2935, 2829, 1730, 1283, 1101; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H, Ar*H*), 6.14 (s, 1H, *H*-6), 4.81–4.76 (m, 2H, *H*-1,4), 4.26 (d, *J*= 10.3 Hz, 1H, *H*-5), 4.09–4.06 (m, 1H, H-5'), 3.10–3.05 (m, 1H, *H*-3), 2.65–2.60 (m, 1H, *H*-2), 2.06 (s, 3H, –COC*H*$_3$), 1.74–1.68 (m, 1H, H-2'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.28, 140.15, 128.59, 128.58, 128.08, 126.16, 103.48, 83.06, 82.58, 74.22, 51.51, 39.84, 21.35; HRMS calcd for $C_{14}H_{16}NaO_4$ [M + Na]$^+$ 271.0946, found 271.0941.

((2*S*,3*R*,5*R*)-3-(Hydroxymethyl)-5-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methyl pivalate (11):

The aldehyde **8c** (500 mg, 1.72 mmol) was dissolved in dry MeOH (5 mL) and cooled to 0 °C. Then, $NaBH_4$ (137 mg, 3.44 mmol) was added to the stirred reaction mixture in portions over 10 min, and stirring continued for 1 h. Subsequently, aqueous NH_4Cl (10 mL) was added dropwise to the reaction mixture until the effervescence ceased. Extraction was done using CH_2Cl_2 (3 × 10 mL), and the extracts were washed with brine (1 × 15 mL) and dried over Na_2SO_4. Removal of solvent under vacuum furnished a crude residue which was subjected to column chromatography to give **11** as a colorless liquid; Yield = 307 mg, 61%; R_f = 0.3 (8/2 hexane/EtOAc); $[\alpha]_D^{25}$ = –29.88° (*c* = 0.20, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3441, 2970, 2873, 1728, 1480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 4.98 (dd, *J* = 7.9, 7.3 Hz, 1H), 4.37–4.27 (m, 2H), 4.11–4.07 (m, 1H), 3.80–3.70 (m, 2H), 2.43–2.34 (m, 1H), 2.22–2.16 (m, 1H), 2.04–1.96 (m, 1H), 1.87 (br s, 1H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.93, 142.58, 128.48, 127.55, 125.78, 80.65, 80.44, 66.26, 64.37, 43.60, 39.03, 37.93, 27.39; HRMS calcd for $C_{18}H_{23}F_3NaO_4$ [M + Na]$^+$ 383.1446, found 383.1443.

((2*S*,3*S*,5*R*)-3-(Iodomethyl)-5-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methyl pivalate (12):

To a solution of compound **11** (300 mg, 0.83 mmol) in toluene (10 mL) were added PPh_3 (656 mg, 2.5 mmol), imidazole (170 mg, 2.5 mmol) and iodine (632 mg, 2.5 mmol). The reaction mixture was stirred at 90 °C for 2 h. After completion of the reaction (confirmed by TLC) toluene was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (8 mL), washed with saturated $Na_2S_2O_3$ (2 x 5 mL) (to quench the unreacted iodine), brine (1 x 5 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo and the residue purified by flash column chromatography to afford the compound **12** as a colorless liquid. Yield = 373 mg, 91%; R_f = 0.9 (9/1 hexane/EtOAc); $[\alpha]_D^{25}$ = –9.71° (*c* = 0.46, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2970, 2871, 1729, 1282, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 4H), 5.03 (dd, *J* = 8.3, 6.9 Hz, 1H), 4.29–4.28 (m, 2H), 4.02 (dt, *J* = 5.7, 4.4 Hz, 1H), 3.3–3.26 (m, 2H), 2.54–2.46 (m, 1H), 2.26–2.19 (m, 1H), 2.13–2.05 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.45, 142.07, 128.51, 127.67, 125.69, 82.59, 79.67, 65.25, 43.65, 42.48, 38.99, 27.40, 8.47; HRMS calcd for $C_{18}H_{22}F_3INaO_3$ [M + Na]$^+$ 493.0463, found 493.0463.

((2*S*,3*S*,5*R*)-3-Methyl-5-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methanol (13):

To a stirred suspension of $LiAlH_4$ (48 mg, 1.49 mmol) in THF (2 mL) was added compound **12** (200 mg, 0.42 mmol) in THF (1 mL) at 0 °C. After completion of addition, the reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C and quenched with ethyl acetate followed by aqueous NH_4Cl solution. After 15 min of stirring at room temperature, the reaction mixture was filtered through a celite® pad, washed with ethyl acetate (3 x 5 mL) and the filtrate evaporated under vacuum. The residue was purified through silica gel column chromatography to afford compound **13** as a colorless liquid: Yield = 85 mg, 76%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{25}$ = +6.18° (*c* = 1.03, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3416, 2958, 2930, 1452, 1109; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 4H), 5.01 (t, *J* = 7.1 Hz, 1H), 3.81–3.78 (m, 1H), 3.69–3.63 (m, 2H), 2.42 (br s, 1H), 2.23–1.95 (m, 3H), 1.09 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.13, 128.46, 127.46, 125.96, 87.25, 79.85, 64.08, 42.75, 34.37, 17.71; HRMS calcd for $C_{13}H_{15}F_3O_2$ [M + Na]$^+$ 260.1024, found 260.1021.

(2*R*,3*S*,*E*)-3-(Benzyloxy)-2-hydroxy-6-(trimethylsilyl)hex-4-en-1-yl pivalate (15):

The alcohol **14** (300 mg, 1.02 mmol) was dissolved in dry dichloromethane (5 mL), and Grubbs' second generation catalyst (43 mg, 0.05 mmol) was added. The solution was refluxed for 5 h, and the solvent removed under a vacuum. The crude residue was purified by column chromatography gave **15** as a dark black thick liquid; Yield = 335 mg, 86%; R_f = 0.4 (9/1 hexane/EtOAc); $[\alpha]_D^{25}$ = +13.02° (*c* = 0.23, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3477, 2957, 2904, 1731, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 5.79–5.71 (m, 1H), 5.34–5.28 (m, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.34 (d, *J* = 11.8 Hz, 1H), 4.20–4.11 (m, 2H), 3.91–3.86 (m, 1H), 3.76 (dd, *J* = 8.7, 5.1 Hz, 1H), 2.36 (d, *J* = 4.2 Hz, 1H), 1.63–1.54 (m, 2H), 1.18 (s, 9H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.66, 138.28, 135.04, 128.50, 127.91, 127.73, 124.08, 80.96, 72.09, 69.84, 65.27, 38.88, 27.27, 23.44, -1.76; HRMS calcd for $C_{21}H_{34}NaO_4Si$ [M + Na]$^+$ 401.2124, found 401.2122.

((2*R*,3*S*,5*R*)-3-(Benzyloxy)-5-(*p*-tolyl)-4-vinyltetrahydrofuran-2-yl)methyl pivalate (16):

Pale yellow liquid; Yield = 182 mg, 84%; R_f = 0.4 (9/1 hexane/EtOAc); IR ($\tilde{\nu}_{max}$/cm^{-1}) 2925, 2855, 1730, 1284, 1160; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers (α/β = 0.8:1) δ 7.37–7.09 (m, 18H, both isomers), 6.09–6.00 (m, 1H, minor isomer), 5.46–5.37 (m, 1H, major isomer), 5.24–5.23 (m, 1H, major isomer), 5.14–5.11 (m, 1H, minor isomer), 5.05– 4.87 (m, 5H, both isomers), 4.67–4.52 (m, 4H, both isomers), 4.38–4.35 (m, 1H, major isomer), 4.31–4.30 (m, 2H, both isomers), 4.24–4.16 (m, 2H, both isomers), 4.02 (dd, *J* = 5.8, 2.1 Hz, 1H, minor isomer), 3.91–3.89 (m, 1H, major isomer), 3.17–3.13 (m, 1H, major isomer), 2.68 (td, *J* = 9.5, 5.8 Hz, 1H, major isomer), 2.32 (s, 3H, minor isomer), 2.31 (s, 3H, major isomer), 1.22 (s, 18H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.48, 178.37, 138.01, 137.82, 137.50, 136.95, 136.73, 136.21, 135.59, 132.64, 128.98, 128.79, 128.63, 128.57, 128.02, 127.89, 127.64, 126.43, 126.29, 119.26, 117.04, 85.80, 84.22, 83.66, 82.20, 81.85, 81.74, 72.07, 64.80, 64.12, 56.95, 55.03, 38.94, 27.38, 27.35, 21.28; HRMS calcd for $C_{26}H_{36}NO_4$ [M + NH_4]$^+$ 426.2644, found 426.2643.

((2*R*,3*S*,4*R*,5*R*)-3-(Benzyloxy)-5-(*p*-tolyl)-4-vinyltetrahydrofuran-2-yl)methanol (17a):

Compound **17a** was prepared from **16** (200 mg, 0.48 mmol) following the same procedure as was used for the preparation of compound **9**. Colorless liquid; Yield = 68 mg, 43%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{25}$ = +16.28° (*c* = 0.47, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3433, 2922, 2868, 1454, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.08 (m, 9H, Ar*H*), 5.45–5.34 (m, 1H, *H*-6), 5.24 (d, *J* = 6.4 Hz, 1H, *H*-1), 4.97–4.86 (m, 2H, *H*-7,7'), 4.66 (d, *J* = 11.7 Hz, 1H, –C*H*$_2$Ph), 4.54 (d, *J* = 11.7 Hz, 1H, –C*H*$_2$Ph), 4.08–4.03 (m, 1H, *H*-4), 3.94–3.88 (m, 2H, *H*-3&5), 3.75 (dd, *J* = 11.9, 5.2 Hz, 1H, *H*-5), 3.17–3.12 (m, 1H, *H*-2), 2.31 (s, 3H), 2.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.99, 136.81, 136.08, 135.56, 128.82, 128.58, 127.95, 127.84, 126.39, 116.98, 85.51, 84.37, 82.44, 72.09, 63.08, 55.05, 21.25; HRMS calcd for $C_{21}H_{24}NaO_3$ [M + Na]$^+$ 347.1623, found 347.1620.

((2*R*,3*S*,4*S*,5*R*)-3-(Benzyloxy)-5-(*p*-tolyl)-4-vinyltetrahydrofuran-2-yl)methanol (17b):

Colorless liquid; Yield = 55 mg, 35%; R_f = 0.5 (8/2 hexane/EtOAc); $[\alpha]_D^{25}$ = +52.17° (*c* = 1.51, CH_2Cl_2); IR ($\tilde{\nu}_{max}$/cm^{-1}) 3534, 2976, 2863, 1470, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.12 (m, 9H, Ar*H*), 6.08–5.98 (m, 1H, *H*-6), 5.13–5.10 (m, 1H, *H*-7), 4.96–4.92 (m, 1H, *H*-7'), 4.86 (d, *J* = 9.9 Hz, 1H, *H*-1), 4.61–4.53 (m, 2H, –CH_2Ph), 4.20– 4.17 (m, 1H, *H*-4), 4.04 (dd, *J* = 6.3, 2.8 Hz, 1H, *H*-3), 3.78–3.75 (m, 1H, *H*-5), 3.68–3.64 (m, 1H, H-5'), 2.70 (td, *J* = 9.4, 6.5 Hz, 1H, *H*-2), 2.32 (s, 3H, –CH_3), 2.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.15, 137.75, 136.64, 132.85, 129.11, 128.54, 127.85, 127.74, 126.68, 119.08, 84.64, 84.39, 82.93, 72.08, 63.69, 56.68, 21.29; HRMS calcd for $C_{21}H_{24}NaO_3$ [M + Na]$^+$ 347.1623, found 347.1620.

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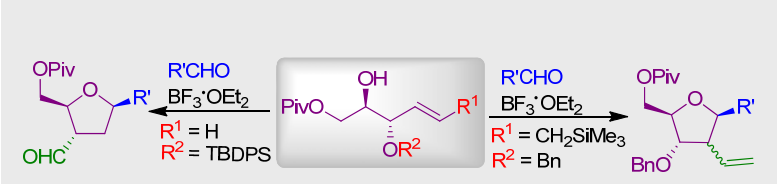

Studies toward synthesis of the 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides and 2-deoxy-2C-branched β-*C*-aryl furanoside were described using D-mannitol derived homoallylic alcohols with carbonyl compounds in the presence of $BF_3{\cdot}OEt_2$ as a catalyst.

C*-Furanosides

*Sateesh Dubbu, Anirban Bardhan, Ande Chennaiah and Yashwant D. Vankar**

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A Cascade of Prins Reaction and Pinacol-Type Rearangement: Access to 2,3-Dideoxy-3C-Formyl β-*C*-Aryl/Alkyl Furanosides and 2-Deoxy-2C-Branched β-*C*-Aryl Furanoside