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ARTICLE TYPE

Linearization of carbohydrate derived polycyclic frameworks

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We report an easy access to carbohydrate derived diverse tricyclic skeletons which could be beneficial for exploring polyfunctionalized chiral alicycles. The key reaction to assemble sugar fused tricyclic core is intermolecular tandem esterification and 1,3-dipolar cycloaddition. The framework was elaborated using amide forming reactions, opening of isoxazolidine rings followed by N and O-acylations. The sequences provide distinct, spatially separated and encoded chemical entities that may pave the way to investigate cell functions.

Introduction:

The powerful effects of structurally complex small molecules having stereochemical and skeletal diversity and functionalities have been manifested to exhibit highly specific biological responses. In this area, complexity of small molecules is essential since many biological processes are significantly dependent upon protein-protein interactions, and most of the small molecules known to interrupt these interactions are structurally complex natural products and natural product like molecules (Figure 1). The natural products; Taxol and Discodermolide bind and activate, the protein tubulin,[1] which itself was discovered as the protein target of colchicines.[2,3,4]

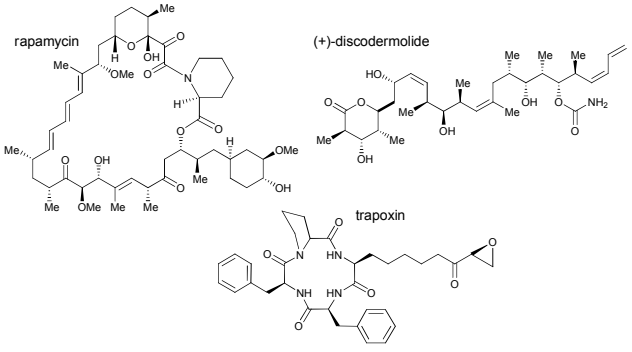


Figure 1

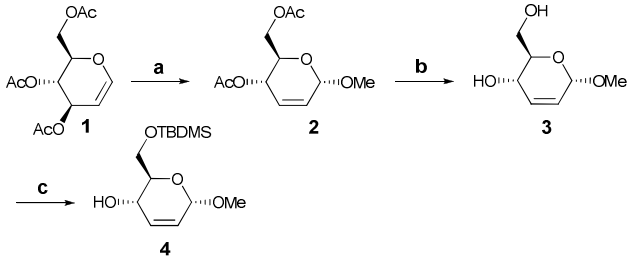
Diversity is also important since in these screens, there is no particular target and whereas an eventual target could be any one of the cells or organisms entire collection of macromolecules in phenotypic screening of small molecules. In this context, new methodologies have to be designed for stereoselective synthesis of small molecule with distinct skeletal frameworks having structural features reminiscent of natural products.

Following our interest in the field of synthesis of structurally complex small molecules, we employed carbohydrates as chiral pool that would provide an access to a large array of molecules since it display a high density of functional groups, are available as single enantiomers and contain multiple sites for attachment of recognition groups.

Decrease in the conformational freedom of small molecules can facilitate protein binding and specificity by dropping the entropic cost of binding. In natural products, macrocyclic, polycyclic, or highly substituted linear structures result restriction in conformational freedom (Figure 1). Proper combination of hydrogen bonding and hydrophobic functional groups offer the enthalpic driving force for protein binding. Herein, we report a strategy for highly efficient access to similarly constructed molecules from carbohydrate derived tricyclic rigid framework. We have also described our efforts towards generation of an acyclic series of highly functionalized compounds with defined chirality after disintegrating sugar based skeleton.

Result and discussion:

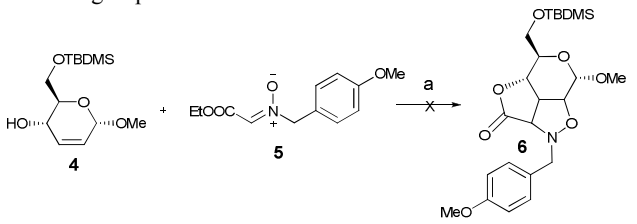
Initially, we focused our attention to synthesize tricyclic compounds by coupling of glucal derived allylic alcohol **4**[6] with nitrone ester **5** by using a reaction catalyzed by lewis acid followed by intramolecular 1,3-dipolar cycloaddition.[5] Synthesis of **4** was commenced from commercially available tri-*O*-acetylglucal **1**. Treatment of **1** with dry methanol in presence of catalytic amount of iodine furnished **2**[6] *via* ferrier rearrangement.[7] Deacetylation of **2** using K_2CO_3 in methanol furnished diol **3**[8] which on selective protection of primary alcohol as TBDMS ether yielded allylic alcohol **4** (scheme 1).



Reagents and condition: (a) Methanol, I_2, THF, 1.5h, 85% (b) K_2CO_3, MeOH, 30 min; 90% (c) TBDMS-Cl, imidazole, dry DCM, 30 min, 95%.

Scheme 1

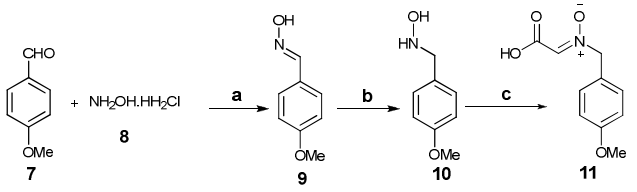
1,3-dipolar cycloaddition[9,10] was attempted between nitrone ester **5** and allyl alcohol **4**. Unfortunately, instead of tricyclic product **6**, complex mixture of products was observed (Scheme 2). This might be due to the presence of acid labile TBDMS group.



Reagents and conditions: (a) $TiCl_4$, 4A^{o}MS, DCE, rt, overnight.

Scheme 2

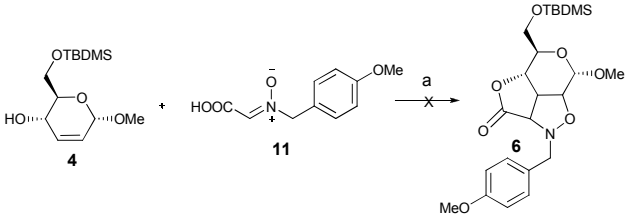
However, it has been reported that reaction of lewis acid on a molecule having template similar to **4** gave rearranged product 2-substituted furan.[11] Since Lewis acid catalyzed reaction was not successful with our substrates, we decided to follow Schreiber's methodology[12] in order to get tricyclic framework. Towards this goal, nitrone carboxylic acid **11** was synthesized.[13] Synthesis of **11** was started with oxime **9** which was synthesized through condensation of 4-methoxy benzaldehyde **7** with hydroxylamine hydrochloride **8**. Reduction of **9** using $NaBH_3CN$ under acidic condition gave *N*-alkyl hydroxyl amine **10.**[14] Condensation of *N*-alkyl hydroxyl amine **10** with glyoxylic acid mono hydrate furnished **11** (scheme 3).



Reagent and conditions: (a) 10% KOH:H_2O, 0^{0}C, 2h, 74% (b) $NaBH_3CN$, MeOH, 2N HCl, 3h, 72% (c) CHO-COOH, DCM, overnight, 75%.

Scheme 3

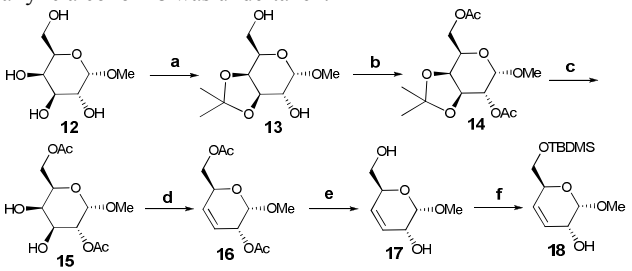
Unfortunately 1,3 dipolar cycloaddition of **4** with nitrone corboxylic acid **11** did not yield any tricyclic product (scheme 4).



Reagents and conditions: (a) PyBroP, DIPEA, DMAP, DCM, 0^{o}C-rt, overnight.

Scheme 4

Disappointing with these results, we decided to design some new sugar derived allylic alcohol. In this context, galactose derived allylic alcohol **18** was undertaken.

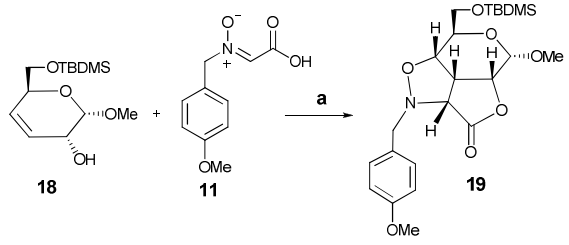


Reagents and conditions: (a) DMP, CSA, acetone, 12h, 60% (b) Ac_2O, pyridine, 12h, 91% (c) 80% AcOH:H_2O, 80 ^{o}C, 2 h, 94% (d) PPh_3, CHI_3, imidazole, toluene, reflux, 2.5 h, 94% (e) NaOMe, MeOH, 30min, 95% (f) TBDMSCl, imidazole, DCM, 30 min, 95%.

Scheme 5

Synthesis of **18** was started with commercially available methyl α-methyl-D-galactopyranoside **12** as shown in scheme **4**. Compound **13** was obtained by acetonation of **12** with 2,2-dimethoxypropane (DMP) and catalytic amount of camphor sulfonic acid (CSA) in acetone. Acetylation of diol **13**[15] provided protected **14**[16] which on acidic hydrolysis with 80% AcOH furnished diol **15**.[17] Removal of vicinal diol by treatment with PPh_3, CHI_3, imidazole in toluene under refluxing condition provided olefin **16**[18], which on subsequent deacetylation and TBDMS protection of primary alcohol **17**[19] furnished allylic alcohol **18**[20] (scheme 5).

Treatment of the allylic alcohol **18**, with **11**, under esterification conditions yielded tricyclic compound **19** with complete regio- and stereoselectivity, presumably *via* tandem acylation and 1,3-dipolar cycloaddition.[9] No intermediate nitrone ester or carboxy isoxazolidine structures was observed (Scheme 6).



Reagents and conditions: (a) PyBroP, DIPEA, DMAP, DCM, 0^{o}C-rt, overnight, 95%.

Scheme 6

The stereochemistry of **19** was confirmed on the basis of 1H and 2D NMR spectrum. The appearance of two doublet of doublet at 4.62 δ (J = 4.4, 3.2) and 4.17, and two doublet at 5.03 δ (J = 2.9) and 4.36 δ (J = 5.8) in 1H NMR data of **19** clearly indicated the cis relationship between H1, H2, H3, H3' and H4**.** The small coupling constant confirmed the stereochemistry of **19**. In addition to this, significant NOESY correlations are shown in Figure 2 whereas H-3' showed the NOESY correlation to H-3 and H-2. H-3 showed NOESY correalation to H3', H-4 and H-2. All these correlations confirmed the stereochemistry of tricyclic **19**.

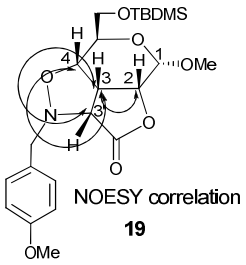
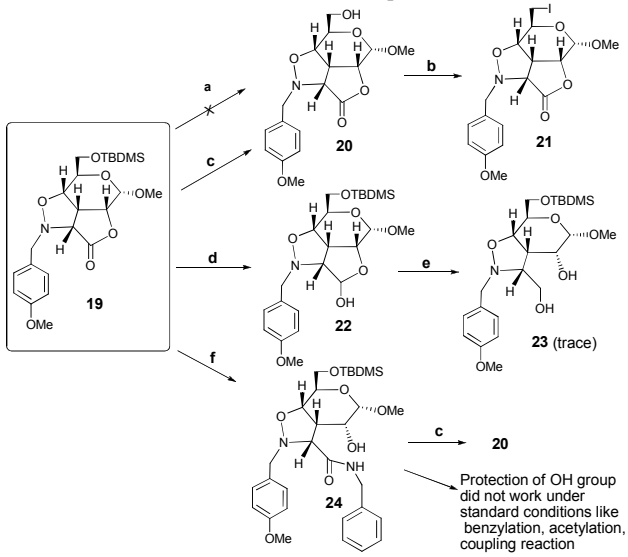


Figure 2

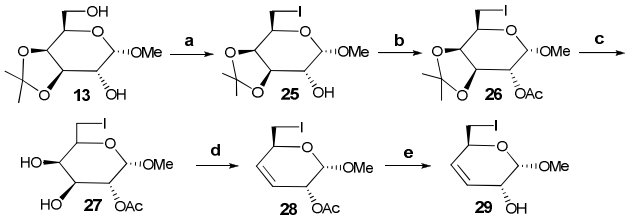
With tricyclic framework in hand, we tried to access a series of linear molecule having structural features reminiscent of natural products from tandem ring opening on carbohydrate derived rigid tricyclic skeleton **19**. The nucleophile can react with electrophilic lactone of **19** while simultaneously unmasking alcohols for successive reactions. Furthermore, reductive N-O bond cleavage would offer two additional appendages for functionalization. In this endeavor, we first selected to open the sugar ring. The reaction sequence involved was opening of silyl group by tetrabutyl ammonium fluoride (TBAF) in dry THF. Unfortunately, we did not get any deprotected product but complex mixture of products was observed. However, treatment of **19** by 1(N) aq. HCl in THF furnished alcohol **20**. Next plan was to convert alcohol **20** into iodo compound **21**.



Reagents and conditions: (a) TBAF, dry THF, 30 min.; (b) PPh_3, I_2, imidazole, dry toluene, reflux, 3h; (c) 1N aq. HCl, THF, 30 min, 95% (d) LAH, dry THF, 0^{o}C, 1h, 95% (e) LAH, dry THF, reflux, 3 days; (f) DIBAL-H, amine, dry THF, 0 ^{o}C to rt, 2.5h, 85%.

Scheme 7

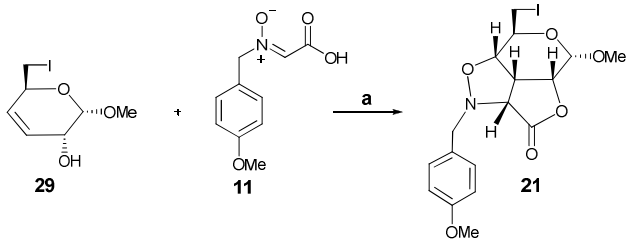
Treatment of **20** with PPh_3, I_2 and imidazole in dry toluene under refluxing condition provided iodo compound **21** (Scheme 7).[21] Purification of **21** was problematic due to the much similar R_f value of side product triphenyl phosphine oxide and **21**. So we decided first to open the lactone ring of **19** before opening of sugar ring, thinking that it may change the polarity of products making purification of iodo compound easier. Reduction of lactone of **19** with reducing agents like $NaBH_4$ and LAH gave hemiacetal **22**. However, reaction of **19** with LAH under refluxing condition for 3 days gave diol **23** in trace amount leaving the unreacted hemiacetal **22**. The reason for the inertia to reduction may presumably be due to an initial formation of a highly stable complex.[22] Failure of reduction of lactone of **19** prompted us to investigate other reactions on it. Gratifyingly, aminolysis of **19** with DIBALH-NH_2R complex in dry THF furnished amide **24**.[23] Protection of secondary alcohol did not work under standard condition like benzylation, acetylation and coupling reactions. So we thought to proceed further with **24**. Towards our aim of opening the sugar ring, treatment of **24** with 1(N) aq. HCl for deprotection of silyl ether unfortunately furnished the recovery of compound **20** (Scheme 7). Above mentioned unsuccessful attempts to get diverse acyclic molecules from tricyclic **19** prompted us to synthesize a new tricyclic compound containing iodo functionality. Thus, we synthesized an allylic alcohol **29**.



Scheme 8

Reagent and conditions: (a) I_2, PPh_3, Imidazole, toluene, 60^{o}C, 2.5 h, 75% (b) Ac_2O, pyridine, 12h, 95% (c) 80%AcOH:H_2O, 80^{0}C, 1.5h, 85% (d) PPh_3, CHI_3, imidazole, toluene, reflux, 2.5h, 68% (e) K_2CO_3, MeOH, 30min, 78%.

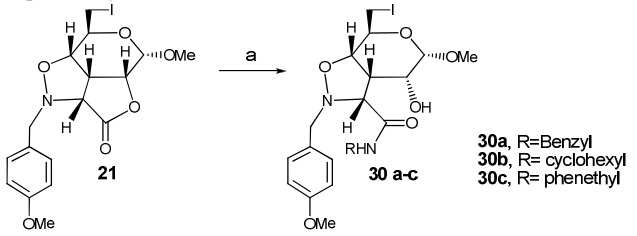
Synthesis of **29** was commenced with **13** as shown in scheme **8**. Selective replacement of primary alcohol by iodo group using I_2, triphenylphosphine, imidazole in toluene at 60 ^{o}C furnished alcohol **25**.[24] Acetylation of **25** provided protected compound **26**[25] which on acidic hydrolysis with 80% AcOH furnished diol **27**. Removal of vicinal diol by treatment with PPh_3, CHI_3, imidazole in toluene under refluxing condition provided olefin **28**, which on subsequent deacetylation furnished allylic alcohol **29** (scheme 8). Treatment of **29** with nitrone carboxylic acid **18** under above mentioned esterification condition yielded tricyclic compound **21** (scheme 9). In this case also, intermediate nitrone ester or carboxy isoxazolidine structures were not observed.



Scheme 9

Reagent and conditions: (a) PyBroP, DIPEA, DMAP, DCM, 0^0C-rt, overnight, 72%.

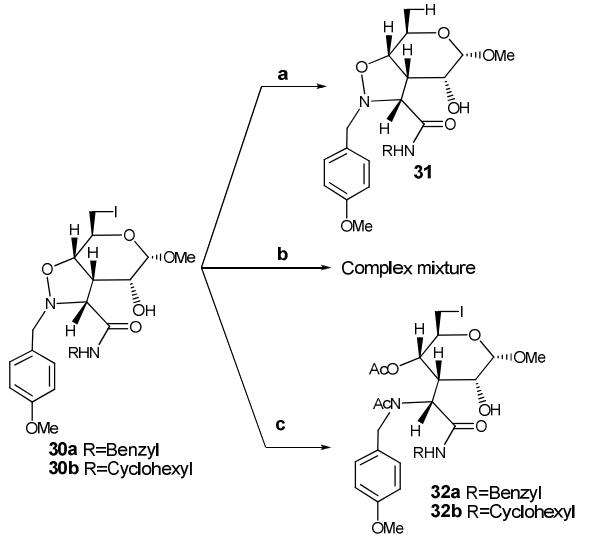
To synthesize highly functionalized diverse acyclic compounds, we initiated reactions to functionalize tricyclic **21**. In this endeavour, lactone ring was first undertaken. Aminolysis of lactone of **21** under above mentioned condition furnished amides **30a-c**. This reaction proceeded very well with number of aliphatic, cyclic and aromatic amines as shown in scheme **10**.



Reagents and conditions: (a) DIBAL-H, Amine, Dry THF, 4h.

Scheme 10

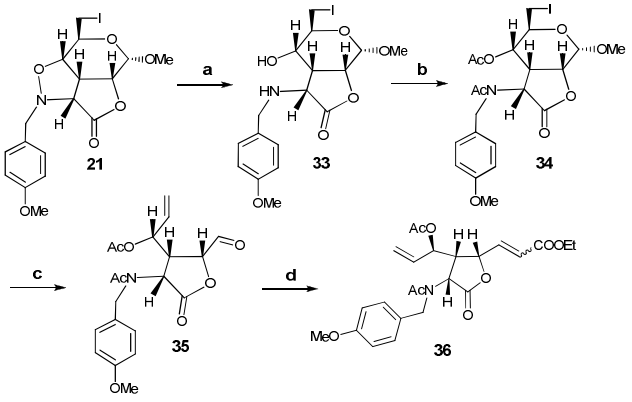
With compounds **30a-c** in hand, we aimed to open isoxazolidine ring. Treatment of **30** with Zn dust, NH_4Cl and THF at 65 ^{o}C furnished complex mixture of products. However, hydrogenolysis with $Pd(OH)_2$ under H_2 atmosphere gave hydrogenated product **31**. Gratifyingly, treatment with $Mo(CO)_6$ in acetonitrile and water mixture (15:1) under refluxing condition provided amino alcohol which was further protected by acetyl group to give **32**. (Scheme 11)



Reagents and condition:(a) $Pd(OH)_2$, H_2, overnight;(b) Zn, NH_4Cl, THF, 65 ^{o}C, 1.5h; (c) (i) $Mo(CO)_6$, ACN:H_2O, reflux, 5h; (ii) Ac_2O, pyridine, overnight.

Scheme 11

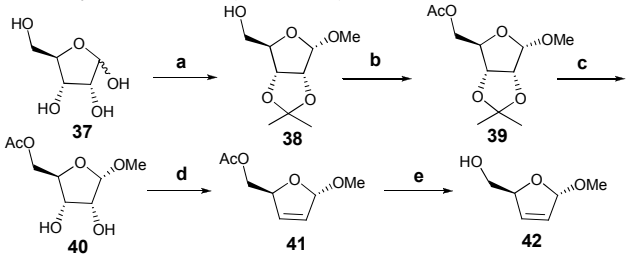
The successful functionalization of lactone and isoxazolidine ring encouraged us to further derivatize the sugar ring. Treatment of tricyclic compound **21** with $Mo(CO)_6$ in acetonitrile and water mixture under refluxing condition gave amino alcohol **33**. On purification, amino alcohol **33** was not stable on column forcing us to proceed without purification. Treatment of **33** with acetic anhydride in pyridine yielded **34** which on treatment with zinc, ammonium chloride in THF and water mixture provided aldehyde **35**. Wittig olefination of crude aldehyde **35** with (carbethoxymethylene)triphenylphosphorane in dry CH_2Cl_2 at room temperature furnished α,β-unsaturated ester **36** (Scheme 12).



Reagents and condition:(a) $Mo(CO)_6$, ACN:H_2O, reflux (b) Ac_2O, pyridine, overnight, 72% over 2 steps (c) Zn, THF:H_2O, 65^oC (d) Ph_3PCH_2COOEt, DCM, rt , overnight, 65%.

Scheme 12

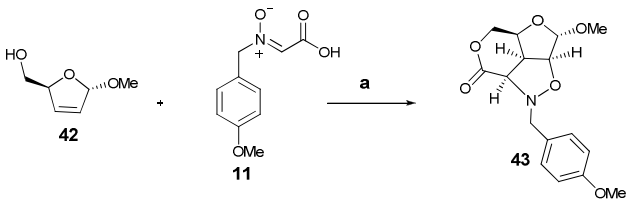
The successful synthesis and functionalization of tricyclic compound **21** derived from α-D-galactopyranoside inspired us to initiate further application of this strategy for the synthesis of another structurally related tricyclic derivatives using D-ribose derived homoallylic alcohol **42** and α-D-glucopyranoside derived allylic alcohol **52**. The synthesis of **42** was achieved from D-ribose. Methylation of anomeric hydroxyl group of **37** using acetyl chloride in methanol followed by acetonation with 2,2-dimethoxypropane (DMP) and catalytic amount of camphor sulfonic acid (CSA) in acetone gave major isomer **38**[26] with trace amount of other isomer. Acetylation of **38** provided protected compound **39**[27] which on acidic hydrolysis with 80% AcOH furnished diol **40**.[28] Removal of vicinal diol by treatment with PPh_3, CHI_3, imidazole in toluene under refluxing condition provided olefin **41**, which on subsequent deacetylation furnished homoallylic alcohol **42** (scheme 13).



Reagent and conditions: (a) (i) CH_3COCl, methanol, reflux, 12h, (ii) DMP, CSA, acetone, 12h, 78% (b) Ac_2O, pyridine, 12h, 95% (c) 80%AcOH:H_2O, 80^0C, 1.5h, 81% (d) PPh_3, CHI_3, imidazole, toluene, reflux, 4h, 62% (e) NaOMe, MeOH, 30min, 78%.

Scheme 13

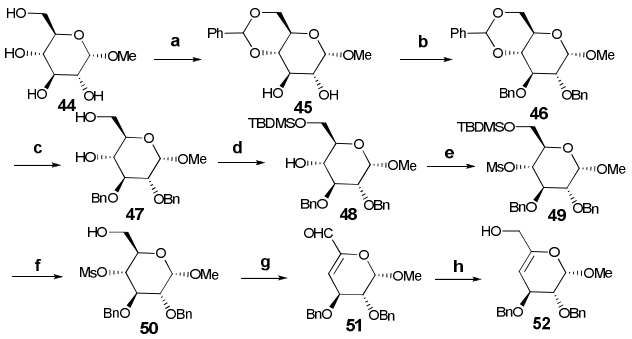
Synthesis of tricyclic compound **43** was achieved from coupling of homoallylic alcohol **42** with nitrone **12** by following the same reaction sequence as that described for **21** (scheme 14). Stereochemistry of tricyclic **43** was confirmed by 2-D NMR spectrum.



Reagent and conditions: (a) PyBroP, DIPEA, DMAP, DCM, 0^0C-rt, 62%.

Scheme 14

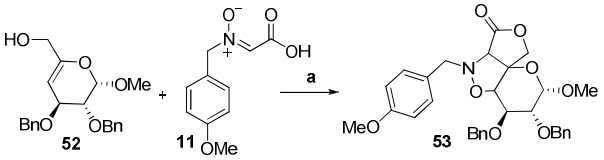
Next, we turned our attention to synthesize α,D-glucopyranoside derived alcohol **52.** Benzylidine protection of **44** using benzylidine dimethyl acetal and catalytic amount of camphor sulphonic acid (CSA) in acetone furnished diol **45**.[29] Protection of diol **45** as benzyl ether using BnBr, NaH in DMF yielded **46**.[30] Benzylidine deprotection of **46** using I_2 in methanol under refluxing condition for followed by TBDMS protection of primary alcohol **47**[31] and mesyl protection of secondary alcohol **48**[32] gave **49**.[33] Deprotection of TBDMS group of **49** using TBAF followed by swern oxidation of primary alcohol **50**[34] and subsequent reduction of aldehyde **51**[35] by sodium borohydride in methanol produced allylic alcohol **52**[36] in good yield (scheme 15).



Reagent and conditions: (a) Benzylidine dimethyl acetal, CSA, acetone, overnight; (b) BnBr, NaH, DMF; (c) I_2, methanol ,reflux; (d) TBDMSCl, imidazole, DMF, 97% (e) MsCl, Et_3N, DCM, 0^oC to rt, 80% (f) TBAF, THF, 30min, 95% (g) $(COCl)_2$, DMSO, DCM, DMAP, -78^oC; (h) $NaBH_4$, methanol, 94%.

Scheme 15

Tricyclic compound **53** by using α-D-glucopyranoside derived allylic alcohol **52** was also easily synthesized following the same procedure as described for **21** but **53** was not diastereomericaly pure but it was racemic (scheme 16).



Reagent and conditions: (a) PyBroP, DIPEA, DMAP, DCM, 0^0C-rt, 62%.

Scheme 16

Conclusion:

In summary, we have synthesized four carbohydrate derived tricyclic skeletons which could be useful for accessing polyfunctionalized chiral alicycles having structural features reminiscent of natural products. These tricyclic compounds were synthesized by using intermolecular coupling reaction followed by 1,3-dipolar cycloaddition among nitrone carboxylic acid and galactose, glucose derived allylic and ribose derived homoallylic alcohol. Among them, galactose derived tricyclic framework furnished densely functionalized molecules. These four step reaction sequences resulted in a collection of compounds containing number of distinct, spatially separated, and encoded chemical entities that may pave the way for exploring chemical genetic approach. Efforts in this direction are currently underway.

EXPERIMENTAL SECTION

General

Organic solvents were dried by standard methods. All the products were characterized by ^{1}H, ^{13}C, two-dimensional homonuclear COSY (correlation spectroscopy), heteronuclear single quantum coherence (HSQC), Nuclear Overhauser effect spectroscopy (NOESY), IR, ESI-MS. Analytical TLC was performed using 2.5 x 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254) using UV light as visualizing agent and an acidic solution of ninhydrin, and heat as developing agents. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on 300 MHz (^{1}H) and 50, 75 MHz (^{13}C). Experiments were recorded in $CDCl_3$, $(CD_3)_2CO$ and CD_3OD at 25 ^{o}C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR reference $CDCl_3$ appeared at 77.00 ppm. IR spectra were recorded on FT-IR spectrophotometers. Optical rotations were determined by using a 1 dm cell at 28 ^{o}C in chloroform and methanol as the solvents; concentrations mentioned are in g/100 mL.

Experimental Procedures and Characterization Data

((2*R*,3*S*,6*S*)-3-acetoxy-6-methoxy-3,6-dihydro-2H-pyran-2-yl)methyl acetate 2:

To a solution of **1** (5 g, 0.18 mol), methanol (1.5 mL) in THF (75 mL) was added iodine (0.90 g, 3.00 mmol). After being stirred on room temperature for 1.5 h under N_2 atmosphere, the mixture

was diluted with ether. The resulting dark red coloured mixture was washed with 50 mL of a 10% aq.$Na_2S_2O_3$ under stirring until the solution becomes colorless. The aqueous phase was extracted with ether. The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated under vacuo and residue was purified by column chromatography to give **2** (3.84 g, 85 %) as white gum. $[\alpha]_D^{28}$= +140.1 (*c* 1.1, $CHCl_3$); eluent column chromatography: EtOAc/Hexane (5/45, v/v); R_f 0.30 (2/3 EtOAc/Hexane); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.87-5.77 (m, 2H), 5.29-5.25 (m, 1H), 4.88 (br s, 1H), 4.25- 4.12 (m, 2H), 4.05-3.99 (m, 1H), 3.43 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H). ^{13}CNMR (75MHz, $CDCl_3$): δ 170.1, 169.7, 129.2, 127.7, 95.4, 66.9, 65.3, 62.8, 55.7, 20.8, 20.6; MS (ESI): *m*/*z* 245 (M^++H). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.15; H, 6.65.

(2*R*,3*S*,6*S*)-2-((tert-butyldimethylsilyloxy)methyl)-6-methoxy-3,6-dihydro-2H-pyran-3-ol 4:

To the stirred solution of **3** (0.90 g, 5.61 mmol) in dry DCM (15 mL), TBDMSCl (0.93 g, 6.18 mmol) and imidazole (0.57 g, 8.42 mmol) were added at 0 ^oC and allowed to stir for 30 min. After completion of reaction, it was diluted with water and extracted with dichlomethane (15 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **4** (1.46 g, 95%) as colorless gum. $[\alpha]_D^{28}$= + 69.2 (*c* 0.03, MeOH). R_f 0.80 (1/1 EtOAc/Hexane). Eluent for column chromatography: EtOAc/Hexane (7.5/22.5, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.93-5.87 (m, 1H), 5.72-5.64 (m, 1H), 4.79 (d, 1H, *J* = 1.3), 4.14- 4.06 (m, 1H), 3.93-3.81 (m, 2H), 3.79-3.59 (m, 1H), 3.40 (s, 3H), 2.82 (s, 1H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75MHz, $CDCl_3$): δ 133.2, 125.7, 95.2, 70.6, 66.5, 65.1, 55.5, 25.9, 18.4, -5.36, -5.38; MS (ESI): *m*/*z* 275 (M^++H). Anal. Calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55. Found: C, 56.99; H, 9.63.

***N*-(2-ethoxy-2-oxoethylidene)-N-(4-methoxybenzyl)hydroxylammonium 5:**

To the solution of diethyl-d-tartrate (1.20 g, 6.00 mmol) in dry ether (20 mL) cooled in a cold water bath was added paraperiodic acid (1.33 g, 6.00 mmol) in portion over 1 h under nitrogen with stirring. The milky reaction mixture was then stirred for a few minutes until the ether solution had become almost clear and a white solid separated. The ether phase was decanted, dried with molecular sieves, evaporated, and distilled through a column to give clear ethyl glyoxylate (1.02 g, 82 %). To an ice cooled mixture of **10** (1.60 g, 11.00 mmol) and calcium chloride (0.29 g, 2.00 mmol) in 29 mL of ether, ethyl glyoxylate (1.02 g, 7.00 mmol) was added drop wise, after which the whole residue was stirred at 0 ^oC for 1 h. The solids were removed by filtration through an anhydrous Na_2SO_4, and the filtrate was evaporated to give **5** (1.64 g, 88%). Mp 84.0-86.5 ^oC; IR (KBr): 1720, 1560, 1200, 1045, 965, 825, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 5H), 7.17 and 7.09 (s, 1H), 5.69 and 4.96 (s, 2H), 4.25 and 4.22 (q, 2H, *J* = 7.0), 1.30 and 1.27 (t, 3H, *J* = 7.0); MS (ESI): *m*/*z* 238 (M^++H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.82; H, 6.31; N, 5.96.

4-methoxybenzaldehyde oxime 9:

To the solution of hydroxyl amine hydrochloride **8** (7.65g, 0.11mol) in saturated solution of KOH, was added p-methoxy benzaldehyde **7** (10g, 0.07 mol) and allowed to stir for 2 hour at 0 ^oC. After completion of reaction, reaction mixture was filtered and residue was washed with cold water (200ml) and dried in air to give **9** (10.2g, 92%) as white solid. R_f 0.5 (1.5/3.5 EtOAc/Hexane); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 8.06 (s, 1H), 7.50 (t, 2H, *J* = 6.8), 6.95 (t, 2H, *J* = 1.9), 3.82 (s, 3H); MS (ESI): *m*/*z* 152 (M^++H). Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.09; N, 9.34.

***N*-(4-methoxybenzyl)hydroxylamine 10:**

To a solution of oxime **9** (1.78 g, 0.01 mol) and $NaBH_3CN$ (1.11 g, 0.02 mmol) in 17 mL of methanol was added a trace of bromocresol green. A solution of 2 ***N*** HCl methanol was then added drop wise with stirring to maintain the yellow color. After *ca*. 15 min, the color changed very slowly. The solution was stirred for 3 h, and the methanol was removed at reduced pressure. The residue was dissolved in 10 mL of water, raised to pH >9 with 6 ***N*** KOH, saturated with sodium chloride, and extracted with four 15-ml portions of chloroform. The combined extracts were dried over Na_2SO_4 and evaporated *in vucuo* to give (1.35 g, 72%) of **10** as white solid. R_f 0.5 (1.5/3.5 EtOAc/Hexane); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 7.40 (d, 2H, *J* = 8.7), 6.91-6.88 (m, 2H), 4.97 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 160.1, 130.0, 127.7, 114.3, 63.4, 55.3; MS (ESI): *m*/*z* 152 (M^++H). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14; Found: C, 62.82; H, 7.31; N, 9.21.

N-(carboxymethylene)-1-(4-methoxyphenyl)methanamine oxide 11:

To the solution of **10** (0.30 g, 1.95 mmol) in dry DCM (10 mL), glyoxalic acid (0.19 g, 2.05 mmol) was added and allowed to stir for overnight. After completion of reaction, it was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **11** (0.30 g, 75%) as white semi solid. R_f 0.2 (EtOAc); IR (Neat): 3450, 2926, 2366, 1718, 1253, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.6 (brs, 1H), 7.33 (d, 2H, *J* = 8.6), 6.97 (d, 2H, *J* = 8.6), 4.99 (s, 2H), 3.84 (s, 3H); MS (ESI): *m*/*z* 210 (M^++H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.49; H, 5.40; N, 6.61.

(3a*S*,4*R*,6*S*,7*R*,7a*R*)-4-(hydroxymethyl)-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol 13:

To the solution of **12** (8.0 g, 0.04 mol) in acetone (250 mL) was added 2,2-dimethoxypropane (6.07 mL, 0.05 mol) followed by catalytic amount of camphorsulfonic acid. After 12 h of stirring, the reaction mixture was concentrated under reduced pressure to a colorless oil which on column chromatographic purification gave the pure compound **13** (5.78 g, 60 %) as a white semi solid. $[\alpha]_D^{28}$= +17.5 (*c* 9.8, MeOH); R_f 0.4 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (30/20, v/v); IR (Neat): 3452, 3018, 2363, 1379, 1217 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (d, 1H, *J* = 2.1), 4.19-4.16 (m, 2H), 4.08-3.96 (m, 1H), 3.87-3.70 (m, 3H), 3.38 (s, 3H), 3.10 (d, 1H, *J* = 6.3), 2.82 (d, 1H, *J* = 3.5); ^{13}C NMR (75 MHz, $CDCl_3$): 109.5, 98.6, 76.1, 73.6, 69.5, 67.9, 62.2, 55.3, 27.6, 25.8; MS (ESI): *m*/*z* 235 (M^++H). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75; Found: C, 51.34; H, 7.82.

((3a*S*,4*R*,6*S*,7*R*,7a*S*)-7-acetoxy-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)methyl acetate 14:

To the solution of **13** (2.03 g, 0.008 mol) in pyridine (10 mL) was added acetic anhydride (3.27 mL, 0.03 mol). After 12 h of stirring, the reaction mixture was concentrated under reduced pressure to a colorless oil which on column chromatographic purification gave the pure compound **14** (2.50 g, 91%) as a colorless gum. $[\alpha]_D^{28}$= +17.0 (*c* 11.8, MeOH); R_f *0*.8 (1/1 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (10/40, v/v); IR (Neat): 3433, 2995, 2364, 1735, 1377, 1236, 1036 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.92-4.90 (m, 1H), 4.85 (d, 1H, *J* = 3.5), 4.42- 4.28 (m, 3H), 4.24-4.15 (m, 2H), 3.39 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.52 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.6, 170.3, 109.9, 96.9, 73.34, 73.31, 71.6, 65.4, 63.5, 55.3, 27.7, 26.2, 20.8, 20.7; MS (ESI): *m*/*z* 319 (M^++H). Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97; Found: C, 52.90; H, 6.88.

((2*R*,3*R*,4*S*,5*R*,6*S*)-5-acetoxy-3,4-dihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl acetate 15:

To compound **14** (2.20 g, 0.007 mol), 80 % acetic acid (25 mL) was added and stirred for 2 h at 80 °C. After completion of reaction (TLC), the acidic solution was concentrated under reduced pressure to give a crude product which was purified by column chromatography to yield compound **15** (1.80 g, 94 %) as a colorless gum. R_f 0.2 (1/1 EtOAc:Hexane). $[\alpha]_D^{28}$= +99.5 (*c* 1.6, $CHCl_3$); Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3461, 3021, 1735, 1238, 1053, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.98- 4.94 (m, 1H), 4.82 (d, 1H, *J* = 3.6), 4.32- 4.26 (m, 1H), 4.21- 4.15 (m, 1H), 3.92- 3.91 (m, 3H), 3.55 (bs, 1H), 3.31 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H); MS (ESI): *m*/*z* 279 (M^++H). Anal. Calcd for $C_{11}H_{18}O_8$: C, 47.48; H, 6.52; Found: C, 47.54; H, 6.61.

((2*S*,5*R*,6*S*)-5-acetoxy-6-methoxy-5,6-dihydro-2H-pyran-2-yl)methyl acetate 16:

Compound **15** (1.37 g, 0.005 mol) was dissolved in dry toluene (200 mL) under nitrogen atmosphere and stirred for 30 min. at room temperature. Then triphenyl phosphine (5.28 g, 0.02 mol), iodoform (3.96 g, 0.01 mol) and imidazole (0.68 g, 0.01 mol) were successively added and the reaction mixture was heated to reflux for 2.5 h with vigorous heating. After cooling to room temperature, methanol and saturated solution of sodium bicarbonate were added. The organic layer was separated and aqueous layer was extracted with ether. The combined organic portion were dried over Na_2SO_4 and concentrated under vacuo to give a crude product which was purified by column chromatography to yield compound **16** (1.80 g, 94 %) as a colorless. R_f 0.8 (1/1 EtOAc:Hexane). $[\alpha]_D^{28}$= +1.1.2 (*c* 1.6, $CHCl_3$); Eluent for column chromatography: EtOAc/Hexane (7.5/42.5, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (d, 1H, *J* = 11), 5.79 (d, 1H, *J* = 11), 5.32- 5.31 (m, 1H), 5.10 (d, 1H, *J* = 4.1), 4.39 (d, 1H, *J* = 2.1), 4.18 (d, 1H, *J* = 5.0), 3.50 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.5, 127.8, 124.3, 95.9, 66.7, 66.5, 65.3, 56.1, 20.9, 20.8; MS (ESI): *m*/*z* 245 (M^++H). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; Found: C, 54.17; H, 6.69

(2*S*,3*R*,6*S*)-6-(hydroxymethyl)-2-methoxy-3,6-dihydro-2H-pyran-3-ol 17:

To the stirred solution of **16** (1.80 g, 0.007 mol) in methanol, anhydrous K_2CO_3 (2.54 g, 0.2 mol) was added and allowed to stir for 30 min. After completion of reaction, methanol was evaporated in vacuo and residue was diluted with water. Aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **17** (1.12 g, 95%) as white gum. $[\alpha]_D^{28}$= +93.2 (*c* 0.9, $CHCl_3$); R_f 0.2 (1/1 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (40/10, v/v); IR (Neat): 3469, 2928, 1742, 1372, 1245, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (d, 1H, *J* = 10.6), 5.69 (d, 1H, *J* = 10.6), 4.91 (d, 1H, *J* = 4.1), 4.21- 4.20 (m, 2H), 3.74- 3.57 (m, 2H), 3.53 (s, 3H), 2.38 (d, 1H, *J* = 11), 2.19 (bs, 1H); MS (ESI): *m*/*z* 161 (M^++H). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55; Found: C, 52.56; H, 7.64.

(2*S*,3*R*,6*S*)-6-((tert-butyldimethylsilyloxy)methyl)-2-methoxy-3,6-dihydro-2H-pyran-3-ol 18:

To the stirred solution of **17** (0.19 g, 1.23 mmol) in dry DCM (5 mL), TBDMSCl (0.20 g, 1.35 mmol) and imidazole (0.13 g, 1.85 mmol) were added at 0 °C and allowed to stir for 30 minutes. After completion of reaction, it was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **18** (0.30 g, 95%) as colorless gum. $[\alpha]_D^{28}$= -9.1 (*c* 1.5, $CHCl_3$); R_f 0.80 (1/4 EtOAc/Hexane). Eluent for column chromatography: EtOAc/Hexane (2.5/47.5, v/v); IR (Neat): 3447, 3021, 2359, 1216, 1056, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (d,

1H, J = 10.6), 5.73 (d, 1H, J = 10.6), 4.87 (d, 1H, J = 4.3), 4.20-4.09 (m, 2H), 3.72- 3.56 (m, 2H), 3.51 (s, 3H), 2.24 (d, 1H, J = 11.1), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 127.6, 127.3, 97.9, 77.6, 76.9, 76.3, 69.0, 65.4, 64.3, 55.9, 25.8, 18.3, -5.33, -5.37; MS (ESI): m/z 275 (M^++H). Anal. Calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55 Found: C, 56.99; H, 9.63.

Compound 19:

To the solution of **18** (0.20 g, 0.73 mmol), **11** (0.31 g, 1.45 mmol) and PyBroP (0.68 g, 1.45 mmol) in DCM was DIPEA (0.51 ml, 2.91 mmol), DMAP (0.09 g, 0.80 mmol) were added at 0 ^oC under argon atmosphere. After overnight stirring, it was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo and purified by column chromatography to give **19** (0.30 g, 95%) as yellowish gum. $[\alpha]_D^{28}$= + 123.2 (c 0.23, $CHCl_3$), R_f 0.3 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (30/20, v/v); IR (Neat): 3426, 2931, 1664, 1249, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, 1H, J = 8.5), 6.80 (d, 1H, J = 8.5), 5.03 (d, 1H, J = 2.9), 4.62 (dd, 1H, J = 4.4, 3.2), 4.36 (d, 1H, J = 5.8), 4.23 (d, 1H, J = 10.1), 4.17 (brs, 1H), 3.95- 3.91 (m, 2H), 3.84- 3.80 (m, 5H), 3.50 (s, 3H), 3.47- 3.42 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 172.5, 159.3, 130.4, 127.7, 113.9, 95.4, 72.3, 72.1, 67.2, 65.0, 56.4, 55.2, 43.0, 31.4, 25.8, -5.5; MS (ESI): m/z 466 (M^++H). Anal. Calcd for $C_{23}H_{35}NO_7Si$: C, 59.33; H, 7.58; N, 3.01. Found: C, 59.41; H, 7.67; N, 3.10.

Compound 20:

To the solution of **19** (0.05 g, 0.11 mmol) in THF, 1N HCl was added and stirred for 30 min. at room temperature. After completion of reaction, it was diluted with water. Aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **20** (0.30 g, 95%) as white semi solid. $[\alpha]_D^{28}$= +53.2 (c 0.35, MeOH). R_f 0.3 (0.2/9.8 MeOH/Chloroform); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, 1H, J = 8.5), 6.83 (d, 1H, J = 8.5), 4.94 (d, 1H, J = 3.9), 4.59- 4.38 (m, 4H), 3.91- 3.87 (m, 2H), 3.86- 3.77 (m, 4H), 3.55-3.50 (m, 1H), 3.33 (s, 3H), 2.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 170.3, 158.6, 129.8, 128.9, 113.8, 97.3, 75.2, 72.7, 68.1, 62.1, 555.4, 55.2, 48.3; MS (ESI): m/z 352 (M^++H). Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.20; H, 6.10; N, 3.90.

Compound 22:

To a solution of **19** (0.05 g, 0.11 mmol) in dry THF, LAH (0.005 g, 0.15 mmol) was added at 0 ^oC and stirred for 1h at room temperature. After completion of reaction, it was quenched by water and extracted by ethyl acetate (5 mL × 3). The combined organic portion were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. Crude was purified by column chromatography to give **22** (0.04 g, 95%) as colourless oil. $[\alpha]_D^{28}$= + 93.5 (c 0.43, $CHCl_3$). R_f 0.4 (3/2EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (20/30, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.5), 6.85 (d, 2H, J = 8.5), 5.26 (s, 1H), 4.90 (d, 1H, J = 4.3), 4.63 (t, 1H, J = 4.7), 4.26 (t, 1H, J = 7.8), 3.99- 3.94 (m, 2H), 3.89- 3.88 (m, 2H), 3.81 (s, 3H), 3.77- 3.68 (m, 2H), 3.31 (s, 3H), 3.29- 3.22 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (ESI): m/z 467 (M^++H). Anal. Calcd for $C_{23}H_{37}NO_7Si$: C, 59.07; H, 7.98; N, 3.00; Found: C, 59.13; H, 7.70; N, 3.10.

Compound 23:

To a solution of **22** (0.05 g, 0.11 mmol) in dry THF, LAH (0.012 g, 0.33 mmol) was added at 0 ^oC and refluxed for 3 days. After that, it was quenched by water and extracted by ethyl acetate (5 mL × 3). The combined organic portion were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. Crude was purified by column chromatography to give **23** (0.005 g, 10%) as colourless oil. $[\alpha]_D^{28}$= + 110.2 (c 0.52, $CHCl_3$). R_f 0.3 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (40/10, v/v); IR (Neat): 3420, 2920, 2361, 1612, 1504, 1246, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.5), 6.84 (d, 2H, J = 8.5), 4.62 (s, 1H), 4.61-4.24 (m, 1H), 4.18 (t, 1H, J = 4.2), 4.02-4.00 (m, 3H), 3.99-3.90 (m, 3H), 3.89- 3.84 (m, 1H), 3.83 (s, 3H), 3.69-3.64 (m, 1H), 3.49 (s, 3H), 3.41-3.34 (m, 1H), 2.92-2.30 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.5, 128.3, 113.8, 98.1, 73.1, 71.6, 67.3, 65.9, 64.3, 61.3, 55.5, 55.2, 45.6, 31.9, 25.9, 22.7, -5.3; MS (ESI): m/z 470 (M^++H). Anal. Calcd for $C_{23}H_{39}NO_7Si$: C, 58.82; H, 8.37; N, 2.98; Found: C, 58.91; H, 8.43; N, 2.90.

Compound 24:

A solution of DIBAL–H (1.0 M in toluene, 0.62 mL, 0.62 mmol) was added to a cooled (0–5°C) solution of benzylamine (0.07 mL, 0.63 mmol) in THF (0.27 mL) under nitrogen. The mixture was allowed to warm up and stirred at RT for 2 h. To a solution of **19** (0.05 g, 0.11 mmol) in THF (0.40 mL) was added, under nitrogen at rt, the DIBAL–H–amine complexes (0.27 mL). After stirring at rt for 2 h, the reaction was cooled to 0°C, and then quenched with H_2O (1.5 mL) and a 1 M aqueous solution of $KHSO_4$ (4 mL). The resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography to give **24** (0.05 g, 85%). $[\alpha]_D^{28}$= + 106.3 (c 0.85, $CHCl_3$). R_f 0.5 (1.5/3.5 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3370, 2925, 2363, 1657, 1518, 1251 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (t, 1H, J = 5.2), 7.32- 7.22 (m, 3H), 7.17- 7.13 (m, 4H), 6.78 (d, 1H, J = 8.5), 4.62 (d, 1H, J = 3.6), 4.53- 4.46 (m, 1H), 4.32 (t, 1H, J = 7.4), 4.24- 4.10 (m, 3H), 3.94- 3.83 (m, 4H), 3.78- 3.74 (s, 4H), 3.71- 3.68 (m, 1H), 3.42 (s, 3H), 3.23- 3.21 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 159.3, 137.7, 130.8, 128.5, 127.6, 127.3, 114.0, 98.0, 74.4, 70.2, 68.1,

65.9, 64.2, 62.4, 55.4, 55.2, 47.6, 43.3, 25.9, -5.34; MS (ESI): *m/z* 569 (M^++H). Anal. Calcd for $C_{30}H_{44}N_2O_7Si$: C, 62.91; H, 7.74; N, 4.89; Found: C, 62.90; H, 7.81; N, 4.96**.**

(3a*R*,4*S*,6*S*,7*R*,7a*R*)-4-(iodomethyl)-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol 25:

To the solution of **12** (0.10 g, 0.43 mmol) in dry toluene (10 mL), triphenyl phosphine (0.15 g, 0.59 mmol), iodine (0.16 g, 0.64 mol) and imidazole (0.08 g, 1.28 mmol) were successively added and the reaction mixture was heated at 60 ^oC for 2.5 h with vigorous heating. After cooling to room temperature, organic layer was separated and aqueous layer was extracted with ether. The combined organic portion were dried over Na_2SO_4 and concentrated under vacuo to give a crude product which was purified by column chromatography to yield compound **25** (0.11 g, 75 %) as a colorless oil. $[\alpha]_D^{28}$= +119 (*c* 1.0, $CHCl_3$); R_f 0.8 (1/1EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (5/45, v/v); IR (Neat): 3445, 2918, 1638, 1216, 1066, 761cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69 (d, 1H, *J* = 3.8), 4.26- 4.19 (m, 2H), 4.08- 4.04 (m, 1H), 3.79- 3.76 (m, 1H), 3.44 (s, 3H), 3.28- 3.24 (m, 2H), 2.69 (br s, 1H), 1.42 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 109.5, 98.2, 75.6, 73.4, 69.1, 55.4, 27.3, 25.6, 2.7; MS (ESI): *m/z* 345 (M^++H). Anal. Calcd for $C_{10}H_{17}IO_5$: C, 34.90; H, 4.98; Found: C, 34.98; H, 4.90.

(3a*R*,4*S*,6*S*,7*R*,7a*S*)-4-(iodomethyl)-6-methoxy-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl acetate 26:

As described for **13**, compound **26** was prepared from compound **25** (0.10 g, 0.29 mmol), dry pyridine (2 mL) and acetic anhydride (0.05 mL, 0.58 mmol). Crude product was purified by column chromatography to yield compound **26** (0.10g, 95%) as a colorless. $[\alpha]_D^{28}$= +19.1 (*c* 1.5, $CHCl_3$); R_f 0.6 (1/4 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (5/45, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91(dd, 1H, *J* = 10.3, 6.6), 4.84 (d, 1H, *J* = 3.4), 4.37- 4.30 (m, 2H), 4.11 (d, 1H, *J* = 7.5), 3.43 (s, 3H), 3.36- 3.33 (m, 2H), 2.13 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.4, 109.7, 97.3, 73.8, 73.4, 71.5, 68.2, 55.6, 27.8, 26.3, 20.9, 2.1; MS (ESI): *m/z* 387 (M^++H). Anal. Calcd for $C_{12}H_{19}IO_6$: C, 37.32; H, 4.96; Found: C, 37.40; H, 4.90.

(2*S*,3*R*,4*S*,5*R*)-4,5-dihydroxy-6-(iodomethyl)-2-methoxytetrahydro-2H-pyran-3-yl acetate 27:

As described for **14**, compound **27** was prepared from compound **26** (0.01 g, 0.25 mmol), 80% acetic acid. Crude product was purified by column chromatography to yield compound **27** (0.07 g, 85 %) as a colorless. R_f 0.2 (1/1 EtOAc:Hexane). $[\alpha]_D^{28}$= +87.5 (*c* 1.1, $CHCl_3$); Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (dd, 1H, *J* = 10.3, 6.6), 4.88 (d, 1H, *J* = 3.4), 4.15 (d, 1H, *J* = 2.5), 4.02- 3.94 (m, 2H), 3.45 (s, 3H), 3.36 (d, 2H, *J* = 6.9), 3.26 (bs, 2H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.8, 97.3, 71.0, 70.5, 70.3, 68.3, 55.6, 21.1, 2.7; MS (ESI): *m/z* 346 (M^++H). Anal. Calcd for $C_9H_{15}IO_6$: C, 31.23; H, 4.37; Found: C, 31.31; H, 4.30.

(2*S*,3*R*,6*S*)-6-(iodomethyl)-2-methoxy-3,6-dihydro-2H-pyran-3-yl acetate 28:

As described for **15**, compound **28** was prepared from compound **27** (1.8 g, 0.005 mol), PPh_3 (7.56 g, 0.02 mol), iodoform (4.24 g, 0.01 mol) and imidazole (1.41 g, 0.003 mol). Crude product was purified by column chromatography to yield compound **28** (1.22 g, 68 %) as a colorless oil. $[\alpha]_D^{28}$= +103.5 (*c* 1.8, $CHCl_3$); R_f 0.8 (1/1 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (7.5/42.5, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88- 5.73 (m, 2H), 5.30- 5.27 (m, 1H), 5.11 (d, 1H, *J* = 3.9), 4.22- 4.21 (m, 1H), 3.49 (s, 3H), 3.33- 3.20 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.4, 129.9, 124.2, 96.2, 67.0, 66.4, 56.0, 20.9, 8.5; MS (ESI): *m/z* 312 (M^++H). Anal. Calcd for $C_9H_{13}IO_4$: C, 34.63; H, 4.20; Found: C, 34.70; H, 4.28.

(2*S*,3*R*,6*S*)-6-(iodomethyl)-2-methoxy-3,6-dihydro-2H-pyran-3-ol: 29

To the stirred solution of **28** (0.85 g, 2.71 mmol) in methanol, anhydrous K_2CO_3 (0.56 g, 4.06 mmol) was added and allowed to stir for 30 min. After completion of reaction, methanol was evaporated in vacuo and residue was diluted with water. Aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo and crude product was purified by column chromatography to yield compound **29** (0.57 g, 78%) as a colorless gum. $[\alpha]_D^{28}$= 59.3 (*c* 0.32, MeOH). R_f 0.5 (1.5/8.5 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (6/44, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85- 5.72 (m, 2H), 5.72- 5.68 (m, 1H), 4.91 (d, 1H, *J* = 4.2), 4.21- 4.20 (m, 2H), 3.53 (s, 3H), 3.32- 3.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 128.8, 127.9, 98.4, 67.0, 64.0, 56.1, 9.0; MS (ESI): *m/z* 270 (M^++H). Anal. Calcd for $C_7H_{11}IO_3$: C, 31.13; H, 4.11; Found: C, 31.21; H, 4.20.

Compound 21:

As described for **19**, compound **21** was prepared from compound **29** (0.10 g, 0.37 mmol), **11 (**0.09 g, 0.44 mmol), PyBroP (0.34 g, 0.74 mmol), DIPEA (0.25 mL, 1.48 mmol) and DMAP (0.05 g, 0.40 mmol). Crude product was purified by column chromatography to yield compound **21** (1.22 g, 72%) as a white solid. $[\alpha]_D^{28}$= 49.3 (*c* 0.02, MeOH); R_f 0.5 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (30/20, v/v); IR (Neat): 3345, 2926, 2365, 1750, 1247, 1033 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, *J* = 8.5), 6.85 (d, 2H, *J* = 8.5), 4.99 (d, 1H, *J* = 4.1), 4.65- 4.63 (m, 1H), 4.43 (s, 2H), 4.32 (d, 1H, *J* = 7.1), 3.79 (s, 3H), 3.57- 3.47 (m, 2H), 3.41 (s, 3H), 3.39- 3.27

(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 158.8, 131.7, 129.8, 128.9, 124.9, 114.0, 97.3, 75.5, 72.3, 71.6, 55.7, 55.3, 48.8, 5.9; MS (ESI): *m/z* 462 (M^++H). Anal. Calcd for $C_{17}H_{20}INO_6$: C, 44.27; H, 4.37; N, 3.04; Found: C, 44.33; H, 4.43; N, 3.11.

Compound 30 a:

As described for **24**, compound **30a** was prepared from compound **21** (0.05 g, 0.11 mmol), benzylamine (0.07 mL, 0.63 mmol) in THF (0.27 mL), DIBAL-H (0.62 mL, 0.62 mmol). Crude product was purified by column chromatography to give **30a** (0.05 g, 85%) as gum. $[\alpha]_D^{28}$= + 63.2 (*c* 0.03, $CHCl_3$) R_f 0.5 (1.5/3.5 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD): δ 7.20- 7.17 (m, 3H), 7.13- 7.10 (m, 2H), 7.01 (d, 2H, *J* = 6.2), 6.70 (d, 2H, *J* = 8.5), 4.47 (d, 1H, *J* = 3.5), 4.45- 4.17 (m, 1H), 4.25- 4.15 (m, 1H), 4.15- 4.05 (m, 1H), 4.00- 3.95 (m, 1H), 3.95-3.75 (m, 3H), 3.68 (s, 3H), 3.41- 3.32 (m, 4H), 3.24- 3.13 (m, 1H), 3.10 (t, 2H, *J* = 8.1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 159.5, 128.6, 127.8, 127.7, 127.5, 127.3, 114.3, 97.2, 74.9, 67.6, 67.5, 58.4, 56.0, 55.3, 53.5, 37.1, 4.7; MS (ESI): *m/z* 569 (M^++H). Anal. Calcd for $C_{24}H_{29}IN_2O_6$: C, 50.71; H, 5.14; N, 4.93; Found: C, 50.70; H, 5.20; N, 4.90**.**

Compound 30b:

As described for **24**, compound **30b** was prepared from compound **21** (0.05 g, 0.11 mmol), cyclohexylamine (0.07 mL, 0.63 mmol) in THF (0.27 mL), DIBAL-H (0.62 mL, 0.62 mmol). Crude product was purified by column chromatography to yield compound **30b** (0.05 g, 85%) as a light yellow semi solid. $[\alpha]_D^{28}$= 52.8 (*c* 0.03, $CHCl_3$); R_f 0.5 (3/2EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD): δ 7.16 (d, 1H, *J* = 8.5), 6.78 (d, 1H, *J* = 8.5), 4.49 (s, 1H), 4.15- 4.01 (m, 3H), 3.83- 3.74 (m, 3H), 3.50 (s, 3H), 3.44- 3.25 (m, 2H), 3.09- 3.06 (m, 2H), 1.77-1.73 (m,1H), 1.59- 1.49 (m, 5H), 1.30- 1.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$+MeOH): δ 169.1, 158.9, 130.3, 126.8, 113.5, 97.7, 78.1, 69.2, 67.4, 65.0, 61.7, 55.1, 54.5, 49.2, 48.8, 48.3, 47.9, 47.5, 47.0, 46.6, 31.7, 31.5, 24.8, 24.0, 5.8; MS (ESI): *m/z* 561 (M^++H). Anal. Calcd for $C_{23}H_{33}IN_2O_6$: C, 49.29; H, 5.94; N, 5.00; Found: C, 49.37; H, 5.88; N, 5.09.

Compound 30c:

As described for **24**, compound **30c** was prepared from compound **19** (0.5 g, 0.11 mmol), phenethyl amine **(**0.08 mL, 0.64 mmol) in THF (0.27 mL) and DIBAL-H (0.62 mL, 0.62 mmol). Crude product was purified by column chromatography to yield compound **30c** (0.05 g, 85%) as a white semi solid. $[\alpha]_D^{28}$= +181.4 (*c* 0.03, $CHCl_3$) R_f 0.5 (3/2 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD): δ 7.33- 7.19 (m, 5H), 7.12 (d, 2H, *J* = 8.5), 6.83 (d, 2H, *J* = 8.5), 4.55 (d, 1H, *J* = 3.6), 4.20-4.01 (m, 3H), 3.89- 3.84 (m, 2H), 3.83- 3.79 (m, 4H), 3.51-3.50 (m, 4H), 3.45- 3.35 (m, 3H), 3.23- 3.12 (m, 2H), 2.65- 2.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+MeOH): δ 170.4, 159.3, 138.6, 130.6, 128.6, 127.2, 126.5, 113.9, 98.4, 78.2, 67.6, 66.2, 62.0, 55.8, 55.2, 47.5, 40.3, 35.2, 7.1; MS (ESI): *m/z* 582 (M^++H). Anal. Calcd for $C_{25}H_{31}IN_2O_6$: C, 51.55; H, 5.36; N, 4.81; Found: C, 51.62; H, 5.43; N, 4.90.

Compound 32a:

To a stirred solution of **30a** (0.05 g, 0.08 mmol) in acetonitrile-water (1.30 mL, 15:1) was added $Mo(CO)_6$ (0.03 g, 0.11 mmol) and the mixture was heated at reflux under nitrogen atmosphere for 5 h. It was concentrated under vacuum and the residue was used in next reaction without further purification. The crude was taken in pyridine (1 mL) and DMAP (cat.) and 3 drops of acetic anhydride were added at 0 ^{o}C, and the mixture was kept at room temperature for 12 h. After completion of reaction, pyridine was evaporated under vacuo to yield the crude which was purified by column chromatography to give compound **32a** (0.04 g, 75 %) as a white semi solid. $[\alpha]_D^{28}$= +55.8 (*c* 0.9, $CHCl_3$); R_f 0.5 (1/4 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (6/44, v/v); IR (Neat): 3416, 2920, 2368, 1610, 1503, 1240, 1032 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, *J* = 6.4), 7.24-7.20 (m, 4H), 7.05-6.95 (m, 1H), 6.86 (d, 2H, *J* = 6.4), 6.75 (m, 1H), 4.93- 4.86 (m, 2H), 4.68 (d, 1H, *J* = 12.1), 4.44 (d, 1H, *J* = 12.1), 4.38- 4.32 (m, 2H), 3.74 (s, 3H), 3.72-3.69 (m, 1H), 3.59- 3.58 (m, 1H), 3.42-3.38 (m, 2H), 3.35- 3.31 (m, 4H), 3.14-3.11 (m, 1H), 2.12 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 170.1, 169.2, 159.5, 128.6, 128.5, 127.8, 127.7, 127.5, 127.3, 114.4, 97.2, 74.9, 67.6, 67.5, 58.4, 56.0, 55.3, 53.5, 37.1, 21.7, 20.9, 4.7; MS (ESI): *m/z* 655 (M^++H). Anal. Calcd for $C_{28}H_{35}IN_2O_8$: C, 51.38; H, 5.39; N, 4.28; Found: C, 51.45; H, 5.47; N, 4.35.

Compound 32b:

As described for **32a**, compound **32b** was prepared from compound **30b** (0.05 g, 0.09 mmol), $Mo(CO)_6$ (0.04 g, 0.13 mmol), acetonitrile: water (1.5 ml, 15:1) and acetic anhydride (0.1 mL). Crude product was purified by column chromatography to yield compound **32b** (0.04 g, 78%) as a white semisolid. R_f 0.5 (1:4 EtOAc:Hexane). $[\alpha]_D^{28}$= +65.3 (*c* 0.7, $CHCl_3$); Eluent for column chromatography: EtOAc/Hexane (10/40, v/v); IR (Neat): 3420, 2925, 2351, 1615, 1512, 1246, 1038 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, *J* = 6.5), 6.85 (d, 2H, *J* = 6.5), 4.93-4.90 (m, 1H), 4.86 (d, 1H, *J* = 2.9), 4.68 (d, 1H, *J* = 12.1), 4.56 (d, 1H, *J* = 12.1), 4.38-4.32 (m, 2H), 3.74 (s, 3H), 3.71-3.69 (m, 1H), 3.58-3.57 (m, 2H), 3.42 (t, 1H, *J* = 1.8), 3.40 (s, 3H), 3.39-3.30 (m, 1H), 3.14-3.09 (m, 1H), 2.23 (m, 1H), 2.23 (s, 3H), 2.11 (s, 3H). 1.26-1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.4, 170.1, 169.2, 159.4, 128.5, 127.3, 114.2, 97.1, 74.8, 67.6, 67.4, 58.3, 55.9, 55.2, 53.4, 37.0, 29.2, 29.0, 27.1, 24.7, 22.6, 21.6, 20.9, 4.7; MS (ESI): *m/z* 647 (M^++H). Anal. Calcd for $C_{27}H_{39}IN_2O_8$: C, 50.16; H, 6.08; N, 4.33; Found: C, 50.22; H, 6.15; N, 4.41.

Compound 34:

To a stirred solution of **21** (0.05 g, 0.11 mmol) in acetonitrile-water (1.80 mL, 15:1) was added $Mo(CO)_6$ (0.04 g, 0.16 mmol) and the mixture was heated at reflux under nitrogen atmosphere for 5 h. It was concentrated under vacuum and the residue was used in next reaction without further purification. The crude was taken in pyridine (1 mL) and DMAP (cat.) and 3 drops of acetic anhydride were added at 0 ^oC, and the mixture was kept at room temperature for 12 h. After completion of reaction, pyridine was evaporated under vacuo to yield the crude which was purified by column chromatography to give compound **34** (0.04 g, 72 %) as a white semi solid. $[\alpha]_D^{28}$= 28.7 (*c* 0.8, $CHCl_3$); R_f 0.7 (1/1EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (6/44, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, *J* = 6.5), 6,86 (d, 2H, *J* = 6.5), 4.92- 4.85 (m, 2H), 4.65 (d, 1H, *J* = 12.1), 4.46- 4.40 (m, 1H), 4.38- 4.32 (m, 2H), 3.74 (s, 3H), 3.62- 3.51 (m, 1H), 3.46- 3.38 (m, 1H), 3.33 (s, 3H), 3.15-3.05 (m 1H), 2.11 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 170.1, 169.1, 159.4, 128.5, 127.3, 114.2, 97.1, 74.8, 67.5, 67.4, 58.3, 55.9, 55.2, 53.4, 36.9, 22.5, 21.6, 20.8, 4.6; MS (ESI): *m/z* 548 (M^++H). Anal. Calcd for $C_{21}H_{26}INO_8$: C, 46.08; H, 4.79; N, 2.56; Found: C, 46.15; H, 4.86; N, 2.63.

Compound 36:

To a stirred suspension of zinc dust (0.08 g, 0.15 mmol) and NH_4Cl (1.9 mL) in THF (1.9 mL) was added compound **34** (0.08 g, 0.15 mmol) and refluxed for 1.5 h. After completion of reaction, it was diluted with water. The resulting mixture was extracted with ethyl acetate (5×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuo to give crude as oil. The oil without further purification was taken in DCM (10 mL) and (carbethoxymethylene)triphenylphosphorane (0.04 g, 0.13 mmol) was added at 0°C. After overnight stirring, solvent was evaporated under vacuo to give crude which on column purification yielded **36** (0.04 g, 65%) as a colorless oil. R_f 0.8 (1/1EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (6/44, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, 1H, *J* = 6.3), 6.84 (d, 2H, *J* = 6.3), 6.70- 6.66 (m, 1H), 5.88- 5.76 (m, 1H), 5.75- 5.70 (m, 1H), 5.32- 5.27 (m, 3H), 5.24- 5.06 (m, 1H), 4.64 (d, 1H, *J* = 12.4), 4.22- 4.19 (m, 3H), 3.74 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.23 (t, 3H, *J* = 5.4); ^{13}C NMR (75 MHz, $CDCl_3$): 171.6, 171.4, 169.2, 165.2, 159.5, 141.6, 131.6, 128.4, 127.2, 124.7, 119.9, 114.5, 78.7, 70.3, 60.9, 55.3, 45.5, 29.6, 21.9, 20.8, 14.2; MS (ESI): *m/z* 460 (M^++H). Anal. Calcd for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; N, 3.05; Found: C, 62.81; H, 6.43; N, 3.13.

((3a*R*,4*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol 38:

As described for **12**, compound **38** was prepared from compound **37** (0.52 g, 3.16 mmol), 2,2-DMP (0.39 g, 3.80 mmol) and acetone (40 mL). Crude product was purified by column chromatography to yield compound **38** (0.05 g, 78%) as a colorless. R_f 0.5 (1/1 EtOAc:Hexane). $[\alpha]_D^{28}$= -72.5 (*c* 0.8, MeOH); Eluent for column chromatography: EtOAc/Hexane (13/37, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, 1H, *J* = 5.7), 4.51- 4.47 (m, 1H), 4.29- 4.25 (m, 1H), 3.82- 3.76 (m, 1H), 3.71-3.66 (m, 2H), 3.46 (s, 3H), 2.71 (d, 1H, *J* = 5.5), 1.54 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 109.8, 101.3, 73.0, 72.8, 68.4, 61.8, 55.8, 26.5, 25.2; MS (ESI): *m/z* 205 (M^++H). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90; Found: C, 52.83; H, 7.98.

((3a*R*,4*R*,6*S*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl acetate 39:

As described for **13**, compound **39** was prepared from compound **38** (0.11 g, 0.55 mmol), acetic anhydride (0.10 mL, 1.11 mmol). Crude product was purified by column chromatography to yield compound **39** (0.12 g, 95 %) as a colorless gum. $[\alpha]_D^{28}$= -13.52 (*c* 7.5, MeOH); R_f 0.6 (1/4EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (4/46, v/v); IR (Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.91- 4.88 (m, 1H), 4.74 (d, 1H, *J* = 6.1), 4.57- 4.54 (m, 1H), 4.31 (d, 1H, *J* = 7.1), 3.81 (d, 1H, *J* = 2.2), 3.77 (d, 1H, *J* = 2.25), 3.41 (s, 3H), 2.16 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.1, 110.1, 98.5, 73.4, 71.5, 69.9, 62.1, 55.4, 26.2, 25.1, 21.0; MS (ESI): *m/z* 247 (M^++H). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37; Found: C, 53.71; H, 7.45.

((2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-5-methoxytetrahydrofuran-2-yl)methyl acetate 40:

As described for **14**, compound **40** was prepared from compound **39** (0.5 g, 2.03 mmol) and 80% acetic acid (10 mL). Crude product was purified by column chromatography to yield compound **40** (0.3 g, 81 %) as a colorless gum. $[\alpha]_D^{28}$= -5.16 (*c* 18.5, MeOH); R_f 0.5 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3422, 2930, 1733, 1244, 1069 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.96 (t, 1H, *J* = 2.5), 4.70 (d, 1H, *J* = 2.2), 4.00- 3.97 (m, 1H), 3.91- 3.87 (m, 1H), 3.81- 3.80 (m, 2H), 3.40 (s, 3H), 2.91 (d, 1H, *J* = 8.1), 2.63 (d, 1H, *J* = 10.2), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 169.9, 98.8, 71.7, 68.6, 64.7, 63.1, 55.5. 21.0; MS (ESI): *m/z* 207 (M^++H). Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84; Found: C, 46.69; H, 6.92.

((2*S*,5*S*)-5-methoxy-2,5-dihydrofuran-2-yl)methyl acetate 41:

As described for **15**, compound **41** was prepared from compound **40** (0.52 g, 2.54 mmol), PPh_3, (2.66 g, 10.16 mmol), iodoform (2.00 g, 5.08 mmol) and imidazole (0.34 g, 5.08 mmol). Crude product was purified by column chromatography to yield compound **41** (0.26 g, 62%) as a colorless. R_f 0.8 (1/1 EtOAc:Hexane). $[\alpha]_D^{28}$= - 41.5 (*c* 0.4, MeOH); Eluent for column chromatography: EtOAc/Hexane (7.5/42.5, v/v); IR

(Neat): 3416, 2920, 2367, 1608, 1508, 1246, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.10-6.00 (m, 2H), 4.94 (t, 1H, J = 3.1), 4.89 (d, 1H, J = 2.3), 4.13 (dd, 1H, J = 13.0, 2.7), 3.83 (d,1H, J = 13.3), 3.43 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.6, 130.7, 125.0, 94.0, 63.3, 61.2, 55.7, 21.1; MS (ESI): m/z 173 (M^++H). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02; Found: C, 55.90; H, 7.10.

((2*S*,5*S*)-5-methoxy-2,5-dihydrofuran-2-yl)methanol 42:

As described for **16**, compound **42** was prepared from compound **41** (0.5 g, 2.89 mmol) and anhy. K_2CO_3 (0.59 g, 4.33 mmol). Crude product was purified by column chromatography to yield compound **42** (0.29 g, 78%) as a colorless gum. R_f 0.5 (1/1EtOAc:Hexane). $[\alpha]_D^{28}$= -6.24 (*c* 18.5, $CHCl_3$) Eluent for column chromatography: EtOAc/Hexane (12.5/47.5, v/v); IR (Neat): 3408, 2924, 2357, 1598, 1218, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.16- 6.10 (m, 1H), 5.88 (dd, 1H, J = 10.0, 3.6), 4.82 (d,1H, J = 2.7), 4.11- 4.06 (m, 1H), 3.81- 3.77 (m, 2H), 3.43 (s, 3H), 2.35 (d, 1H, J = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$): 129.2, 128.2, 94.2, 64.2, 61.4, 55.6; MS (ESI): m/z 131 (M^++H). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74; Found: C, 55.45; H, 7.82.

Compound 43:

As described for **19**, compound **43** was prepared from compound **42** (0.05 g, 3.84 mmol), **11** (1.21 g, 5.76 mmol), PyBroP (3.58 g, 7.68 mmol), DIPEA (2.66 mL, 15.36 mmol) and DMAP (0.52g, 4.22 mmol). Crude product was purified by column chromatography to yield compound **43** (0.07 g, 62%) as a white gum. $[\alpha]_D^{28}$= -53.85 (*c* 0.13, $CHCl_3$). R_f 0.4 (EtOAc). Eluent for column chromatography: EtOAc/Hexane (25/25, v/v); IR (Neat): 3294, 2932, 2370, 1604, 1248, 1027, 836 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 7.38 (d, 2H, J = 8.5), 6.92 (d, 2H, J = 8.5), 4.68 (s, 1H), 4.61 (d, 1H, J = 7.4), 4.47 (d, 1H, J = 8.4), 4.12-4.08 (m, 2H), 3.96- 3.90 (m, 2H), 3.81- 3.78 (m, 5H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 159.3, 130.3, 128.7, 113.6, 95.8, 72.0, 70.3, 56.4, 54.6, 54.4, 38.3; MS (ESI): m/z 322 (M^++H). Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36; Found: C, 59.90; H, 5.90; N, 4.45.

(2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-bis(benzyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-6-methoxytetrahydro-2H-pyran-3-ol 48:

To the stirred solution of **47** (0.79 g, 2.11 mmol) in dry DCM (15 mL), TBDMSCl (0.35 g, 2.32 mmol) and imidazole (0.29 g, 4.22 mmol) were added at 0 ^oC and allowed to stir for 30 minutes. After completion of reaction, it was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **48** (1.0 g, 97 %) as colourless gum. $[\alpha]_D^{28}$= +58.8 (*c* 0.45, MeOH); R_f 0.5 (1:1 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (6/44, v/v); IR (Neat): 3453, 2927, 2365, 1218, 1055, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40- 7.29 (m, 10H), 5.02 (d, 1H, J = 11.4), 4.80 (dd, 1H, J = 11.4, 3.5), 4.71-4.65 (m, 2H), 3.87- 3.81 (m, 3H), 3.66- 3.50 (m, 3H), 3.41 (s, 3H), 2.64 (s, 1H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 138.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 97.9, 81.4, 79.6, 75.4, 73.0, 71.5, 70.7, 63.6, 54.9, 25.8, 18.3, -5.5; MS (ESI): m/z 489 (M^++H). Anal. Calcd for $C_{27}H_{40}O_6Si$: C, 66.36; H, 8.25; Found: C, 66.41; H, 8.31.

(2*R*,3*R*,4*R*,5*R*,6*S*)-4,5-bis(benzyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-6-methoxytetrahydro-2H-pyran-3-yl methanesulfonate 49:

To the stirred solution of **48** (1.0 g, 2.10 mmol) in dry DCM (25 mL), MsCl (0.19 mL, 2.50 mmol) and Et_3N (0.52 mL, 0.38 mmol) were added at 0 ^oC and allowed to stir for 1h. After completion of reaction, it was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, and dried over Na_2SO_4. The organic fraction was concentrated in vacuo to give **49** (0.95 g, 80 %) as colourless gum. $[\alpha]_D^{28}$= +90.2 (*c* 0.45, MeOH); R_f 0.5 (1/4 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (5/45, v/v); IR (Neat): 3021, 2927, 2858, 2365, 1360, 1176, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36- 7.34 (m, 10H), 5.06 (d, 1H, J = 10.9), 4.98- 4.72 (m, 2H), 4.67- 4.63 (m, 2H), 4.47 (t, 1H, J = 9.5), 4.06- 3.94 (m, 2H), 3.82- 3.72 (m, 1H), 3.42 (s, 3H), 2.86 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 137.6, 128.5, 128.4, 128.1, 127.7, 97.2, 80.3, 78.8, 78.1, 75.4, 73.3, 70.2, 62.1, 55.1, 38.5, 25.8, 18.2, -5.4; MS (ESI): m/z 589 (M^++Na). Anal. Calcd for $C_{28}H_{42}O_8SSi$: C, 59.34; H, 7.47; Found: C, 59.39; H, 7.51.

(2*R*,3*R*,4*R*,5*R*,6*S*)-4,5-bis(benzyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2H-pyran-3-yl methanesulfonate 50:

To a cooled solution of **49** (0.86 g, 1.52 mmol) in dry THF (25 mL), solution of TBAF (1.0M in THF, 0.56 mL) was added, and allowed to stir for 30 min. After completion of the reaction, mixture was concentrated in vacuo; the residue was diluted with ethyl acetate. The combined organic layer was washed with water followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to colourless oil, which on column chromatographic purification gave the pure compound **50** as white gum (0.64 g, 95 %). $[\alpha]_D^{28}$= +77.5 (*c* 0.6, MeOH); R_f 0.3 (1.5:3.5 EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (15/35, v/v); IR (Neat): 3488, 2921, 2365, 1458, 1354, 1172, 1099, 1039, 954, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 10H), 5.08 (d, 1H, J = 16.7), 4.78- 4.61 (m, 4H), 4.47 (t, 1H, J = 14.3), 4.04 (t, 1H, J = 14.3), 3.95- 3.88 (m, 1H), 3.79- 3.68 (m, 2H), 3.59 (dd, 1H, J = 14.2, 5.3), 3.37 (s, 3H), 2.79 (s, 3H), 2.52 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 137.4, 128.5, 128.4, 128.2, 127.8, 127.7, 97.6, 80.1, 78.4, 77.6, 75.6, 73.2, 69.5, 60.3, 55.4, 38.2. MS (ESI): m/z 475 (M^++Na). Anal. Calcd for $C_{22}H_{28}O_8S$: C, 58.39; H, 6.24; Found: C, 58.45; H, 6.30.

((2*S*,3*R*,4*S*)-3,4-bis(benzyloxy)-2-methoxy-3,4-dihydro-2H-pyran-6-yl)methanol 52:

To the solution of **51** (0.58 g, 1.63 mmol) in methanol (15 mL) at 0 °C was added $NaBH_4$ (0.09 g, 2.29 mmol) and stirred at room temperature. After completion of reaction (TLC control, 30 min.), 5 mL of acetone was added to neutralize excess $NaBH_4$. The solvent was then concentrated to dryness to give the residue that was dissolved in ethyl acetate (15 mL) and was washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil. Crude product was purified by column chromatography to yield compound **52** (0.54 g, 94%) as a white gum. $[\alpha]_D^{28}$= +21.5 (*c* 1.5, $CHCl_3$); R_f 0.5 (1:1, EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (12.5/37.5, v/v); IR (Neat): 3428, 2920, 2366, 1682, 1454, 1094, 745, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38- 7.21 (m, 10H), 4.99 (d, 1H, *J* = 2.9), 4.82 (d, 1H, *J* = 2.2), 4.75 (d, 1H, *J* = 1.5), 4.59 (s, 2H), 4.17-4.15 (m, 1H), 3.99 (s, 2H), 3.76- 3.73 (m, 1H), 3.48 (s, 3H), 2.12 (s, 1H); MS (ESI): *m/z* 379 (M^++Na). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79; Found: C, 70.82; H, 6.85.

(2*S*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-methoxy-6-(4-methoxybenzyl)hexahydrofuro[3,4-c]pyrano[2,3-d]isoxazol-7(9H)-one 53:

As described for **19**, compound **53** was prepared from compound **52** (0.35 g, 0.98 mmol), **11** (0.41 g, 1.97 mmol), PyBroP (0.92 g, 1.97 mmol), DIPEA (0.68 mL, 3.95 mmol) and DMAP (0.13 g, 1.08 mmol). Crude product was purified by column chromatography to yield compound **53** (0.07 g, 62%) as a white solid. R_f 0.4 (4:1, EtOAc:Hexane). Eluent for column chromatography: EtOAc/Hexane (32/18, v/v); IR (Neat): 3010, 2930, 1754, 1678, 1603, 1510, 1452, 1256, 1031, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.23- 8.18 (m, 2H), 7.32-7.31 (m, 10H), 6.92- 6.88 (m, 2H), 5.08 (d, 1H, *J* = 4.4), 4.81 (d, 1H, *J* = 3.6), 4.73 (d, 2H, *J* = 2.6), 4.69 (s, 2H), 4.60-4.59 (m, 1H), 4.35 (d, 1H, *J* = 8.8), 4.20- 4.15 (m, 1H), 3.81 (m, 3H), 3.76 (m, 2H), 3.41 (s, 3H). ^{13}C (75MHz, $CDCl_3$): δ 165.3, 161.5, 160.9, 159.0, 145.9, 138.1, 137.9, 136.9, 130.8, 129.7, 129.1, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 122.8, 114.2, 114.0, 113.8, 101.8, 99.4, 77.6, 76.9, 76.4, 75.8, 73.0, 72.9, 71.4, 67.3, 64.4, 56.6, 55.3, 55.2, 41.5 ; MS (ESI): *m/z* 570 (M^++Na). Anal. Calcd for $C_{31}H_{33}NO_8$: C, 67.99; H, 6.07; N, 2.56; Found: C, 67.91; H, 6.12; N, 2.62.

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Notes and references

CDRI communication no xx

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Linearization of carbohydrate derived polycyclic frameworks

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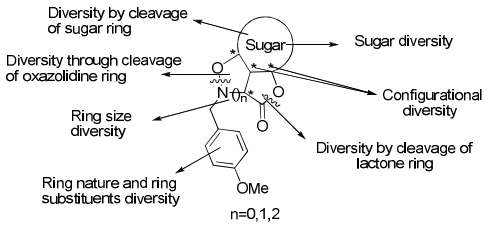

We report an easy access to carbohydrate derived diverse tricyclic skeletons which could be beneficial for exploring polyfunctionalized chiral alicycles.