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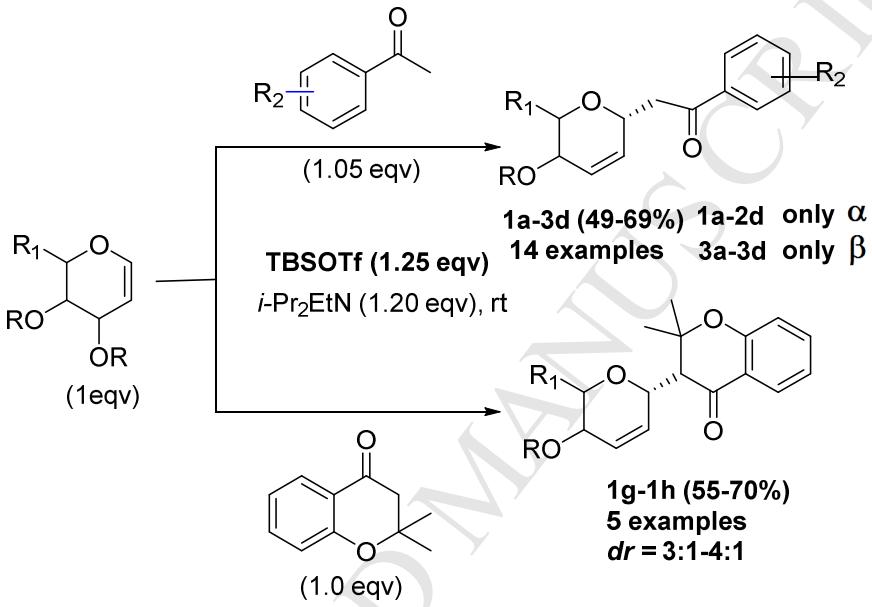

- ✓ TBSOTf acts both as glycosylating and silylating agent
- ✓ *In situ* silylenol ether formation
- ✓ Avoidance of hazardous alkyl lithiums as strong base and cryogenic condition
- ✓ Highly stereoselective glycosylation
- ✓ Application in the syntheses of chromanone-3-*C*-glycosides

One-pot Mukaiyama type carbon-Ferrier rearrangement of glycals: Application in the syntheses of chromanone 3-*C*-glycosides

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A B S T R A C T

One-pot carbon-Ferrier rearrangement of glycals with unactivated aryl methyl ketones has been developed under mild Silyl triflate catalysis. Keto methyl group of various aryl methyl ketones without being converted into silyl enol ether could directly attack anomeric position of glycals to form keto functionalized *C*-glycosides in moderate to good yields with high α-selectivity. The versatility of this method has been extended to the synthesis of a small library of chromanone 3-*C*-glycosides.

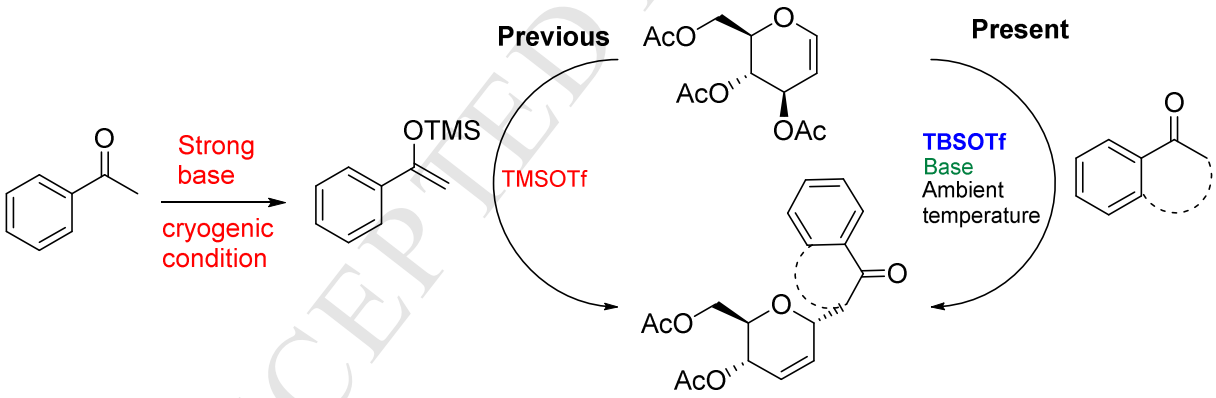
Key Words

Carbon-Ferrier rearrangement, chromanone 3-*C*-glycosides, acetophenones, 2,3-unsaturated glycosides, Lewis acid, glycopyranosides

1. Introduction

The Ferrier rearrangement involves a reaction of suitably protected 1,2-glycals with nucleophiles under Lewis acid catalysis to form the corresponding 2,3-unsaturated glycosides after concomitant loss of a substituent at C-3.[1] The carbon-Ferrier rearrangement utilizes carbon nucleophiles such as allylsilanes,[2] silyl cyanides,[3] silyl ketene acetals,[4] olefins,[5] aromatic

nucleophiles,[6] unactivated alkynes,[7] isocyanides,[8] etc, in the presence of a Lewis acid catalyst to form the corresponding 2,3-unsaturated glycosides. When α-methylene carbons of ketones have been used as carbon nucleophiles for carbon-Ferrier reaction, their downstream glycosides can be served as intermediates in the synthesis of a large number of biologically important natural products such as Aspergillide,[9] Quercetin,[10] Myricetin,[11] Kampferol,[12] etc. Generally, ketones with α-methylene groups are converted into corresponding silyl enol ether which then undergo carbon-Ferrier rearrangement under various Lewis acids such as BF_3-Et_2O,[13] TFA,[14] TMSOTf, [15] $LiClO_4$,[16] $Yb(OTf)_3$,[17,18] H_3PO_4,[19] iodinium catalyst,[20] $InCl_3$,[21] $FeCl_3$,[22] $HClO_4$,[23] etc. Although an efficient protocol for *C*-glycosylation, the major drawback of the above methods lies in the preparation of silyl enol ether which in many cases requires hazardous reagents like alkyl lithiums, [24] under cryogenic conditions (Scheme 1). It is therefore desirable to have a direct method where α–carbon of ketone can directly attack anomeric carbon in carbon-Ferrier rearrangement via *in situ* generated silyl enol ether (Scheme1). With our interest in *C*-glycosylation using glycals,[25] herein we report a one pot carbon-Ferrier reaction with aryl methyl ketones and its application in the synthesis of chromanone *C*-glycosides.



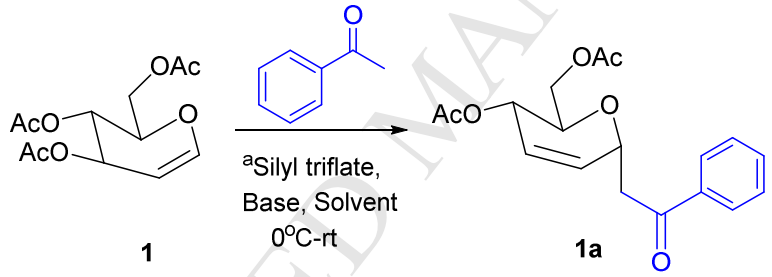
Scheme1: Synthesis of α-keto functionalized glycopyranosides

TMSOTf is a common and readily available silyl triflate used extensively in organic syntheses, [26, 27]. Downey et al. have used a combination of TMSOTf and DIPEA for a variety of reactions e.g. Mukaiyama aldol reaction, addition of catalytically generated zinc acetylides to aldehydes or N-phenyl nitrones, addition of acetylides as wells as thiols to benzylic methyl ethers and dimethyl acetals.[28]

2. Result and discussion

In order to develop an optimum procedure for the carbon-Ferrier rearrangement, we first tried the conditions as per a reported method.[29] When Lewis acid (0.1 eqv.) and base (0.2 eqv.) was used we got very poor yield of about 20% of the desired product. The yield was abruptly increased when TBSOTf was examined as silyl triflate in the presence of *i*Pr_2NEt as amine base in DCM instead of acetonitrile. After experimenting with silyl triflate, bases and solvents we obtained a condition where starting material 3,4,6-tri-*O*-acetyl-D-glucal (**1)** was completely consumed. The reaction proceeded smoothly in 30 minutes and exclusively furnished the required product, **1a** with a satisfactory yield up to 68%. Prolonging the reaction time resulted in the degradation of the products. The results are summarized in the Table 1 below. Use of TBSOTf (1.25 eqv.), *i*-Pr_2NEt (1.20 eqv.) in DCM (5ml/mmol) as solvent (Table 1, entry 6) was found to be optimum for the transformation.

Table.1 Optimization of *C*-glycosylation



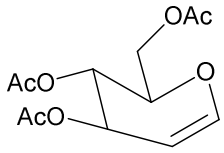
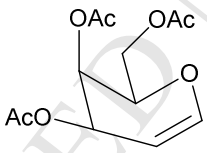
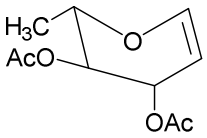
1 1a

Entry	Silyl triflate (eqv.)	Base (eqv.)	Solvent	Yield[b] (%)
1.	TMSOTf (0.1)	*i*-Pr_2NEt (0.2)	DCM	20
2.	TMSOTf (0.2)	Et_3N (0.1)	CH_3CN	22
3.	TMSOTf (1)	Et_3N (0.5)	CH_3CN	25
4.	TMSOTf (1.0)	Et_3N (1.0)	CH_3CN	33
5.	TBSOTf (1.25)	Et_3N(1.20)	DCM	55
6.	TBSOTf (1.25)	*i*Pr_2NEt(1.20)	DCM	68

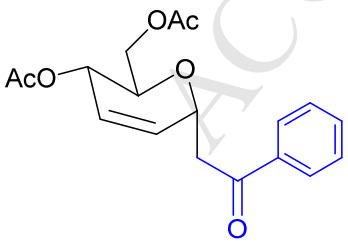
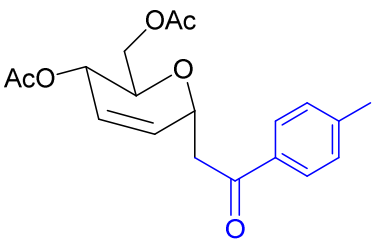
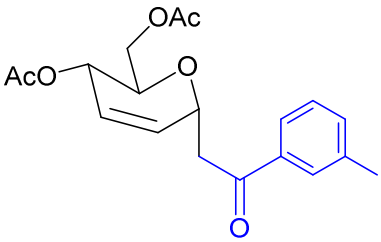
[a]Glucal (1.0 eqv.), Acetophenone (1.05 eqv.), solvent (5 mL/mmol of glucal). [b]Isolated yields after column chromatography.

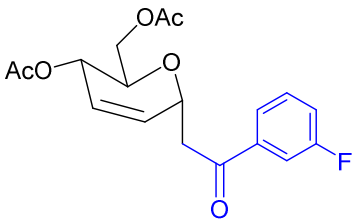
With the optimized condition at our disposal, the generality of the method was established by reacting a series of substituted acetophenones and protected glycals to provide the desired glycosides in moderate to good yields (Table 2). In general, reaction times for L-rhamnal diacetate (**3**) were found to be lower than that of D-glucal triacetate (**1)** and D-Galactal triacetate (**2**). The Ferrier products (**1a-2d)** obtained from D-sugars were α–C glycosides while the products **(3a-3d)** derived from L-sugars were β which is in agreement with the earlier reports.[30] The cause of stereoselectivity probably depends on the stereochemistry of the substituent at C3 of glycal.[30a] ^{1}H NMR spectra of the synthesized products were compared with values reported in the literature.[31]

Table-2: Condensation of glycals with substituted acetophenone under optimized condition[a]

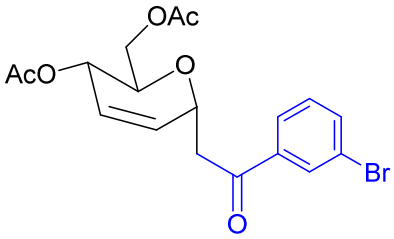
Glycals[b]		
		
1	**2**	**3**

***C*-Glycopyranosides[c]**

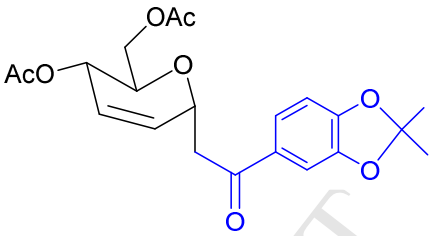
		
1a 66%	**1b** 55%	**1c** 56%



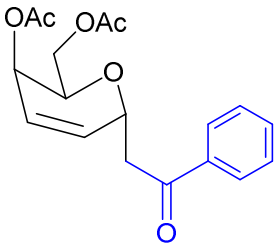
1d 67 %



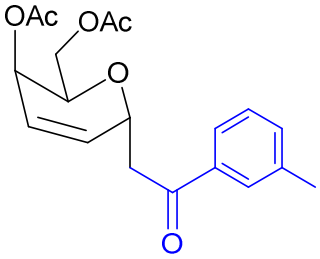
1e 68%



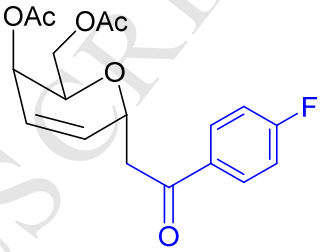
1f 60%



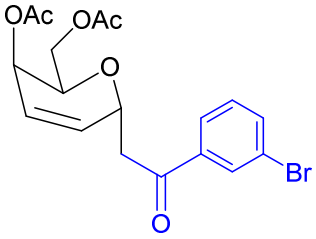
2a 69%



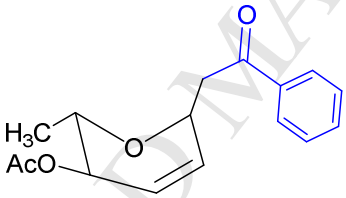
2b 60%



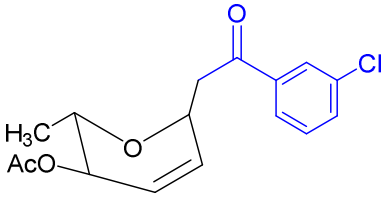
2c 66%



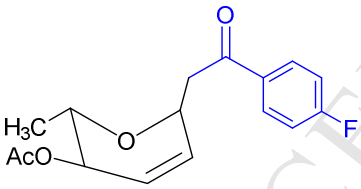
2d 69%

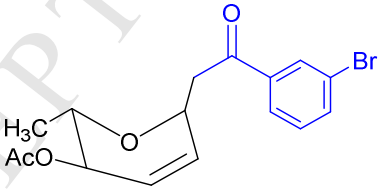


3a 49%



3b 53%



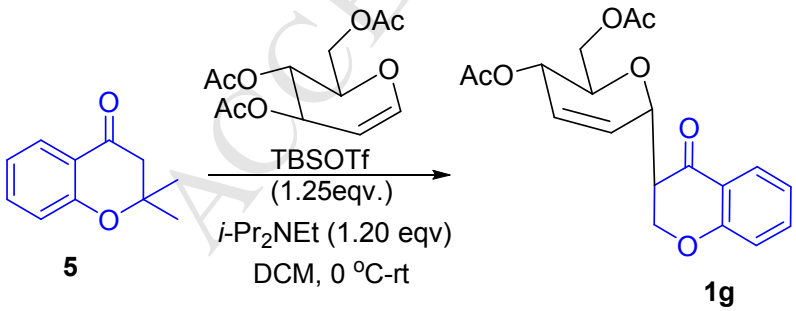


3c 59% **3d** 62%

[a]Reaction conditions: Sugar partner (1 eqv.), acetophenone (1.05 eqv.), TBSOTf (1.25 eqv.), *i*-Pr_2NEt (1.20 eqv.), DCM as solvent (5mL/mmol); [b]All *C*-glycosides derived from D-glucal triacetate and D-galactaltriacetate are α glycosides whereas L-rhamnal diacetate yielded exclusive β-glycosidic linkage; [c]Isolated yield after column chromatography.

After the successful scope studies by obtaining glycosylated acetophenones, we set forth for an application of our work to synthesize chromanone-*C*-3-glycosides. The most abundant flavonoid glycosides in plants are flavone *O/C*-glycosides. Among them the glycosides found typically in nature are 3- or 7-*O*-glycosides. But when biological activity is taken into consideration, *C*-glycosides have proven better than *O*-glycosides.[32] Hence we have made an effort for the synthesis of chromanone *C*-glycosides. In place of aryl methyl ketone (scheme-1) if chromanone can be incorporated, isoflavone-*C*-glycosides mimicking structures can be easily achieved. As reported Chromanone-*C*-glycoside is an important class of compounds widely distributed in nature[33] which plays variety of essential roles in the growth and development of plants.[34] They also posses miscellaneous biological activities such as antioxidant,[35] antidiabetic,[36] antinflammatory,[37] antibacterial and antifungal activities,[38] antitumour,[39] immunomodulatory activity,[40] etc. It is highly desirable to have practical methods for the synthesis of Chromanone-*C*-glycoside to be able to explore their potential as biologically active molecules; we have prepared a small library of chromanone-*C*-glycoside by using our method.

By following our strategy, synthesis of *C*-glycosides of chromanones can be accomplished by using Mukaiyama type reaction of 4-chromanone with glycals in one-pot where carbon-carbon bond formation takes place with glycoside precursors at various carbons of chromanones in a substituent-dependant manner. On this prospect, we reacted, 2,2-dimethyl-4-benzopyranone (**5)** with the glycal partner (**1**) keeping all other variables fixed under previously optimized condition (entry 6, Table 1), which afforded us a diastereomeric mixture **1g**. The ratio of isomers was calculated from crude NMR. Fortunately we were able to separate the major one from the mixture **1g** with a satisfactory yield (66%). (scheme2)

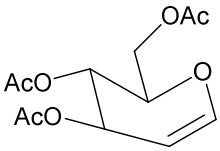


Scheme2: Synthesis of chromanone-3-*C*-glycoside

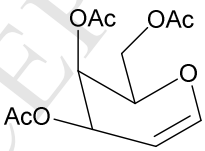
Spectroscopic analysis demoed the appearance of a new chemical shift at δ 2.76 (1H) and 62.12 (CH) with concomitant loss of the methylene signal at δ 2.73 (2H) and 48.36 (CH_2) respectively in ^{1}H and ^{13}C NMR for group signifying the attachment of sugar moiety at C3. Substrate scope for the chromanone-*C*-glycoside (Table 3) was done by taking four different sugar partners (**1a**, **1b**, **1c**, **1d** of Table 3) with three different chromanones (**5**, **6** & **7** of Table 3). It is pertinent to mention that all C-3 chromanone glycosides were obtained as mixture of diastereomers ratio of which were calculated from crude ^{1}H NMR and major diastereomers were purified through column. However when 7-methoxy group is attached to 4-chromanone, the glycal partner was coupled at C-6 position (**1h**) indicating the substituent effect. In case of 4-hydroxy coumarin (**7**), it was interesting to note that 0.25eqv. of TBSOTf was enough to catalyze the reaction and provide the product **1i** in 88% yield. Overall, the present methodology provides an easy access to the compounds like **1g**, **3e** and **1i** and analogs and derivatives thereof, their biological activities like anti-inflammatory, anti-cancer, anti-bacterial, anti-fungal, etc. will be evaluated and published elsewhere.

Table-3: Condensation of glycals with substituted Chromanones under optimized condition[a] to form *C*-glycopyranosides.

Glycals[b]



1



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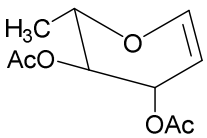

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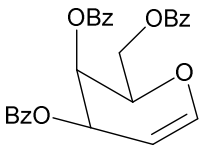
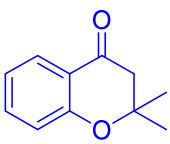
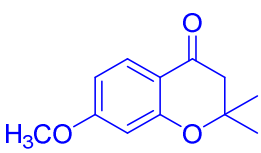
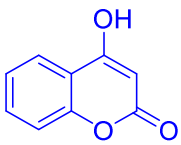


4

Chromanones

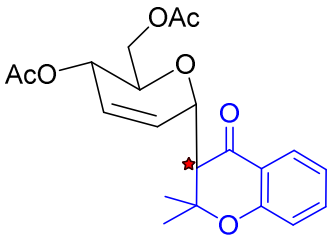




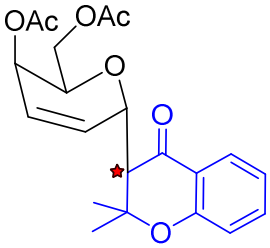


5	6	7

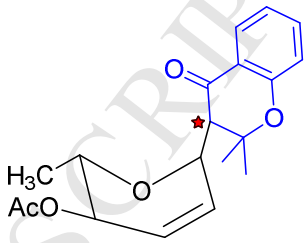
Chromanone *C*-glycosides[c]



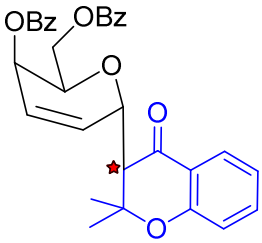
1g 66% *dr* =4:1



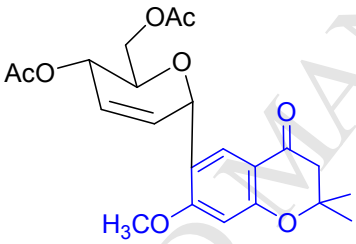
2e 68% *dr* =3:1



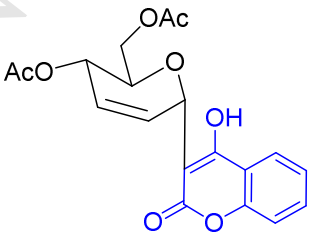
3e 67% *dr* =4:1



4a 55% *dr* =3:1



1h 70%



1i 88%

[a]Reaction conditions: Sugar partner (1.1 eqv.), Chromans (1.05 eqv.), TBSOTf (1.25 eqv.), *i*-Pr_2NEt (1.20 eqv.), reaction temperature 0-30°C, CH_2Cl_2 as solvent (5mL/mmol); [b]time taken for protected glucal and galactal was 30 min while for rhamnal it was 10 mins; [c]isolated yield after column chromatography, ★ epimers differ at this carbon atom, *dr*= diastereomeric ratio.

3. Conclusion

The modulation of traditional carbon-Ferrier rearrangement reaction was done by altering it to one pot Mukaiyama type carbon Ferrier rearrangement reaction avoiding hazardous strong bases. The carbon-Ferrier reaction was accomplished on unactivated aryl methyl ketones (acetophenones) to form different substituted pyranosides. The method was applied to the

chroman systems for the construction of some biologically active chroman C-glycosides. All the synthesized compounds are being evaluated for biological activities, results of which will be disclosed in due course.

4. Experimental

4.1. General information

Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Anhydrous CH_2Cl_2 was purified by passage through a bed of activated alumina. Analytical thin-layer chromatography was performed using silica gel plates. Visualization was accomplished with UV light. ^{1}H NMR spectra were recorded with a 500 MHz spectrometer or 300 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at δ = 7.28 ppm). Data are reported as [ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br= broad; coupling constant(s) in Hz; integration]. Proton-decoupled ^{13}C NMR spectra were recorded with a 125 MHz spectrometer or 75 MHz spectrometer, and are reported in ppm using solvent as an internal standard ($CDCl_3$ at δ = 77.0 ppm). Melting points were determined using a capillary melting point apparatus. The products were purified by column chromatography on silica gel (60-120/100-200/230-400 mesh) using petroleum ether–ethyl acetate as the eluent to obtain the pure products. Reagents used were mostly purchased from Sigma Aldrich if not mentioned otherwise.

(I) General information for the synthesis of glucopyranoside.

To an oven-dried 10-mL round-bottomed flask under N_2 was added CH_2Cl_2 (5.0 mL), Acetophenone/chromanone (1.0 mmol, 200 mg), *i*Pr_2NEt (234 µL, 1.20 mmol), TBSOTf (324 µL 1.25 mmol). After 20 min, protected sugar (1.1 mmol. 335 mg) was added at 0°C, and the mixture was stirred at room temperature for the indicated time. The reaction mixture was passed through a silica gel plug (1cm×5 cm) with Et_2O and was neutralized by aqueous $NaHCO_3$ solution. The Et_2O extract was removed by rotary evaporation. The product was purified by silica gel chromatography (10 to 15% EtOAc/ hexanes) from which only the major product was isolated. The spectral data of representative compounds are shown below.

(II) General information for the synthesis of *4-hydroxy coumarin-3C glycoside* (1i)

To an oven-dried 10-mL round-bottomed flask under N_2 was added CH_2Cl_{l2} (5.0 mL) 4-hydroxy coumarin (1.0 mmol, 200 mg), TBSOTf (48 μL 0.2mmol). After 20 min, protected sugar (1.1 mmol. 368 mg) was added at 0°C, and the mixture was stirred at room temperature for the indicated time. The reaction mixture was passed through a silica gel plug (1cm×5 cm) with Et_2O and was neutralized by aqueous $NaHCO_3$ solution. The Et_2O extract was removed by rotary evaporation. The product was purified by silica gel chromatography (10 to 15% EtOAc/ hexanes) and the major product was isolated. The spectral data of representative compounds are shown below.

4.2 Spectral Data:

4.2.1. 1-((4, 6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-phenylethanone (1a)

Prepared by the general procedure (I) using acetophenone (200 mg, 1.66 mmol.) *i*Pr_2NEt (348 μL, 1.99 mmol), TBSOTf (479 μL 2.07 mmol). Glucal triacetate (1.82 mmol. 498 mg) to obtain **1a** in 66 % (350 mg) yield, Colorless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 2H), 6.01 (d, *J* = 10.3 Hz, 1H), 5.83 – 5.72 (m, 1H), 5.07 (s, 1H), 4.87 (d, *J* = 1.9 Hz, 1H), 4.17 (dd, *J* = 11.9, 6.6 Hz, 1H), 4.06 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.92 (td, *J* = 6.3, 3.7 Hz, 1H), 3.40 (dd, *J* = 16.3, 7.1 Hz, 1H), 3.08 (dd, *J* = 16.3, 6.5 Hz, 1H), 2.02 (s, 3H), 1.95 (s, 3H).
[M+H]+; HRMS: Found m/z 332.1259 calcd. For $C_{18}H_{20}O_6$ (332.1260).

4.2.2. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-(4-methylyphenyl)-ethanone (1b)

Prepared by the general procedure (I) using 4'-methyl acetophenone (200 mg, 1.49 mmol.) *i*Pr_2NEt (311 μL, 1.78 mmol), TBSOTf (427 μL 1.86 mmol). Glucal triacetate (1.63 mmol. 446 mg) to obtain **1b** in 55 % (280 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 89:11),

^{1}H NMR (400 MHz, $CDCl_3$) 7.85 – 7.59 (m, 2H), 7.65 – 7.43 (m, 2H), 6.00 (ddd, *J* = 10.4, 2.4, 1.5 Hz, 1H), 5.83 – 5.69 (m, 1H), 5.08 (dd, *J* = 3.0, 1.5 Hz, 1H), 4.85 (m, 1H), 4.18 (dd, *J* = 11.9,

6.5 Hz, 1H), 4.06 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.92 (td, *J* = 6.3, 3.7 Hz, 1H), 3.50 – 3.30 (m, 1H), 3.06 (m, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H).

[M+H]+; HRMS: Found m/z 346.1414 calcd. For $C_{19}H_{22}O_6$ (346.1416).

4.2.3. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-(3-methylyphenyl)-ethanone (1c)

Prepared by the general procedure (I) using 3'-methylacetophenone (200 mg, 1.49 mmol.) *i*Pr_2NEt (311 µL, 1.78 mmol), TBSOTf (427 µL 1.86 mmol). Glucal triacetate (1.63 mmol. 446 mg) to obtain **1c** in 56 % (288 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 89:11),

^{1}H NMR (400 MHz, $CDCl_3$) 7.68 (d, *J* = 10.9 Hz, 2H), 7.30 (dt, *J* = 14.8, 7.5 Hz, 2H), 6.01 (ddd, *J* = 10.4, 2.4, 1.5 Hz, 1H), 5.86 – 5.69 (m, 1H), 5.05 (dd, *J* = 3.0, 1.5 Hz, 1H), 4.95 – 4.72 (m, 1H), 4.17 (dd, *J* = 11.9, 6.5 Hz, 1H), 4.08 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.91 (d, *J* = 3.6 Hz, 1H), 3.39 (m,1H), 3.05 (m, 1H), 2.36 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H).

[M+H]+; HRMS: Found m/z 346.1415 calcd. For $C_{19}H_{22}O_6$ (346.1416).

4.2.4. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-(3-fluorophenyl)-ethanone (1d)

Prepared by the general procedure (I) using4'-fluoroacetophenone (200 mg, 1.44 mmol.) *i*Pr_2NEt (300 µL, 1.72 mmol), TBSOTf (360 µL 1.80 mmol). Glucal triacetate (1.59 mmol. 432 mg) to obtain **1d** in 67 % (338 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 5.98 (ddd, *J* = 10.4, 2.4, 1.5 Hz, 1H), 5.78 (ddd, *J* = 10.4, 3.0, 2.1 Hz, 1H), 5.06 (ddd, *J* = 6.9, 3.3, 2.0 Hz, 1H), 4.83 (ddd, *J* = 8.8, 4.6, 2.2 Hz, 1H), 4.17 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.91 (td, *J* = 6.3, 3.8 Hz, 1H), 3.35 (m, 1H), 3.05 – 2.99 (m, 1H), 2.01 (s, 3H), 1.96 (s, 3H).

[M+H]+; HRMS: Found m/z 350.1163 calcd. For $C_{18}H_{19}FO_6$ (350.1166).

4.2.5. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-(3-bromophenyl)-ethanone (1e)

Prepared by the general procedure (I) using 4'-bromoacetophenone (200 mg, 1.00 mmol.) *i*Pr_2NEt (209 µL, 1.20 mmol), TBSOTf (287 µL 1.25 mmol). Glucal triacetate (1.11 mmol. 279 mg) to obtain **1e** in 68 % (278 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 92:08).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 5.97 (d, *J* = 0.8 Hz, 1H), 5.80 (s, 1H), 5.06 (ddd, *J* = 6.9, 3.3, 2.0 Hz, 1H), 4.83 (ddd, *J* = 8.8, 4.6, 2.2 Hz, 1H), 4.17 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.05 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.91 (td, *J* = 6.3, 3.8 Hz, 1H), 3.36 (m, 1H), 3.03 (m, 1H), 2.04 – 1.93 (m, 6H).
[M+H]+; HRMS: Found m/z 410.0363 calcd. For $C_{18}H_{19}BrO_6$ (410.0365).

4.2.6. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-1-(3,4-(2,2-dimethyl-1,3-dioxolo)phenyl)-ethanone (1f)

Prepared by the general procedure (I) using 3',4'-methylenedioxyacetophenone (200 mg, 1.21 mmol.) *i*Pr_2NEt (255 µL, 1.46 mmol), TBSOTf (347 µL 1.51 mmol). Glucal triacetate (1.33 mmol. 362 mg) to obtain **1f** in 60 % (273 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.94 (d, *J* = 26.9 Hz, 2H), 5.90 (d, *J* = 10.3 Hz, 1H), 5.68 (d, *J* = 10.3 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 4.75 (s, 1H), 3.94 (td, *J* = 6.3, 3.8 Hz, 1H), 3.80 – 3.59 (m, 1H), 3.29 – 3.17 (m, 1H), 2.92 (dd, *J* = 16.6, 7.4 Hz, 1H), 2.08 – 1.91 (m, 6H).
[M+H]+; HRMS: Found m/z 376.1155 calcd. For $C_{19}H_{20}O_8$ (376.1158).

4.2.7. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1-phenylethanone (2a)

Prepared by the general procedure (I) using acetophenone (200 mg, 1.66 mmol.) *i*Pr_2NEt (348 µL, 1.99 mmol), TBSOTf (479 µL 2.07 mmol). Galactal triacetate (1.82 mmol. 498 mg) to obtain **2a**gin 69 % (347 mg) yield, colorless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.73 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.11 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.96 (ddd, *J* = 10.2, 5.1, 2.1 Hz, 1H), 5.09 – 4.98 (m, 1H), 4.96 (t, *J* = 6.9 Hz, 1H), 4.22 – 4.03 (m, 3H), 3.51 – 3.33 (m, 1H), 3.11 – 2.91 (m, 1H), 2.01 (s, 3H), 1.91 (s, 3H).

[M+H]+; HRMS: Found m/z 332.1259 calcd. For $C_{18}H_{20}O_6$ (332.1260).

4.2.8. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1-(3-methylphenyl)-ethanone (2b)

Prepared by the general procedure (I) using 3'-methylacetophenone (200 mg, 1.49 mmol.) *i*Pr_2NEt (311 µL, 1.78 mmol), TBSOTf (427 µL 1.86 mmol). Galactal triacetate (1.63 mmol. 446 mg) to obtain **2b** in 60 % (309 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 89:11),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.3 Hz, 2H), 7.40 – 7.25 (m, 2H), 6.10 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.95 (ddd, *J* = 10.2, 5.2, 2.1 Hz, 1H), 5.04 (d, *J* = 4.7 Hz, 1H), 5.00 – 4.83 (m, 1H), 4.20 – 3.97 (m, 3H), 3.46 – 3.22 (m, 1H), 3.03 (dd, *J* = 16.1, 6.6 Hz, 1H), 2.34 (d, *J* = 3.9 Hz, 3H), 2.01 (s, 3H), 1.91 (s, 3H).

[M+H]+; HRMS: Found m/z 346.1414 calcd. For $C_{19}H_{22}O_6$ (346.1416).

4.2.9. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1-(4-fluorophenyl)-ethanone (2c)

Prepared by the general procedure (I) using4'-fluoroacetophenone (200 mg, 1.44 mmol.) *i*Pr_2NEt (300 µL, 1.72 mmol), TBSOTf (360 µL 1.80 mmol). Galactal triacetate (1.59 mmol. 432 mg) to obtain **2c** in 66 % (332 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.82 (m, 2H), 7.09 (td, *J* = 8.6, 1.9 Hz, 2H), 6.09 (m, 1H), 6.00 – 5.84 (m, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.94 (s, 1H), 4.13 (m, 3H), 3.39 – 3.29 (m, 1H), 3.01 (m, 1H), 2.01 (s, 3H), 1.91 (s, 3H).

[M+H]+; HRMS: Found m/z 350.1165 calcd. For $C_{18}H_{19}FO_6$ (350.1166).

4.2.10. 1-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1-(3-bromophenyl)-ethanone (2d)

Prepared by the general procedure (I) using 3'-bromoacetophenone (200 mg, 1.00 mmol.) *i*Pr_2NEt (209 µL, 1.20 mmol), TBSOTf (287 µL 1.25 mmol). Galactal triacetate (1.11 mmol. 279 mg) to obtain **2d** in 69 % (282 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 93:07),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.22 – 5.99 (m, 1H), 5.96 (ddd, *J* = 10.2, 5.0, 1.8 Hz, 1H), 5.03 (t, *J* = 5.8 Hz, 1H), 4.93 (t, *J* = 6.6 Hz, 1H), 4.16 – 3.97 (m, 3H), 3.33 (m, 1H), 3.12 – 2.92 (m, 1H), 2.01 (s, 3H), 1.92 (s, 3H).
[M+H]+; HRMS: Found m/z 410.0361 calcd. For $C_{18}H_{19}BrO_6$ (410.0365).

4.2.11. 1-((4-*O*-acetyloxy-5-methyl)-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-1-phenylethanone (3a)

Prepared by the general procedure (I) using acetophenone (200 mg, 1.66 mmol.) *i*Pr_2NEt (348 µL, 1.99 mmol), TBSOTf (479 µL 2.07 mmol). Rhamnal diacetate (1.82 mmol. 389 mg) to obtain **3a** in 49 % (223 mg) yield, Whitish, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.83 (m, 2H), 7.66 – 7.54 (m, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 6.08 (ddd, *J* = 10.3, 2.1, 1.2 Hz, 1H), 5.85 (ddd, *J* = 10.4, 3.5, 2.0 Hz, 1H), 5.02 – 4.82 (m, 2H), 4.03 – 3.84 (m, 1H), 3.47 (m, 1H), 3.16 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.10 (d, *J* = 3.5 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H). [M+H]+; HRMS: Found m/z 274.1203 calcd. For $C_{16}H_{18}O_4$ (274.1205).

4.2.12. 1-((4-*O*-acetyloxy-5-methyl)-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-1-(3-chlorophenyl)-ethanone (3b)

Prepared by the general procedure (I) using 3'-chloroacetophenone (200 mg, 1.49 mmol.) *i*Pr_2NEt (310 µL, 1.78 mmol), TBSOTf (427 µL 1.86 mmol). Rhamnal diacetate (1.63 mmol. 348 mg) to obtain **3b** in 53 % (227 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 93:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.65 (m, 2H), 7.38 (dt, *J* = 14.8, 7.5 Hz, 2H), 6.07 (ddd, *J* = 10.3, 2.1, 1.3 Hz, 1H), 5.84 (ddd, *J* = 10.4, 3.5, 2.1 Hz, 1H), 5.03 – 4.66 (m, 2H), 4.01 – 3.84 (m, 1H), 3.58 – 3.25 (m, 1H), 3.14 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.43 (s, 3H), 2.10 (d, *J* = 3.7 Hz, 3H), 1.34 – 1.11 (m, 3H).
[M+H]+; HRMS: Found m/z 288.1360 calcd. For $C_{17}H_{20}O_4$ (288.1362).

4.2.13. 1-((4-*O*-acetyloxy-5-methyl)-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-1-(4-fluorophenyl)-ethanone (3c)

Prepared by the general procedure (I) using4'-fluoroacetophenone (200 mg, 1.44 mmol.) *i*Pr_2NEt (300 µL, 1.72 mmol), TBSOTf (360 µL 1.80 mmol). Rhamnal diiacetate (1.59 mmol. 342 mg) to obtain **3c** in 59 % (248 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.25 – 6.95 (m, 2H), 6.10 – 5.99 (m, 1H), 5.84 (ddd, *J* = 10.3, 3.4, 2.0 Hz, 1H), 4.97 – 4.78 (m, 2H), 4.03 – 3.82 (m, 1H), 3.41 (m, 1H), 3.10 (m, 1H), 2.09 (d, *J* = 2.7 Hz, 3H), 1.24 (t, *J* = 11.3 Hz, 3H).
[M+H]+; HRMS: Found m/z 292.1109 calcd. For $C_{16}H_{17}FO_4$ (292.1111).

4.2.14. 1-((4-*O*-acetyloxy-5-methyl)-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-1-(3-bromophenyl)-ethanone (3d)

Prepared by the general procedure (I) using 3'-bromoacetophenone (200 mg, 1.00 mmol.) *i*Pr_2NEt (209 µL, 1.20 mmol), TBSOTf (287 µL 1.25 mmol). Rhamnal diacetate (1.11 mmol. 238 mg) to obtain **3d** in 62 % (254 mg) yield, colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 92:08),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.60 (m, 2H), 7.60 – 7.46 (m, 2H), 5.97 (ddd, *J* = 10.3, 2.1, 1.2 Hz, 1H), 5.77 (ddd, *J* = 10.3, 3.6, 2.0 Hz, 1H), 4.96 – 4.66 (m, 2H), 3.86 (dd, *J* = 6.5, 4.5 Hz, 1H), 3.58 – 3.15 (m, 1H), 3.02 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.02 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H).
[M+H]+; HRMS: Found m/z 352.0308 calcd. For $C_{16}H_{17}BrO_4$ (352.0310).

4.2.15. 3-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-2,2-dimethyl-4-chromanone (1g)

Prepared by the general procedure (I) using 2,2-dimethylchroman-4-one (200 mg, 1.13 mmol.) *i*Pr_2NEt (237 µL, 1.36mmol), TBSOTf (324 µL 1.41 mmol), Glucaltriacetate (1.25 mmol., 340 mg) to obtain **1g** in 66 % (291 mg) yield, (*dr* =4:1), major isomer isolated (53%= 233 mg). colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 88:12),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.56 – 7.33 (m, 1H), 7.04 – 6.77 (m, 2H), 6.10 – 5.97 (m, 1H), 5.95 – 5.80 (m, 1H), 5.05 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.77 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.14 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.86 (ddd, *J* = 9.3, 8.8, 3.5 Hz, 2H), 2.77 (d, *J* = 5.6 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H) 1.56 (s, 3H), 1.44 (s, 3H).

^{13}CNMR (126MHz, $CDCl_3$) δ190.4, 69.5, 168.1, 157.5, 134.1, 129.9, 124.6, 122.0, 119.0, 119.0, 116.5, 78.2, 69.1, 67.3, 62.3, 60.4, 56.8, 24.1, 23.8, 19.3, 19.1.

[M+H]+; HRMS: Found m/z 388.1520 calcd. For $C_{21}H_{24}O_7$ (388.1522).

4.2.16. 3-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-2,2-dimethyl-4-chromanone (2e)

Prepared by the general procedure (I) using 2,2-dimethylchroman-4-one (200 mg, 1.13 mmol.) *i*Pr_2NEt (237 µL, 1.36mmol), TBSOTf (324 µL 1.41 mmol), Galactaltriacetate (1.25 mmol., 340 mg) to obtain **2e** in 68 % (300 mg) yield, (*dr* =3:1), major isomer isolated (51 %= 225 mg). colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 89:11),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 – 7.31 (m, 1H), 6.89 (m, 2H), 5.90 (ddd, *J* = 10.2, 5.3, 2.2 Hz, 1H), 5.53 (dd, *J* = 10.3, 3.1 Hz, 1H), 5.07 – 4.89 (m, 1H), 4.71 (dd, *J* = 4.6, 2.8 Hz, 1H), 4.13 (m, 2H), 2.63 (d, *J* = 7.6 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H),1.58 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 170.2, 170.3, 158.8, 136.7, 132.4, 126.8, 123.5, 120.7, 120.0, 117.8, 81.2, 69.3, 68.3, 63.0, 62.6, 57.0, 29.8, 25.9, 25.6, 20.6.

[M+H]+; HRMS: Found m/z 388.1519 calcd. For $C_{21}H_{24}O_7$ (388.1522).

4.2.17. 3-((4-*O*-acetyl-5-methyl)-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranosyl)-2,2-dimethyl-4-chromanone (3e)

Prepared by the general procedure (I) using 2,2-dimethylchroman-4-one (200 mg, 1.13 mmol.) *i*Pr_2NEt (237 µL, 1.36mmol), TBSOTf (324 µL 1.41 mmol), rhamnal diacetate (1.25 mmol., 267 mg) to obtain **3e** in 67 % (255 mg) yield, (*dr*=1:4), major isomer isolated (53.5 %= 204 mg). colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.66 (m, 1H), 7.45 – 7.33 (m, 1H), 7.02 – 6.75 (m, 2H), 5.86 – 5.43 (m, 2H), 4.99 – 4.57 (m, 2H), 3.80 (m, 1H), 3.47 (dd, *J* = 8.7, 6.2 Hz, 1H), 2.67 (d, *J* = 6.6 Hz, 1H), 2.00 (d, *J* = 6.5 Hz, 3H), 1.18 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.0, 170.7, 158.9, 136.0, 131.4, 126.7, 124.7, 120.9, 120.5, 118.2, 81.5, 73.1, 72.7, 67.4, 58.7, 25.7, 24.5, 18.3, 16.9.

[M+H]+; HRMS: Found m/z 330.1465 calcd. For $C_{19}H_{22}O_5$ (330.1467).

4.2.18. 3-((4,6-Di-benzoyloxy)-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-2,2-dimethyl-4-chromanone (4a)

Prepared by the general procedure (I) using 2,2-dimethylchroman-4-one (200 mg, 1.13 mmol.) *i*Pr_2NEt (237 µL, 1.36mmol), TBSOTf (324 µL 1.41 mmol), Galactaltribenzoate (1.25 mmol., 573 mg) to obtain **4a** in 55 % (320 mg) yield, (*dr*=3:1), major isomer isolated (41.2 %= 240 mg). colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 87:13),

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (t, *J* = 7.4 Hz, 4H), 7.82 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (m , 7H), 7.10 – 6.88 (m, 2H), 6.13 (ddd, *J* = 10.2, 5.2, 2.2 Hz, 1H), 5.67 (dd, *J* = 10.3, 3.2 Hz, 1H), 5.44 (dd, *J* = 5.0, 1.8 Hz, 1H), 4.99 – 4.82 (m, 1H), 4.67 (dd, *J* = 10.9, 6.8 Hz, 1H), 4.56 – 4.42 (m, 2H), 2.75 (d, *J* = 7.4 Hz, 1H), 1.63 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 166.1, 165.9, 159.2, 136.5, 133.2, 133.1, 132.6, 129.7, 129.6. 129.6, 128.4, 126.6, 123.2, 121.0, 120.2, 118.2, 81.0, 69.4, 69.0, 64.1, 63.3, 57.6, 26.2, 25.3.

[M+H]+; HRMS: Found m/z 512.1833 calcd. For $C_{31}H_{28}O_7$ (512.1835).

4.2.19. 6-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-7-methoxy-2,2-dimethyl-4-chromanone (1h)

Prepared by the general procedure (I) using 7-methoxy-2,2-dimethylchroman-4-one (200 mg, 0.97mmol.) *i*Pr_2NEt (202 µL, 1.16mmol), TBSOTf (278 µL 1.21 mmol), Glucaltriacetate (1.06 mmol., 291 mg) to obtain **1h** in 70 % (284 mg). Colorless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 90:10),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.30 (s, 1H), 5.81 (dt, *J* = 10.3, 1.6 Hz, 1H), 5.76 – 5.63 (m, 1H), 5.45 (d, *J* = 1.5 Hz, 1H), 5.38 – 5.26 (m, 1H), 4.25 (m, 1H), 4.13 (m, 1H), 3.98 (m, 1H), 3.87 – 3.70 (m, 3H), 2.58 (s, 2H), 2.03 (d, *J* = 3.3 Hz, 6H), 1.37 (d, *J* = 3.9 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8, 171.0, 170.2, 162.8, 161.7, 131.9, 126.5, 124.7, 122.2, 113.7, 99.3, 79.7. 74.9, 70.8, 65.2, 63.5, 55.8, 48.4, 26.6, 26.5, 21.0, 20.8.
[M+H]+; HRMS: Found m/z 418.1626 calcd. For $C_{22}H_{26}O_8$ (418.1628).

4.2.20. 3-((4,6-Di-*O*-acetyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)coumarin (1i)

Prepared by the general procedure (II) using 4-hydroxy-2H-chromen-2-one (200 mg, 0.81 mmol.), TBSOTf (37 µL 0.2 mmol), Glucaltriacetate (0.89 mmol., 243 mg) to obtain **1i** in 68 % (206 mg) yield, (*dr* =4:1), major isomer isolated (68 %= 165 mg). colourless liquid, R_f = 0.5 (petroleum ether/ethyl acetate = 65:35),
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.89 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.68 – 7.37 (m, 1H), 7.29 (m, 2H), 6.02 – 5.85 (m, 1H), 5.40 – 5.16 (m, 1H), 4.94 (dd, *J* = 10.4, 2.7 Hz, 1H), 4.50 – 4.29 (m, 2H), 4.29 – 4.12 (m, 2H), 2.15 (d, *J* = 2.7 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 170.0, 162.4, 161.5, 152.9, 132.2, 123.9, 123.3, 116.4, 116.1, 101.9, 73.5, 72.6, 72.4, 69.0, 62.2, 57.4, 20.9, 20.7.
[M+H]+; HRMS: Found m/z 374.1000 calcd. For $C_{19}H_{18}O_8$ (374.1002).

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Highlights:

- ✓ Use of TBSOTf for highly stereoselective *C*-glycosylation
- ✓ Syntheses of chromanone-3-*C*-glycosides