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CONVERTIBLE FORMATION OF DIFFERENT GLYCOSIDE USING MOLECULAR IODINE

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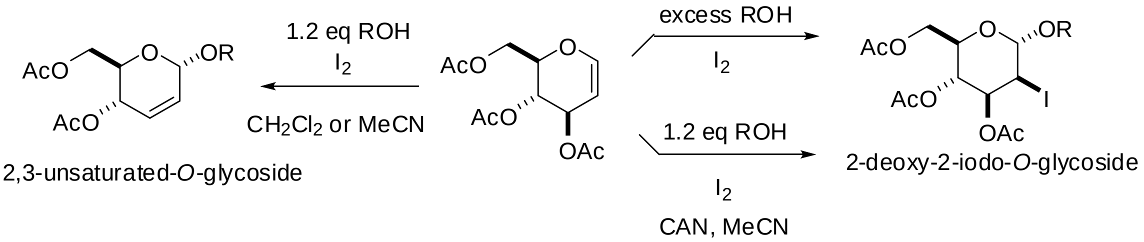
Abstract – The observation of convertible formation between 2-deoxy-2-iodo-*O*-glycosides and 2,3-unsaturated glycoside was described. The selective formation of 2-deoxy-2-iodo-*O*-glycosides was found from the reaction of D-glucal with iodine in the excess alcohol acceptor or the addition of ceric ammonium nitrate as additive while the addition of a stoichiometric amount of alcohol in solvent favored 2,3-unsaturated glycosides formation.

INTRODUCTION

Development a new and convenient method for glycosylation is one of the most fundamental research targets in carbohydrate chemistry.[1] Until now, much attention has been paid to the glycosylation of D-glucal with various nucleophiles leading to 2,3-unsaturated glycoside by Ferrier reactions[2] whereas the synthesis of 2-deoxy-2-haloglycoside is still limited. Recently, the haloglycoside, especially 2-deoxy-2-iodoglycosides have been used as imaging agent DIG (2-deoxy-2-iodo-D-glucose) in the radiopharmaceutical[3] area and proven to be versatile precursor for the synthesis of 2-deoxyglycosides[4,5] which are important structure components in many biological active compounds.[6] The synthesis of these glycosides have been reported by glycosylation of glucals and nucleophiles using I^+ equivalent reagents such as iodonium-*sym*-collidine perchlorate,[7] *N*-iodosuccinimide,[8] hypervalent iodine,[9] polymer-supported iodate reagent,[10] NaI/CAN/HOAc[11] and recently $NH_4I/H_2O_2/Ac_2O$.[12] In our study on glycosylation reaction, we found that iodine can be used as catalyst to produce acetylene-*C*-glycoside.[13] Since iodine[14] is an inexpensive, commercial available, efficient, and environmentally benign reagent, it was recently used by Yadav[15] and Koreeda[16] to produce 2,3-unsaturated glycoside via Ferrier mechanism. In the course of developing new glycosylation method using versatile reagent, we investigated the reaction of D-glucal and acceptor alcohols with iodine as a promoter and found to our surprise that different reaction conditions predominantly led to the formation of different glycosides. Herein, we reported the observation of selective synthesis of 2-deoxy-2-iodoglycoside from D-glucal using iodine in the excess of alcohol acceptor or addition of additive whereas the addition of a stoichiometric amount of alcohol in dichloromethane or acetonitrile favored Ferrier rearrangement leading to the selective formation of 2,3-unsaturated glycosides (Scheme 1).

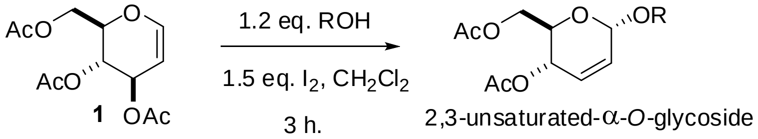


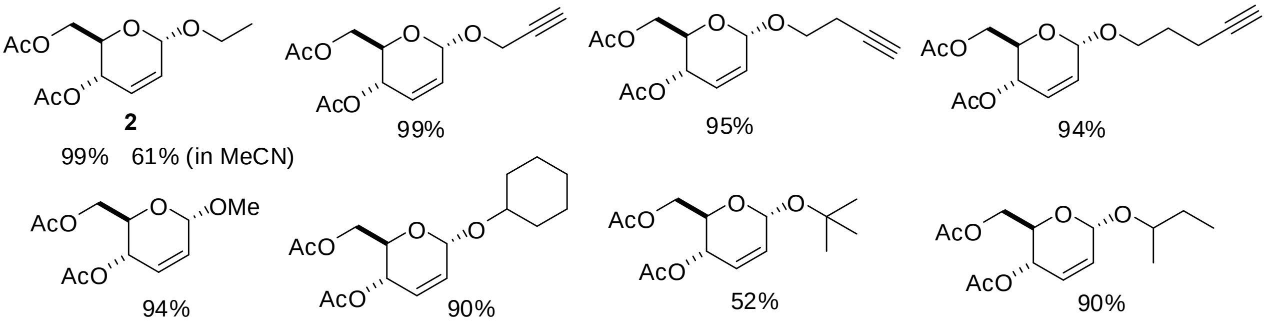
Scheme 1

RESULTS AND DISCUSSION

During investigation reaction of D-glucal using modified Koreeda's method which was performed by conducting the reaction in the presence of a stoichiometric amount of iodine and alcohol in CH_2Cl_2, we found that α-anomer of 2,3-unsaturated-*O*-glycosides was isolated as the sole product in excellent yield except in the case of hindered alcohol *t*-BuOH as shown in Table 1. There was no need to exclude air and moisture form this reaction and the yield for glycoside **2** decreased when acetonitrile was replaced by dichloromethane.

Table 1. Synthesis of 2,3-unsaturated-*O*- glycosides[a] using iodine in the presence of CH_2Cl_2

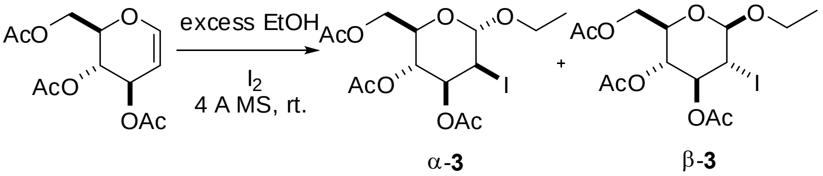




[a] α-anomer was obtained in all cases.

Keeping the iodine and solvent composition fixed, glycoside **2** was observed as a minor product in the glycosylation using 10 eq. of ethanol. On the other hand, 2-deoxy-2-iodoglycoside was obtained as the sole product instead of the expected glycoside **2**, when we carried out the reaction with excess ethanol in the absence of solvent. Encourage by this observation, conditions to effect the selective formation of 2-deoxy-2-iodoglycoside were further studied using ethanol as a model acceptor and the results are summarized in Table 2. Treatment of D-glucal with iodine (1.5 eq.) for 6 h in excess ethanol produced glycoside **3** in moderate yield (entry 1). The reaction was the most effective to promote optimum yield when it was performed within 1 h under iodine 2.5 eq. providing **3** in 83% (entry 5). However, an increase in reaction time decreased the yield of this transformation (entry 4). Based on these results, the condition in entry 5 was chosen as a general procedure for selective synthesis of 2-deoxy-2-iodo-*O*-glycosides.

Table 2 Optimization of conditions for the synthesis of 2-deoxy-2-iodo-*O*-glycoside



α-**3** β-**3**

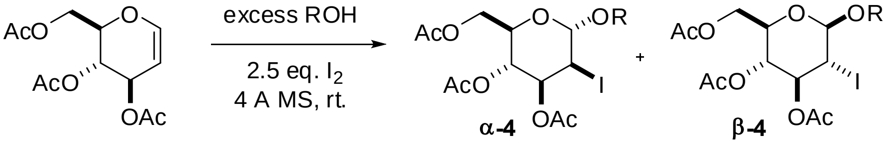
entry	Iodine (eq.)	Time (h)	Yield (%) (α:β)[a]
1	1.5	6	46 (6:1)
2	5.0	2	76 (7:1)
3	2.5	3	79 (6:1)
4	2.5	6	10 (5:1)
5	2.5	1	83 (6:1)

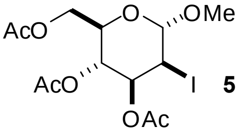
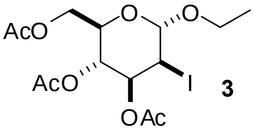
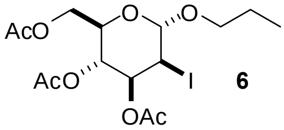
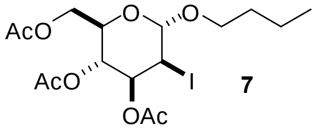
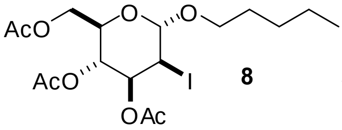
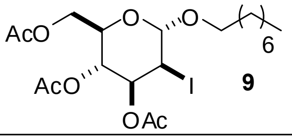
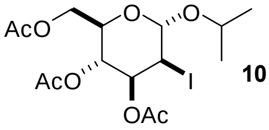
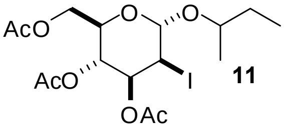
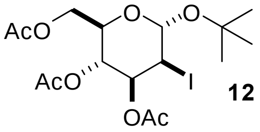
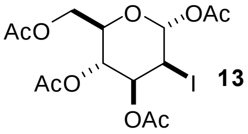
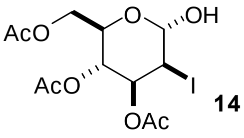
[a] Determined by ^{1}H NMR.

The study was extended by treatment of a series of alcohols as shown in Table 3. The selective formation of 2-deoxy-2-iodo-*O*-glycosides was observed in all cases. The glycosylations of long chain alcohols afforded the products in moderate yields (entries 3, 4, 5 and 6). The reactions proceeded more efficient for the 2°-alcohols such as 2-propanol and 2-butanol and yielding the desired product in 91% as 14:1 and 17:1 α/β mixtures for entries 7 and 8. Glycosylation of hindered acceptor such as *t*-BuOH afforded **12** only in α-form (entry 9). Glycosylations with acetic anhydride (Ac_2O) and water gave rise to quantitative formation of **13** and **14** within 1 h (entries 10 and 11). This observation suggests that the presence of excess alcohol retarded the Ferrier rearrangement which could be accelerated by the resulting HI releasing from the reaction. HI was probably protonated by the excess of alcohol forming softer acid which is not strong enough to promote the Ferrier reaction. Without the strong acid as HI, the reaction can undergo smoothly through the cyclic iodonium bridge resulting in the formation of

2-deoxy-2-iodoglycoside.[17] Molecular sieve was also subjected to reaction to reduce the moisture which can react with iodine to produce HI.

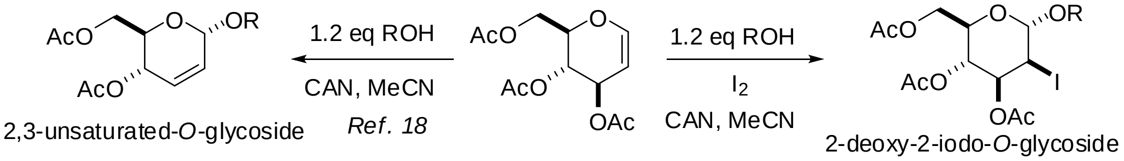
Table 3 Synthesis of 2-deoxy-2-iodoglycoside in the presence of excess alcohol



entry	Major Product[c]	Time	Yield (%) (α:β)[a]
1	 **5**	3 h	72^b (4:1)
2	 **3**	1 h	83 (6:1)
3	 **6**	40 min	61 (7:1)
4	 **7**	30 min	62 (7:1)
5	 **8**	50 min	53 (9:1)
6	 **9**	1 h	52 (25:1)
7	 **10**	1 h	91 (14:1)
8	 **11**	1 h	91 (17:1)
9	 **12**	1 h	89 (1:0)
10	 **13**	1 h	>99^b (1:0)
11	 **14**	1 h	>99^b (2:1)

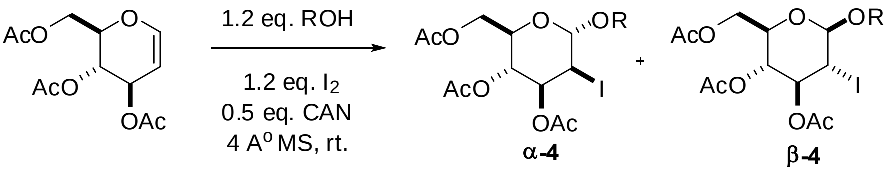
The reactions were carried out on a 0.37 mmol scale of **1** and iodine 2.5 eq. (0.92 M); [a] Determined by ^{1}H NMR. [b] Iodine 2.5 eq. (0.04 M) was employed. [c] 2,3-unsaturated-O-glycosides were not observed.

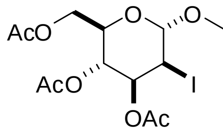
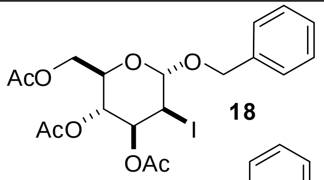
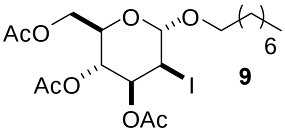
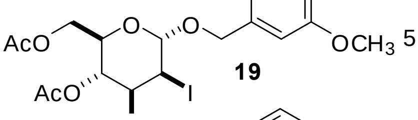
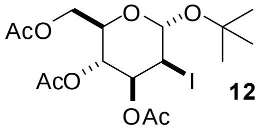
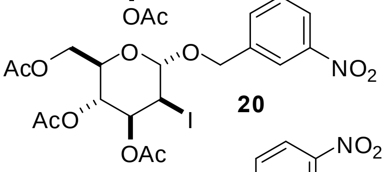
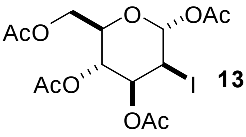
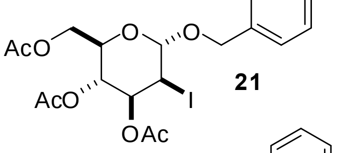
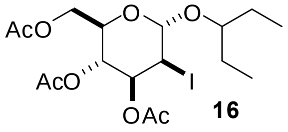
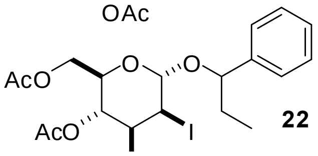
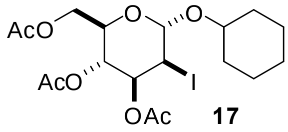
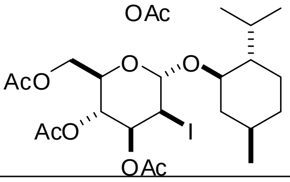
Since ceric ammonium nitrate (CAN) was reported[18] to promote Ferrier rearrangement as iodine, we carried on further study on the glycosylation by employing a combination of iodine and CAN and observed the product formation.



Scheme 2

Table 4 Synthesis of 2-deoxy-2-iodoglycoside in the presence of ceric ammonium nitrate



entry	Major Product^c	Time (h)	Yield (%)^a (α:β)^b	entry	Major Product^c	Time (h)	Yield (%)^a (α:β)^b
1	 **3**	2	82 (5:1)	7	 **18**	3	82 (5:1)
2	 **9**	5	58 (6:1)	8	 **19**	5	58 (6:1)
3	 **12**	4	90 (1:0)	9	 **20**	12	90 (1:0)
4	 **13**	3	84 (1:0)	10	 **21**	12	84 (1:0)
5	 **16**	2	97 (8:1)	11	 **22**	3	97^c (8:1)
6	 **17**	3	77 (8:1)	12	 **23**	4	77 (8:1)

[a] Isolated yields as diastereomeric mixtures and major product can be separated by column chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Diastereomeric mixture from racemic alcohol. [d] 2,3-unsaturated-O-glycosides were not observed.

The addition of CAN[19] as additive can switch the formation to 2-deoxy-2-iodoglycosides as our expectation (Scheme 2). A wide range of alcohols were suitable for this transformation producing moderate to high yield with high stereoselectivity as shown in Table 4.

The combination of CAN with iodine to the glycosylation afforded the products with the yield rather similar to the condition without CAN in excess acceptor alcohols (Tables 2 and 3, compounds **3**, **9**, **12**, and **13**). The glycosylation was extended to a variety of benzyl alcohols and gave the glycoside adducts in excellent yields (entries 7, 9, 10 and 11). Nevertheless, the reaction of methoxy-benzyl alcohol gave the corresponding glycoside **19** in 58% yield (entry 8).

In conclusion, we have observed a simple, efficient and inexpensive method for convertible formation between 2-deoxy-2-iodoglycosides and 2,3-unsaturated-glycoside by performing the glycosylation using versatile reagent as iodine in different condition. The presence of excess alcohol or ceric ammonium nitrate could be switched the formation of the desired products. This report provides a new and simple method for the synthesis of the corresponding 2-deoxy-2-iodo-*O*-glycosides and the availability of these DIG glycosides for medicinal studies.

EXPERIMENTAL

Proton NMR spectra were recorded on a BRUKER AVANC (400 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in ppm relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) as internal standard. Carbon NMR spectra were recorded on a BRUKER AVANC (100 MHz). High-resolution FAB mass spectra were obtained with a Finnigan MAT 95. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Optical rotation was determined with a JASCO P-1020 digital polarimeter.

General procedure for the synthesis of 2,3-unsaturated-*O*-glycosides

To a stirred solution of tri-*O*-acetoxy-D-glucal **1** (100 mg, 0.367 mmol) and alcohol (0.444 mmol) in anhydrous CH_2Cl_2 (25.0 mL) was added iodine powder (140 mg, 0.558 mmol) in portion at room temperature under N_2 atmosphere. The reaction mixture was continued the stirring at room temperature for 3 h. The reaction was quenched with satd aq. $Na_2S_2O_3$. The aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extract was washed with brine, dried over with anhydrous $MgSO_4$, and concentrated under vacuo. The residue was purified by silica gel chromatography to give 2,3-unsaturated-*O*-glycosides.

General procedure for the synthesis of 2-deoxy-2-iodoglycoside in the present of excess alcohol

To a stirred solution of tri-*O*-acetoxy-D-glucal **1** (100 mg, 0.367 mmol) in excess alcohol (1.0 mL) was added 4 A^o MS (100 mg) under N_2 atmosphere. The reaction mixture was stirred for 5 min and then added iodine powder (230 mg, 0.918 mmol) in portion at room temperature. When TLC showed the complete conversion, the reaction was diluted with CH_2Cl_2 (20 mL) and quenched with satd aq. $Na_2S_2O_3$ until color of iodine was disappeared. The aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extract was washed with brine, dried over with anhydrous $MgSO_4$, and concentrated under vacuo. The residue was purified by silica gel chromatography to give 2-deoxy-2-iodoglycoside.

General procedure for synthesis of 2-deoxy-2-iodoglycoside in the present of CAN

A mixture of iodine powder (150 mg, 0.600 mmol), alcohol (0.600 mmol), ceric ammonium nitrate (137 mg, 0.250 mmol) and 4 A^o MS (150 mg) was dissolved in anhydrous MeCN (2.0 mL) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 30 min and then cooled to -25 ^oC.

Tri-*O*-acetoxy-D-glucal **1** (136 mg, 0.499 mmol) was added in portion under N_2 atmosphere. The reaction mixture was maintained at -25 ^oC for 1 h and allowed to warm to room temperature. When TLC showed the complete conversion, the reaction was diluted with EtOAc (20 mL) and quenched with satd aq. $Na_2S_2O_3$ until color of iodine was disappeared, followed by addition of satd aq. $NaHCO_3$. The aqueous solution was extracted with EtOAc (3 x 20 mL) and the organic extract was washed with brine, dried over with anhydrous $MgSO_4$, and concentrated under vacuo. The residue was purified by silica gel chromatography to give 2-deoxy-2-iodoglycoside.

Compound 3; $[\alpha]_D^{28}$ +7.89 (c 1.02, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.0 Hz, H-2’), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.14 (s, 3H, Ac), 3.56 (dq, 1H, *J* = 10.0, 7.0 Hz, H-1’a), 3.75 (dq, 1H, *J* = 10.0, 7.0 Hz, H-1’b), 4.05 (ddd, 1H, *J* = 9.5, 5.0, 2.5 Hz, H-5), 4.16 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6a), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6b), 4.54 (dd, 1H, *J* = 4.5, 1.0 Hz, H-2), 4.68 (dd, 1H, *J* = 9.5, 4.5 Hz, H-3), 5.20 (brs, 1H, H-1), 5.39 (t, 1H, *J* = 9.5 Hz, H-4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.98, 20.67, 20.75, 20.97, 29.80, 62.29, 64.11, 67.66, 69.05, 69.12, 101.10, 169.53, 169.89, 170.75. IR ($CHCl_3$): 2980, 2930, 1748, 1370, 1231, 1052 cm^{-1}. HRMS: $C_{14}H_{21}IO_8$ (M^+ + Na). Cal. 467.0175. Found, 467.0183.

Compound 5; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.09 (s, 3H, Ac), 3.38 (s, 3H, H-1’), 3.97 (ddd, 1H, *J* = 9.5, 5.0, 2.5 Hz, H-5), 4.13 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6a), 4.20 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6b), 4.50 (dd, 1H, *J* = 4.5, 1.0 Hz, H-2), 4.59 (dd, 1H, *J* = 9.5, 4.5 Hz, H-3), 5.05 (brs, 1H, H-1), 5.33 (t, 1H, *J* = 9.5 Hz, H-4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.60, 20.69, 20.88, 29.22, 55.38, 62.25, 67.52, 69.0, 69.18, 102.28, 169.48, 169.81, 170.68. IR ($CHCl_3$): 2940, 2838, 1747, 1369, 1231, 1052, 967, 902, 602 cm^{-1}. HRMS: $C_{13}H_{19}IO_8$ (M^+ + Na). Cal. 453.0022. Found, 453.0031.

Compound 6; $[\alpha]_D^{28}$ +1.64 (c 1.01, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, *J* = 7.4 Hz, H-3’), 1.57-1.73 (m, 2H, H-2’), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.13 (s, 3H, Ac), 3.45 (dt, 1H, *J* = 9.6, 6.8 Hz, H-1’a), 3.64 (dt, 1H, *J* = 9.6, 6.8 Hz, H-1’b), 4.04 (ddd, 1H, *J* = 9.6, 5.0, 2.8 Hz, H-5), 4.16 (dd, 1H, *J* = 12.0, 2.8 Hz, H-6a), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6b), 4.55 (dd, 1H, *J* = 4.4, 1.2 Hz, H-2), 4.66 (dd, 1H, *J* = 9.6, 4.4 Hz, H-3), 5.19 (brs, 1H, H-1), 5.38 (t, 1H, *J* = 9.6 Hz, H-4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 10.60, 20.67, 20.75, 20.97, 22.65, 29.78, 62.30, 67.65, 69.07, 69.16, 70.25, 101.29, 169.54, 169.88, 170.73. IR ($CHCl_3$): 2959, 2936, 1745, 1432, 1366, 1220, 1019, 743 cm^{-1}. HRMS: $C_{15}H_{23}IO_8$ (M^+ + Na). Cal. 481.0336. Found, 481.0339.

Compound 7; $[\alpha]_D^{28}$ +14.75 (c 1.08, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J* = 7.1 Hz, H-4’), 1.34-1.45 (m, 2H, H-3’), 1.54-1.65 (m, 2H, H-2’), 2.06 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.12 (s, 3H, Ac), 3.47 (dt, 1H, *J* = 9.0, 6.6 Hz, H-1’a), 3.68 (dt, 1H, *J* = 9.0, 6.7 Hz, H-1’b), 4.02 (ddd, 1H, *J* = 9.5, 4.5, 2.0 Hz, H-5), 4.15 (dd, 1H, *J* = 12.1, 2.0 Hz, H-6a), 4.23 (dd, 1H, *J* = 12.1, 4.5 Hz, H-6b), 4.53 (d, 1H *J* = 4.0 Hz, H-2), 4.65 (dd, 1H, *J*= 9.5, 4.0 Hz, H-3), 5.17 (brs, 1H, H-1), 5.37 (t, 1H, *J* = 9.5 Hz, H-4).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 13.79, 19.29, 20.67, 20.75, 20.97, 29.79, 31.40, 62.31, 67.63, 69.41, 69.07, 69.14, 101.29, 169.52, 169.86, 170.70. IR (CHCl$_3$): 2959, 2874, 1742, 1433, 1366, 1219, 1117, 1038, 673 cm^{-1}. HRMS: C$_{16}$H$_{25}$IO$_8$ (M$^+$ + Na). Cal. 495.0492. Found, 495.0481.

Compound 8; [α]$_D$^{28} +1.63 (c 1.06, CHCl$_3$). ^{1}H-NMR (400 MHz, CDCl$_3$): δ 0.87 (3H, t, *J* = 6.8 Hz, H-5'), 1. 27-1.30 (4H, m, H-3', H-4'), 1.53-1.59 (2H, m, H-2'), 2.01 (3H, s, Ac), 2.03 (3H, s, Ac), 2.07 (3H, s, Ac), 3.42 (1H, dt, *J* = 9.6, 6.7 Hz, H-1'a), 3.61 (1H, dt, 9.6, 6.7 Hz, H-1'b), 3.97 (1H, ddd, *J* = 10.0, 4.9, 2.4 Hz, H-5), 4.10 (1H, dd, *J* = 12.2, 2.4 Hz, H-6a), 4.18 (1H, dd, *J* = 12.2, 4.9 Hz, H-6b), 4.49 (1H, dd, *J* = 4.4, 1.2 Hz, H-2), 4.59 (1H, dd, *J* = 9.5, 4.4 Hz, H-3), 5.12 (1H, brs, H-1), 5.32 (1H, t, *J* = 9.8, H-4), IR (CHCl$_3$): 2928, 2857, 1748, 1456, 1368, 1229, 1120, 1047, 738 cm^{-1}. HRMS: C$_{17}$H$_{27}$IO$_8$ (M$^+$ + Na). Cal. 509.0648. Found, 509.0555.

Compound 9; [α]$_D$^{28} +16.79 (c 1.02, CHCl$_3$). ^{1}H-NMR (400 MHz, CDCl$_3$): δ 0.89 (7H, m, H-6', H-7', H-8'), 1.27 (6H, m, H-3', H-4', H-5'), 1.55 (2H, m, H-2'), 2.04 (3H, s, Ac), 2.07 (3H, s, Ac), 2.10 (3H, s, Ac), 3.44 (1H, ddd, *J* = 13.2, 6.0, 3.0 Hz, H-1a'), 3.64 (1H, ddd, *J* = 13.2, 6.0, 3.0 Hz, H-1b'), 4.00 (1H, ddd, *J* = 9.8, 4.8, 2.4 Hz, H-5), 4.13 (1H, dd, *J* = 12.1, 2.4 Hz, H-6a), 4.21 (1H, dd, *J* = 12.1, 4.8 Hz, H-6b), 4.51 (1H, dd, *J* = 4.4, 1.1 Hz, H-2), 4.63 (1H, dd, *J* = 9.8, 4.4 Hz, H-3), 5.15 (1H, brs, H-1), 5.35 (1H, t, *J* = 9.8 Hz, H-4). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 14.09, 20.68, 20.76, 20.99, 22.64, 26.07, 29.20, 29.3, 29.34, 29.81, 31.80, 62.29, 67.63, 68.75, 69.06, 69.16, 101.29, 169.54, 169.89, 170.74. IR (CHCl$_3$): 3056, 2929, 1748, 1455, 1423, 1368, 1265, 1229, 1047, 739 cm^{-1}. HRMS: C$_{20}$H$_{33}$IO$_8$ (M$^+$ + Na). Cal. 551.1118. Found, 551.0984.

Compound 10; [α]$_D$^{28} +1.83 (c 1.01, CHCl$_3$), ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.17 (d, 3H, *J* = 6.0 Hz, H-2'a), 1.23 (d, 3H, *J* = 6.0 Hz, H-2'b), 2.05 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.10 (s, 3H, Ac), 3.80-4.00 (m, 1H, H-1'), 4.08 (ddd, 1H, *J* = 9.5, 5.0, 2.4 Hz, H-5), 4.14 (dd, 1H, *J* = 12.0, 2.4 Hz, H-6a), 4.22 (dd, 1H, *J* = 12.2, 5.0 Hz, H-6b), 4.48 (d, 1H, *J* = 4.3 Hz, H-2), 4.66 (dd, 1H, *J* = 9.5, 4.3 Hz, H-3), 5.26 (brs, 1H, H-1), 5.36 (t, 1H, *J* = 9.7 Hz, H-4). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 20.62, 20.68, 20.92, 21.60, 23.03, 30.56, 62.30, 67.75, 69.05, 69.08, 71.06, 99.61, 169.47, 169.77, 170.60. IR (CHCl$_3$): 2972, 2925, 1742, 1433, 1367, 1220, 1113, 1032, 736 cm^{-1}. HRMS: C$_{15}$H$_{23}$IO$_8$ (M$^+$ + Na). Cal. 481.0336. Found, 481.0324.

Compound 11; (mixture of diastereomers)**:** [α]$_D$^{28} +1.90 (c 1.05, CHCl$_3$), ^{1}H-NMR (400 MHz, CDCl$_3$): δ 0.77-0.93 (m, 6H, H-4', isomer A, isomer B), 1.07 (d, 3H, *J* = 5.0 Hz, H-2', isomer A), 1.14 (d, 3H, *J* = 5.3 Hz, H-2', isomer B), 1.31-1.63 (m, 4H, H-3', isomer A, isomer B), 1.99 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.04 (s, 3H, Ac), 3.55-3.68 (m, 2H, H-1', isomer A, isomer B), 3.98-4.19 (m, 6H, H-5, H-6, isomer A, isomer B), 4.42 (d, 1H, *J* = 4.5 Hz, H-2, isomer A), 4.41 (d, 1H, *J* = 4.5 Hz, H-2, isomer B), 4.53-4.63 (m, 2H, H-3, isomer A, isomer B), 5.19 (brs, 1H, H-1, isomer A), 5.21 (brs, 1H, H-1, isomer B), 5.29 (t, 2H, *J*= 9.7 Hz, H-4, isomer A, isomer B). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 9.57, 10.17, 18.59, 20.45, 20.65, 20.69, 20.94, 28.99, 29.76, 30.42, 30.65, 62.37, 67.74, 67.82, 69.13, 69.19, 69.25, 75.22, 77.68, 98.92, 101.00, 169.51, 169.80, 170.63. IR ($CHCl_3$): 2970, 2936, 1748, 1369, 1230, 1040, 599 cm^{-1}. HRMS: $C_{16}H_{25}IO_8$ (M^+ + Na). Cal. 495.0492. Found, 495.0499.

Compound 12: $[\alpha]_D^{28}$ +18.19 (c 1.02, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H, H-2'), 2.06 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.10 (s, 3H, Ac), 4.09-4.26 (m, 3H, H-5, H-6), 4.41 (d, 1H, *J* = 4.0 Hz, H-2), 4.70 (dd, 1H, *J* = 9.5, 4.0 Hz, H-3), 5.36 (t, 1H, *J* = 9.5 Hz, H-4), 5.42 (brs, 1H, H-1). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.66, 20.71, 20.97, 28.38, 32.03, 62.47, 67.98, 68.74, 69.19, 76.86, 96.21, 169.55, 169.90, 170.70. IR ($CHCl_3$): 2977, 2937, 1748, 1370, 1231, 1046, 882, 602 cm^{-1}. HRMS: $C_{16}H_{25}IO_8$ (M^+ + Na). Cal. 495.0492. Found, 495.0490.

Compound 13: $[\alpha]_D^{28}$ +16.68 (c 1.04, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 2.05 (3H, s, Ac), 2.07 (3H, s, Ac), 2.10 (3H, s, Ac), 2.15 (3H, s, Ac), 4.04-4.20 (2H, m, H-5, H-6b), 4.07 (1H, dd, *J* = 2.5, 12.5 Hz, H-6a), 4.32 (1H, dd, *J* = 5.0, 12.5 Hz, H-2), 5.09 (1H, t, *J* = 5.0 Hz, H-3), 5.33 (1H, ddd, *J* = 5.0, 9.5, 12.5 Hz, H-4), 6.27 (1H, brd, *J* = 2.5 Hz, H-1). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.6, 20.7, 20.9, 21.0, 33.9, 62.0, 68.5, 68.7, 70.2, 90.9, 168.9, 169.7, 170.3, 170.7. IR ($CHCl_3$): 2963, 1755, 1371, 1231, 1052, 747, 602 cm^{-1}. HRMS: $C_{14}H_{19}IO_9$ (M^+ + Na). Cal. 480.9971. Found, 480.9849.

Compound 14: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.05 (3H, s, Ac), 2.07 (3H, s, Ac), 2.10 (3H, s, Ac), 4.16 (2H, t, *J* = 3.5 Hz, H-6), 4.26 (1H, dt, *J* = 3.5, 10.0 Hz, H-5), 4.45 (1H, dd, *J* = 1.0, 4.0 Hz, H-2), 4.70 (1H, dd, *J* = 4.0, 10.0 Hz, H-3), 5.37 (1H, t, *J* = 10.0 Hz, H-4), 5.57 (1H, brs, H-1). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.7, 20.8, 20.9, 30.6, 62.3, 67.7, 68.8, 71.1, 95.8, 169.7, 170.1, 171.1. IR ($CHCl_3$): 3455, 2960, 1755, 1433, 1371, 1240, 1043 cm^{-1}. HRMS: $C_{12}H_{17}IO_8$ (M^+ + Na). Cal. 438.9866. Found, 438.9745.

Compound 16: $[\alpha]_D^{28}$ +2.03 (c 1.06, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H, *J* = 7.2 Hz, H-4', H-6'), 1.34-1.41 (m, 4H, H-3', H-5'), 1.40-1.50 (m, 1H, H-2'), 2.07 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.12 (s, 3H, Ac), 3.36 (dd, 1H, *J* = 9.4, 5.6 Hz, H-1'a), 3.61 (dd, 1H, *J* = 9.4, 5.6 Hz, H-1'b), 4.01 (ddd, 1H, *J* = 9.8, 5.0, 2.4 Hz, H-5), 4.16 (dd, 1H, *J* = 12.2, 2.4 Hz, H-6a), 4.23 (dd, 1H, *J* = 12.2, 5.0 Hz, H-6b), 4.55 (d, 1H, *J* = 4.4 Hz, H-2), 4.64 (dd, 1H, *J* = 9.8, 4.3 Hz, H-3), 5.16 (brs, 1H, H-1), 5.37 (t, 1H, *J* = 9.8 Hz, H-4) .^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.02, 11.12, 20.68, 20.74, 20.97, 23.23, 23.30, 29.77, 40.93, 62.35, 67.62, 69.19, 69.20, 70.97, 101.55, 169.55, 169.88, 170.71. IR ($CHCl_3$): 3056, 2964, 1747, 1458, 1368, 1266, 1229, 1045, 738 cm^{-1}. HRMS: $C_{18}H_{29}IO_8$ (M^+ + Na). Cal. 523.0805. Found, 523.0687.

Compound 17: $[\alpha]_D^{28}$ +22.03 (c 1.05, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.05-1.55 (m, 6H, H-3', H-4', H-5'), 1.60-1.85 (m, 4H, H-2', H-6'), 1.99 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.04 (s, 3H, Ac), 3.52 (tt, 1H, *J* = 9.3, 3.9 Hz, H-1'), 4.04 (ddd, 1H, *J* = 9.6, 4.9, 2.5 Hz, H-5), 4.08 (dd, 1H, *J* = 12.1, 2.5 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.1, 4.9 Hz, H-6b), 4.42 (dd, 1H, *J* = 4.3, 1.2 Hz, H-2), 4.60 (dd, 1H, *J* = 9.5, 4.3 Hz, H-3), 5.23 (brs, 1H, H-1), 5.29 (t, 1H, *J* = 9.6 Hz, H-4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.68, 20.74, 20.99, 23.84, 24.10, 25.44, 30.68, 31.58, 33.19, 62.37, 67.84, 69.14, 69.20, 76.93, 99.58, 169.57, 169.90, 170.72. IR ($CHCl_3$): 2933, 2857, 1743, 1449, 1366, 1219, 1114, 1033, 672 cm^{-1}. HRMS: $C_{18}H_{27}IO_8$ (M^+ + Na). Cal. 521.0649. Found, 521.0643.

Compound 18: $[\alpha]_D^{28}$ +35.76 (c 1.09, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.14 (s, 3H, Ac), 4.05 (ddd, 1H, *J* = 9.5, 4.7, 2.4 Hz, H-5), 4.10 (dd, 1H, *J* = 12.2, 2.4 Hz, H-6a), 4.24 (dd, 1H, *J* = 12.2, 4.7 Hz, H-6b), 4.57 (d, 1H, *J* = 11.8 Hz, H-1'a), 4.58 (dd, 1H, *J* = 4.4, 1.0 Hz, H-2), 4.69 (dd, 1H, *J* = 9.5, 4.4 Hz, H-3), 4.72 (d, 1H, *J* = 11.8 Hz, H-1'b), 5.27 (brs, 1H, H-1), 5.41 (t, 1H, *J* = 9.5 Hz, H-4), 7.29-7.50 (m, 5H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.67, 20.78, 20.96, 29.55, 62.16, 67.55, 69.10, 69.33, 70.03, 100.53, 128.21, 128.30, 128.62, 136.34, 169.50, 169.85, 170.71. IR ($CHCl_3$): 3055, 2986, 1746, 1455, 1422, 1368, 1265, 1121, 1042, 896, 738 cm^{-1}. HRMS: $C_{19}H_{23}IO_8$ (M^+ + Na). Cal. 529.0335. Found, 529.0323.

Compound 19; $[\alpha]_D^{28}$ +33.04 (c 1.08, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.06 (3H, s, Ac), 2.09 (3H, s, Ac), 2.14 (3H, s, Ac), 3.83 (3H, s, H-8'), 4.06 (1H, ddd, *J* = 9.8, 4.6, 2.3 Hz, H-5), 4.12 (1H, dd, *J* = 12.2, 2.3 Hz, H-6b), 4.24 (1H, dd, *J* = 12.2, 4.6 Hz, H-6a), 4.54 (1H, d, *J* = 12.0 Hz, H-1'a), 4.58 (1H, dd, *J* = 4.3, 1.2 Hz, H-2), 4.69 (1H, d, *J* = 12.0 Hz, H-1'b), 4.70 (1H, dd, *J* = 9.8, 4.3 Hz, H-3), 5.25 (1H, brs, H-1), 5.41 (1H, t, *J* = 9.8 Hz, H-4), 6.88 (1H, d, *J* = 7.6 Hz, Ph), 6.89 (1H, s, Ph), 6.93 (1H, d, *J* = 7.6 Hz, Ph), 7.29 (1H, t, *J* = 7.6 Hz, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.68, 20.79, 20.97, 29.52, 55.28, 62.17, 67.54, 69.09, 69.34, 69.80, 100.42, 113.64, 113.75, 115.51, 120.39, 129.68, 159.79, 169.56, 169.90, 170.70. IR ($CHCl_3$): 3055, 2986, 1747, 1588, 1490, 1457, 1368, 1265, 1231, 1042, 738 cm^{-1}. HRMS: $C_{20}H_{25}IO_9$ (M^+ + Na). Cal. 559.0441. Found, 559.0309.

Compound 20; $[\alpha]_D^{28}$ +27.45 (c 1.02, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.15 (s, 3H, Ac), 4.05 (ddd, 1H, *J* = 9.7, 5.0, 2.4 Hz, H-5), 4.16 (dd, 1H, *J* = 12.2, 2.4 Hz, H-6b), 4.26 (dd, 1H, *J* = 12.2, 5.0 Hz, H-6a), 4.62 (d, 1H, *J* = 4.4 Hz, H-2), 4.64 (d, 1H, *J* = 12.5 Hz, H-1a'), 4.66 (dd, 1H, *J* = 9.7, 4.3 Hz, H-3), 4.82 (d, 1H, *J* = 12.5 Hz, H-1b'), 5.29 (brs, 1H, H-1), 5.42 (t, 1H, *J* = 9.7 Hz, H-4), 7.59 (t, 1H, *J* = 8.6 Hz, Ph), 7.71 (d, 1H, *J* = 8.6 Hz, Ph), 8.21 (s, 1H, Ph), 8.22 (d, 1H, *J* = 8.6 Hz, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.63, 20.74, 20.91, 28.70, 62.15, 67.44, 68.69, 68.93, 69.66, 100.89, 122.79, 123.26, 129.71, 133.82, 138.40, 148.39, 169.43, 169.82, 170.62. IR ($CHCl_3$): 3055, 2986, 1747, 1607, 1532, 1351, 1265, 1230, 1045, 738 cm^{-1}. HRMS: $C_{19}H_{22}INO_{10}$ (M^+ + Na). Cal. 574.0186. Found, 574.0034.

Compound 21; $[\alpha]_D^{28}$ +35.57 (c 1.08, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.15 (s, 3H, Ac), 4.05 (ddd, 1H, *J* = 9.7, 4.7, 2.5 Hz, H-5), 4.16 (dd, 1H, *J* = 12.3, 2.5 Hz, H-6b), 4.26 (dd, 1H, *J* = 12.3, 4.7 Hz, H-6a), 4.63 (d, 1H, *J* = 4.4 Hz, H-2), 4.65 (d, 1H, *J* = 13.0 Hz, H-1a'), 4.66 (dd, 1H, *J* = 9.7, 4.4 Hz, H-3), 4.84 (d, 1H, *J* = 13.0 Hz, H-1b'), 5.29 (brs, 1H, H-1), 5.43 (t, 1H, *J* = 9.7 Hz, H-4), 7.54 (d, 2H, *J* = 8.4 Hz, Ph), 8.26 (d, 2H, *J* = 8.4 Hz, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.63, 20.74, 20.93, 28.59, 62.12, 67.41, 68.53, 68.95, 69.69, 100.97, 123.87, 128.17, 143.62, 148.13, 169.42, 169.89, 170.61. IR ($CHCl_3$): 3055, 2987, 1748, 1607, 1522, 1348, 1265, 1230, 1047, 738 cm^{-1}. HRMS: $C_{19}H_{22}INO_{10}$ (M^+ + Na). Cal. 574.0186. Found, 573.9964.

Compound 22 (mixture of isomers): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77 (t, 3H, *J* = 7.4 Hz, H-3', isomer A), 0.84 (t, 3H, *J* = 7.4 Hz, H-3', isomer B), 1.66 (m, 2H, H-2', isomer B), 1.84 (m, 2H, H-2', isomer B), 1.90, 1.95, 2.00, 2.01, 2.05 (6s, 18H, Ac, isomer A and B), 3.39 (dd, 1H, *J* = 12.5, 2.0 Hz, H-6a, isomer A), 3.49 (m, 1H, H-5, isomer A), 3.84 (dd, 1H, *J* = 12.5, 4.0 Hz, H-6b, isomer A), 4.08 (m, 1H, H-5, isomer B), 4.12 (dd, 1H, *J* = 12.5, 2.0 Hz, H-6a, isomer B), 4.18 (dd, 1H, *J* = 12.5, 5.0 Hz, H-6b, isomer B), 4.30 (t, 1H, *J* = 6.5, H-1', isomer A), 4.37 (m, 1H, H-2, isomer A), 4.39 (t, 1H, *J* = 6.5, H-1', isomer B), 4.55 (m, 1H, H-2, isomer B), 4.52-4.56 (m, 1H, H-3, isomer B), 4.65 (dd, 1H, *J* = 9.5, 4.5 Hz, H-3, isomer A), 4.86 (brs, 1H, H-1, isomer B), 5.24 (t, 1H, *J* = 10.0, H-4, isomer B), 5.30 (brs, 1H, H-1, isomer A), 5.31 (t, 1H, *J* = 9.5, H-4, isomer A), 7.16-7.31 (m, 5H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 9.99, 10.05, 10.62, 20.56, 20.70, 20.91, 20.96, 29.79, 30.00, 30.70, 61.48, 62.45, 67.32, 67.81, 69.23, 69.33, 69.38, 69.46, 80.67, 84.13, 98.34, 102.11, 102.16, 126.68, 127.00, 127.87, 128.21, 128.37, 128.64, 140.16, 141.65, 169.29, 169.45, 169.81, 170.51, 170.55. IR (NaCl): 3058, 2967, 2938, 1747, 1493, 1455, 1368, 1266, 1230, 1117, 1040, 738 cm^{-1}. HRMS: $C_{21}H_{27}IO_8$ (M^+ + Na). Cal. 557.0648. Found, 557.0511.

Compound 23: $[\alpha]_D^{28}$ +64.18 (c 1.01, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.70 (d, 3H, *J* = 7.0 Hz, H-9'), 0.73-1.05 (m, 10H, menthol ring, H-8', H-8''), 1.15-1.39 (m, 2H, menthol ring), 1.48-1.75 (m, 3H, menthol ring), 1.99 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.04 (s, 3H, Ac), 3.30 (dt, 1H, *J* = 10.6, 4.2 Hz, H-1'), 4.02-4.18 (m, 3H, H-5, H-6), 4.44 (d, 1H, *J* = 4.1 Hz, H-2), 4.59 (dd, 1H, *J* = 9.1, 4.1 Hz, H-3), 5.18 (brs, 1H, H-1), 5.27 (t, 1H, *J* = 9.0 Hz, H-4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.33, 20.67, 20.76, 20.92, 20.95, 22.29, 23.33, 25.96, 30.28, 31.60, 34.15, 42.48, 48.26, 62.59, 67.87, 69.12, 69.32, 82.77, 103.03, 169.56, 169.91, 170.69. IR ($CHCl_3$): 3055, 2959, 1748, 1456, 1369, 1233, 1115, 1032, 896, 738 cm^{-1}. HRMS: $C_{22}H_{35}IO_8$ (M^+ + Na). Cal. 577.1274. Found, 577.1274.

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