Isoflavone glycosides: synthesis and evaluation as α-glucosidase inhibitors

Guo Wei and Biao Yu*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China.

*Corresponding author. Tel.: +86 21 54925132; fax: +86 21 64166128
E-mail address: byu@mail.sioc.ac.cn

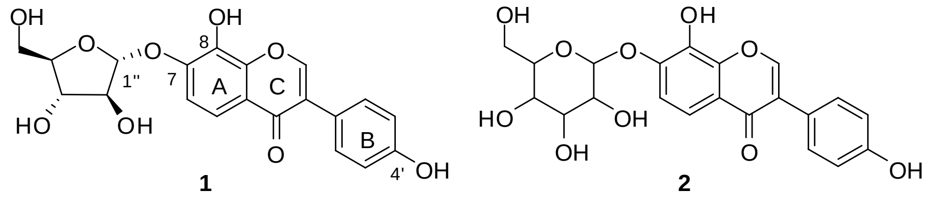
Keywords: α-Glucosidase inhibitor; Isoflavone glycoside; A-76202; Synthesis; Suzuki-Miyaura coupling.

Abstract

Based on the structure of 4',8-dihydroxyisoflavon-7-yl α-D-arabinofuranoside (namely A-76202, **1**), a Rhodococcus metabolite showing potent inhibitory activities against the α-glucosidases of rat liver microsome (IC_{50} = 0.46 ng/mL), 26 analogs each with minor variations at the sugar moiety, the isoflavone A, and B rings, respectively, are readily synthesized. Notably, a new and efficient method is developed for the divergent synthesis of the B-ring congeners of the isoflavone glycosides using Suzuki-Miyaura coupling as the final step. Modifications at the sugar moiety and the isoflavone A ring significantly diminish the activity, while variations on the B ring are largely tolerated for retaining the potent α-glucosidase inhibitory activity.

Introduction

The generation of glycoproteins involves the cotranslational transference of the tetradeca-oligosaccharide $Glc_3Man_9GlcNAc_2$ from the dolichyl diphosphate to the *N*-asparagine of the nascent protein, by the action of the oligosaccharyl-transferase in the lumen of the reticulum endoplasmatic membrane.[1] Then the processing enzymes, α-glucosidase I and II, cleave the Glc(1→2)Glc and Glc(1→3)Glc linkages in this *N*-linked oligosaccharide respectively, to liberate the three terminal glucose residues.[2] This immature glycoprotein is further processed by the concomitant action of glycosidases and transferases to give specific glycoconjugates, which play fundamental roles in the biological processes, such as the immune response, intercellular recognition, cellular differentiation, the stability and solubility of proteins, and in pathological processes, such as inflammation and cancer.[3] Tremendous efforts have been given to the development of glucosidase inhibitors which are of potentially usefulness for the treatment of diabetes,[4] obesity,[5] glycosphingolipid lysosomal storage disease,[6] HIV infections,[7] and tumors.[8] The potent inhibitors with IC_{50} at nM level are largely structural mimics of the transition state of the hydrolyses of the glucosidic linkage.[9] In this regard, 4',8-dihydroxyisoflavon-7-yl α-D-arabinofuranoside (**1**) is an exception which shows potent inhibitory activity (against the α-glucosidases of rat liver mcrosome) with an IC_{50} of 0.46 ng/mL.[10] This isoflavone glycoside, named A-76202, was isolated by Takatsuki et al. in 1996 from Rhodococcus sp. SANK 61694. Shiozaki et al. have synthesized this compound along with several hexopyranoside analogs (**2**), and evaluated their α-glucosidase inhibitory activities.[11] However, these hexose analogs were found inactive. We have developed a general approach to the synthesis of flavone 7-*O*-glycosides, such as A-76202 (**1**).[12] Here we report the synthesis of a series of the analogs of **1**, each with minor variations at the sugar moiety, the isoflavone A, and B rings, respectively, and the evaluation of their α-glucosidase inhibitory activities.



1

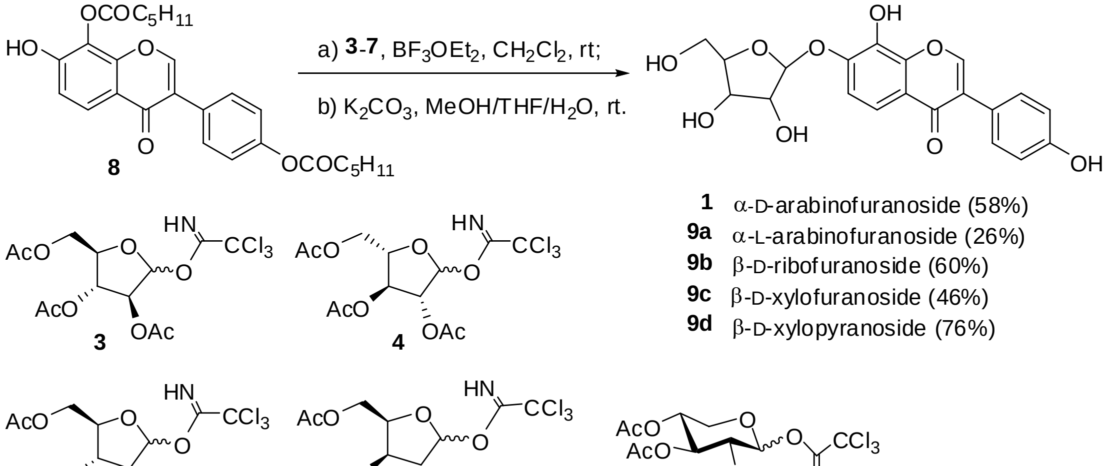
2

Figure 1. A-76202 (**1**) and the hexose analogues (**2**) synthesized by Shiozaki et al.

Results and Discussion

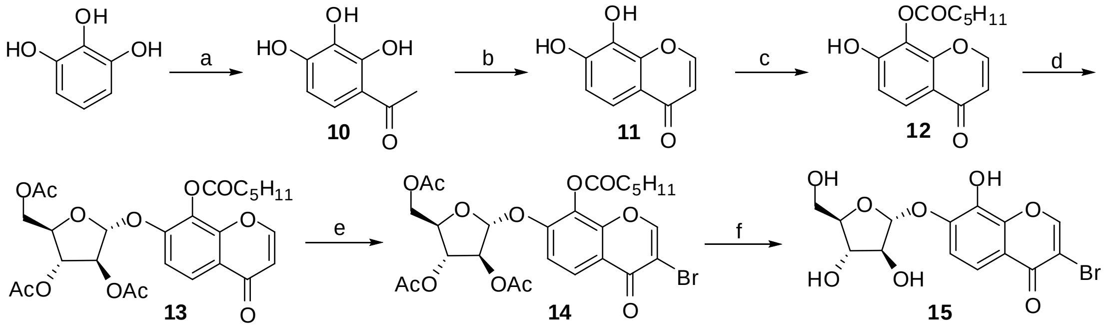
Synthesis

Adopting modification of our previous method for the synthesis of flavone 7-*O*-glycosides,[12] the desired 4',8-dihydroxyisoflavon-7-yl pentosides (**9a-d**) and the natural product **1** as well were readily prepared via glycosylation of the ready available 4',8-di-*O*-hexanoyl isoflavone derivative **8**[12] with the corresponding peracetyl pentosyl trichloroacetimidates **3-7**[13-17] under the promotion of $BF_3{\cdot}OEt_2$ and subsequent removal of the acyl groups with K_2CO_3 in a mixed solvent of $MeOH/THF/H_2O$ (Scheme 1). The yields (over two steps) are only moderate (26%-76%); partial migration of the 8-*O*-hexanoyl group onto the neighboring 7-OH under the glycosylation conditions was observed.

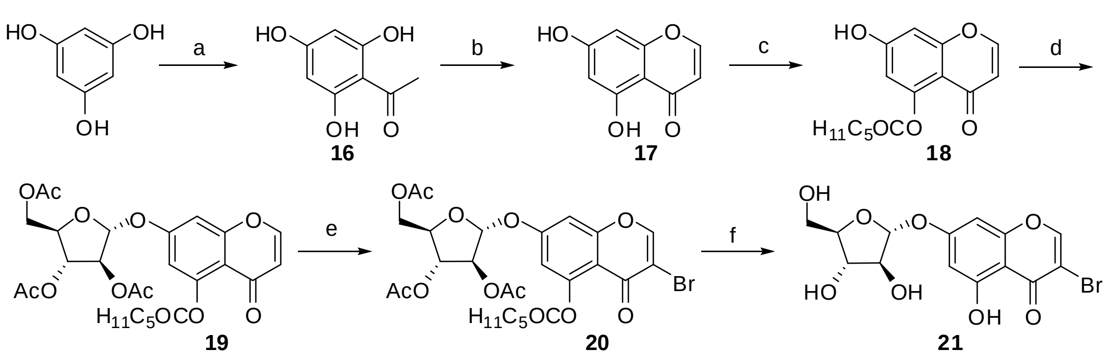


Scheme 1. Synthesis of the 4’,8-dihydroxyisoflavon-7-yl pentosides **1** and **9a-d**.

To synthesize the A and B ring congeners of A-76202 (**1**), a divergent approach by using Suzuki-Miyaura coupling[18] of a 3-bromo-4*H*-chromen-7-yl α-D-arabinofuranoside (i.e., **15** and **21**) with a panel of the commercially available aryl boronic acids as the final step was envisioned. The required chromen-3-bromides **15** and **21** were prepared as shown in Schemes 2 and 3.



Scheme 2. Synthesis of 3-bromo-8-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside **15**. (a) AcOH, $BF_3 \cdot OEt_2$, 90~100°C, 4 h, 96%. (b) $HC(OEt)_3$, 70% $HClO_4$, 85 °C, 12 h, 82%. (c) i) $CH_3(CH_2)_4COCl$, pyridine, 0 °C-rt, 16 h; ii) PhSH, imidazole, NMP, 0 °C-rt, 3 h, 70%. (d) **3**, $BF_3 \cdot OEt_2$, CH_2Cl_2, 4 Å MS, rt, 62%. (e) $PhI(OAc)_2$, TMSBr, CH_2Cl_2, pyridine, 0 °C-rt, 67%. f) K_2CO_3, $MeOH/THF/H_2O$ (2:1:0.2), rt, 77%.



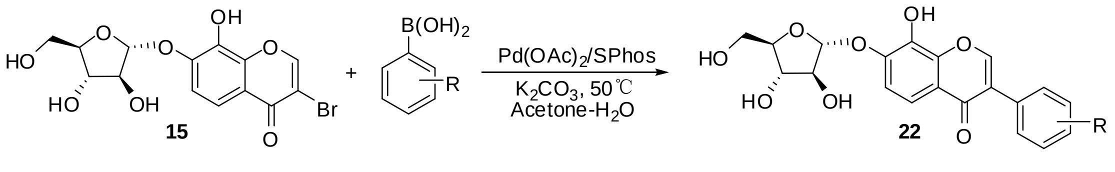
Scheme 3. Synthesis of 3-bromo-5-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside **21**. (a) Ac_2O, $BF_3{\cdot}OEt_2$, rt, 34 h; (b) MsCl, DMF, $BF_3{\cdot}OEt_2$, 50°C, 4 h, 37%. (c) i) $CH_3(CH_2)_4COCl$, pyridine, 0 °C–rt, 16 h; ii) PhSH, imidazole, NMP, 0 °C-rt, 3 h, 64%. (d) **3**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 4 Å MS, rt, 89%. (e) $PhI(OAc)_2$, TMSBr, CH_2Cl_2, pyridine, 0 °C–rt, 63%. (f) K_2CO_3, MeOH/THF/H_2O (2:1:0.2), rt, 42%.

Thus, acylation of pyrogallol with glacial acetic acid under the action of $BF_3{\cdot}OEt_2$ at 90~100°C provided ketone **10**, which was treated with triethyl orthoformate in the presence of 70% $HClO_4$ to afford chromone **11** (Scheme 2). Selective protection of the 5-OH in diol **11** was achieved via 5,7-di-*O*-hexanoate formation and subsequent removal of the 7-*O*-acyl group,[12] which is *para* to the electron-withdrawing pyrone carbonyl function, with PhSH and imidazole in *N*-methyl pyrolidinone (NMP) to give **12** (70% for two steps). Glycosylation of phenol **12** with 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl trichloroacetimidate (**3**) under the promotion of $BF_3{\cdot}OEt_2$ led to the α-glycoside **13** in 62% yield. Bromination of compound **13** was achieved with $PhI(OAc)_2$ and TMSBr at room temperature with pyridine as a base,[19] affording chromone 3-bromide **14**. Removal of the acyl protecting groups in **14** with K_2CO_3 in a mixed solvent of MeOH/THF/H_2O, to compromise the solubility of the reactants, provided the desired 7-α-D-arabinofuranosyloxy-chromon-3-bromide **15**.

Employing a similar procedure described above, the A ring isomer **21** was synthesized with phloroglucinol as the starting material (Scheme 3). Worth noting is that the glycosylation of the 5-*O*-hexanoyl-7-ol **18** with arabinofuranosyl trichloroacetimidate **3** gave the glycoside **19** in a much better 89% yield comparing to the glycosylation of 8-*O*-hexanoyl-7-ol **12** with imidate **3** (and the glycosylation of the isoflavone derivative **8** as well, Scheme 1) under similar conditions (62%). The latter reaction suffered from the migration of the 8-*O*-hexanoyl group onto the neighboring 7-OH under the glycosylation conditions as mentioned.

Although Suzuki-Miyaura reaction has been widely used as one of the most efficient methods for C-C bond formation,[18] in only few examples flavonoid iodides or *O*-triflates have been employed as the coupling partners.[20] In fact, the instability of the 4*H*-pyranones under basic conditions limited the choice of bases in the Suzuki-Miyaura coupling of bromides **15** and **21** with boronic acids. Under the optimized conditions with 2-(2,6-dimethoxybiphenyl)dicyclohexylphosphine (SPhos) as a ligand, as introduced by Buchwald et al,[21] in the presence of $Pd(OAc)_2$ and K_2CO_3, coupling of bromide **15** with a variety of the aryl boronic acids provided the corresponding isoflavone glycosides **22a-n** in moderate yields (Table 1). Reduction of the bromide and degradation of the chromone B ring are the major side reactions.

Table 1. Synthesis of the B-ring congeners (**22**) via Suzuki-Miyaura coupling of **15**.

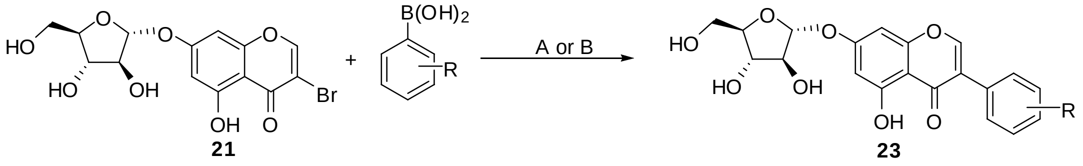


Product	R	Yield (%)
22a	H	65
22b	4-OMe	54
22c	2-OMe	50
22d	3-OMe	75
22e	4-Me	45
22f	2-Me	34

22g	3-Me	58
22h(**1**)	4-OH	48
22i	3-OH	35
22j	4-F	31
22k	4-NMe$_2$	36
22l	4-NHBoc	39
22m	4-CF$_3$	41
22n	4-SiMe$_3$	30

Under similar conditions, the couplings with chromon-3-bromide **21** gave lower yields of the desired product (Table 2), because chromone **21** was found more vulnerable to basic degradation than its region-isomer **15**. An alternative procedure for this coupling was in the absence of ligand and with NaOAc as a base, but the coupling yields were even lower.

Table 2. Synthesis of the A,B-ring congeners (**23**) via Suzuki coupling of **21**.



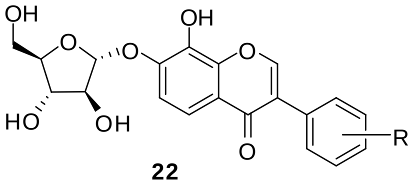
Entry	R	Conditions	Yield (%)
23a	H	A	28
		B	16
23b	4-OMe	A	43
23c	2-OMe	A	39
23d	3-OMe	A	19
23e	4-Me	B	39
23f	3-Me	A	16
23g	4-OH	A	39
		B	12
23h	3-OH	A	35

Conditions A: Pd(OAc)$_2$ (0.05 equiv), SPhos (0.15 equiv), K$_2$CO$_3$ (3.0 equiv), acetone/H$_2$O, 50 °C. Conditions B: Pd(OAc)$_2$ (0.05 equiv), NaOAc (3.0 equiv), MeOH, reflux.

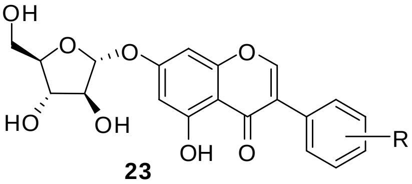
Inhibitory activities against α-glucosidases

The synthetic natural product **1** exhibited potent inhibitory activity against the α-glucosidases of rat liver microsome, with an IC_{50} = 18 nM, that is comparable to the literature value of 14 nM.[11b] However, none of the stereoisomers (**9a-d**) showed remarkable activities at concentrations up to 10 μM. Gratifyingly, all the B ring analogs of **1** (**22a-n**) exhibited activities at 10 nM concentration (Table 3). The 4-OH in the B ring of **1** could be replaced by -OMe, -H, -F, -Me, and -CF_3 without considerably affecting the activity. Their regio-isomers, i.e., the 3-OH, 2-OMe, 3-OMe, 2-Me, and 3-Me derivatives, were similarly potent. Especially, the 3-OMe and 4-NMe_2 derivatives (**22d** and **22l**) were about 3–fold more potent that the 4'-OH natural product (**1**). However, the 5-OH (on the A ring) derivatives, which are regio-isomers of the above 8-OH isoflavone glycosides (**22a-n**) were 1000 times less potent inhibitiors. Worth of noting is that all these compounds, including the natural flavone glycoside **1**, were found inert toward the α-glucosidase from bakers yeast.

Table 3. Inhibitory activities of the isoflavone 7-*O*-α-D-arabinofuranosides **22** and **23** against the α-glucosidases of rat liver microsome.



22



23

R	Compound (IC_{50}, in μM)	
H	**22a** (0.040)	**23a** (10)
4-OMe	**22b** (0.022)	**23b** (8)
2-OMe	**22c** (0.015)	**23c** (10)
3-OMe	**22d** (0.006)	**23d** (10)
4-Me	**22e** (0.035)	**23e** (7)
2-Me	**22f** (0.020)	-
3-Me	**22g** (0.050)	**23f** (5)

4-OH	**22h/1** (0.018)	**23g** (15)
3-OH	**22i** (0.017)	**23h** (33% at 50)
4-F	**22j** (0.015)	-
4-NMe$_2$	**22k** (0.008)	-
4-NHBoc	**22l** (0.020)	-
4-CF$_3$	**22m** (0.030)	-
4-SiMe$_3$	**22n** (35% at 0.050)	-

Conclusions

A concise approach to the synthesis of isoflavone glycosides has been developed, where the Suzuki-Miyaura coupling between glycosyloxy chromon-3-bromides (i.e., **15** and **21**) and aryl boronic acids is employed as the final step. Although there remains room for increasing the coupling yields, and the glycosylation yields as well, the present method provides a quick and divergent access to this type of common natural products. Totally 26 isoflavone glycosides (**9a**-**d**, **22a**-**n**, and **23a**-**h**) have been readily synthesized, which are analogs of the potent α-glucosidase inhibitor A-76202 with minor variations at the sugar moiety, the A, and B rings. Evaluation of the inhibitory activities of these compounds against the α-glucosidases of rat liver microsome has led to a preliminary and clear SAR (structure-activity relationship) conclusion: the stereochemistry of the sugar moiety (the α-D-arabinofuranosyl unit) and the 8-hydroxyl group in the A ring are crucial to the activity, while variations on the B ring of the isoflavone 7-*O*-glycosides are largely tolerated to retain the potent α-glucosidase inhibitory activities.

Experimental

General methods[12]

General procedure for assay of the α-glucosidase inhibitory activity

IC₅₀ value was determined at 37 °C in 0.1 M K_2HPO_4/KH_2PO_4-0.15M KCl buffer (pH 6.8), with *p*-nitrophenyl α-D-glucopyranoside (purchased from Sigma Chemical Co.) as the substrate. Rat liver microsome fraction solubilized with 25% Triton X-100 was used as enzyme. The inhibitor (5 μL, in DMSO), diluted enzyme solution (20 μL), and buffer solution (105 μL) were added to a 96-well microtiter plate, and preincubated for 10 min at 37 °C. The enzymatic reaction was started by the addition of 20 μL of the substrate solution (20 mM). The absorption at 400 nm was measured immediately. The increase of absorption per min at 400 nm was taken as the relative rate for the hydrolysis of the substrate. The increase was linear during all measurements (30 min). IC_{50} values were determined by plotting the relative rate of the substrate hydrolysis *vs.* the inhibitor concentration. The inhibitor concentration corresponding to half of the relative rate measured in the absence of the inhibitor gave the appropriate IC_{50} value. All the experiments were carried out in triplicate.

Synthesis of 4’,8-dihydroxyisoflavon-7-yl pentoses (1 and 9a-d)

General procedure: $BF_3·OEt_2$ (0.1 M in CH_2Cl_2, 0.4 mL) was added slowly to a solution of **8** (100 mg, 0.214 mmol) and glycosyl trichloroacetimidate (250 mg, 0.612 mmol) in dried CH_2Cl_2 (8 mL) in the presence of newly activated 4 Å molecular sieves at 0 °C. The mixture was allowed to warm up to rt and stirred until TLC indicated the completion of the reaction. The solid in the mixture was filtered off by passing it through a celite pad and the filtrate was condensed *in vacuo*. The residue was dissolved in MeOH/THF/H_2O (2 : 1 : 0.2, 5 mL) and K_2CO_3 (119 mg, 0.856 mmol) was added. The mixture was stirred at rt until TLC indicated the completion of the reaction. Dowex-50 (H^+) resin was used to neutralize the reaction mixture. The solution was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to yield **1** or **9** as a white solid.

4’,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside (1, A-76202): Yield = 58%. R_f 0.24 (CH_2Cl_2 : MeOH = 10 : 1); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.22 (s, 1 H), 7.64 (d, *J* = 9.0 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.74 (s, 1 H), 4.37 (d, *J* = 1.5 Hz, 1 H), 4.16 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.07 (m, 1 H), 3.74 (dd, *J* = 11.7 Hz, 3.6 Hz, 1 H), 3.69 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.5, 159.1, 157.7, 154.6, 153.2, 131.8, 126.2, 124.4, 123.1, 119.3, 116.6, 116.3, 110.0, 90.1, 82.4, 79.0, 63.5.

4’,8-Dihydroxyisoflavon-7-yl α-L-arabinofuranoside (9a): Yield = 26%. R_f 0.38 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{22}$ = -106.2 (*c* 0.56, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.21 (s, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.00 (d, *J* = 9.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.90 (s, 1 H), 4.40 (s, 1 H), 4.30 (dd, *J* = 7.8 Hz, 4.5 Hz, 1 H), 4.10 (br s, 1 H), 3.67-3.62 (m, 2 H); ESI-MS (*m/z*): 403.1 (M + H^+); HRMS (ESI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1024.

4’,8-Dihydroxyisoflavon-7-yl β-D-ribofuranoside (9b): Yield = 60%. R_f 0.14 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{23}$ = -107.6 (*c* 0.24, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.59 (br s, 1 H), 8.41 (s, 1 H), 7.55 (d, *J* = 9.0 Hz, 1 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.24 (d, *J* = 9.0 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.52 (s, 1 H), 5.05 (d, *J* = 6.0 Hz, 1 H), 4.30-4.10 (m, 2 H), 3.94 (br s, 1 H), 3.61 (dd, *J* = 12.0 Hz, 1.8 Hz, 1 H), 3.44 (dd, *J* = 12.0 Hz, 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.4, 157.4, 153.4, 148.1, 146.3, 136.4, 130.4, 123.5, 122.7, 120.0, 115.3, 115.2, 115.16, 115.10, 107.2, 84.9, 74.7, 70.2, 62.2; ESI-MS (*m/z*): 403.2 (M + H^+), HRMS (ESI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1023.

4’,8-Dihydroxyisoflavon-7-yl β-D-xylofuranoside (9c): Yield = 46%. R_f 0.20

(CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{22}$ = -100.2 (*c* 0.21, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.45 (br s, 1 H), 8.38 (s, 1 H), 7.55 (d, *J* = 9.0 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 9.0 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 5.57 (s, 1 H), 4.31 (s, 1 H), 4.21 (dd, *J* = 11.1, 4.8 Hz, 1 H), 4.07 (dd, *J* = 4.5, 1.5 Hz, 1 H), 3.70 (dd, *J* = 11.7, 4.8 Hz, 1 H), 3.53 (dd, *J* = 11.7, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.2, 157.2, 153.1, 147.2, 145.9, 137.3, 130.1, 123.4, 122.6, 120.1, 115.6, 115.0, 107.7, 84.6, 80.3, 75.0, 60.1; ESI-MS (*m/z*): 401.3 (M - H^+); HRMS (ESI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1023.

4’,8-Dihydroxyisoflavon-7-yl β-D-xylopyranoside (9d): Yield: 76%. R_f 0.20 (DCM : MeOH = 10 : 1); $[\alpha]_D^{21}$ = - 33.8 (*c* 0.29 , MeOH); ^{1}H NMR（300 MHz，CD_3OD）δ = 8.21 (s, 1 H), 7.63(d, *J* = 8.7 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 8.7 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 2 H), 4.96 (d, *J* = 7.8 Hz, 1 H), 3.90 (dd, *J* = 11.1 Hz, 4.8 Hz, 1 H), 3.60-3.36 (m, 4 H); ^{13}C NMR（75 MHz，CD_3OD）δ = 178.7, 159.0, 155.2, 150.2, 148.3, 137.6, 131.7, 126.0, 124.4, 121.8, 117.0, 116.5, 115.8, 104.2, 77.5, 74.8, 71.2, 67.3; ESI-MS (*m/z*): 401.1 (M – H^+); HRMS (ESI) calcd for $C_{20}H_{18}O_9Na^+$ 425.0843, Found: 425.0813.

Synthesis of 3-bromo-8-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside (15)

1-(2,3,4-Trihydroxyphenyl)ethanone (10): A solution of pyrogallol (12.61 g, 100 mmol) and glacial acetic acid (64 mL, 110.9 mmol) in $BF_3{\cdot}OEt_2$ (37 mL) was heated at 90-100 °C for 4 h in the protection of argon, cooled, and then poured into 10% NaOAc (600 mL), and stirred overnight. The dark solution was extracted with ether (3 × 300 mL). The organic layer was washed with saturated NaCl and dried with anhydrous Na_2SO_4. Removal of the solvent gave **10** (16.1 g, 96%) as a yellow solid. R_f 0.69 (CH_2Cl_2 : MeOH = 10 : 1).

7,8-Dihydroxy-4*H*-chromen-4-one (11): Compound **10** (10.0g, 59.47 mmol) was suspended in ethyl orthoformate (50 mL, 300 mmol) and was treated with 70% $HClO_4$ (6 mL) slowly. The mixture was heated on an oil bath at 85 ^oC for 12 h, and was then cooled, and 200 mL ether was added. The precipitate was filtered off, washed with water, and dried, giving crude **11** (8.72 g, 82%) as yellow solid. R_f 0.45 (CH_2Cl_2 : MeOH =10 : 1).

7-Hydroxy-4-oxo-4*H*-chromen-8-yl hexanoate (12): Hexanoyl chloride (27 mL, 195.6 mmol) was added to a stirring solution of **11** (6.8 g, 38.2 mmol) in pyridine at 0 ^oC, the mixture was allowed to warm up to rt. After stirring for an additional 16 h, the solution was diluted with CH_2Cl_2, and then was washed with 1 N aq. HCl and saturated NaCl. The organic layer was dried with anhydrous Na_2SO_4, and then concentrated in vacuum. The resulting residue was dissolved into dried NMP (60 mL). Imidazole (1.10 g, 15.84 mmol) was added and the solution was cooled to 0 ^oC by an ice-water bath, followed by the addition of PhSH (5.8 mL, 56.94 mmol). The reaction mixture was stirred and allowed to warm up to rt naturally. When TLC indicated the completion of the reaction, CH_2Cl_2 (300 mL) was added, the resulting mixture was washed with 1 N aq. HCl, water, and saturated NaCl sequentially. The organic layer was dried with anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 2 : 1) to yield **12** as a yellow solid (7.64 g, 70% for two steps). R_f 0.17 (petroleum ether : EtOAc = 2 : 1); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (br s, 1 H), 7.98 (d, J = 9.0 Hz, 1 H), 7.79 (d, J = 5.7 Hz, 1 H), 7.11 (d, J = 9.0 Hz, 1 H), 6.32 (d, J = 5.7 Hz, 1 H), 2.71 (t, J = 7.5 Hz, 2 H), 1.82 (p, J = 7.2 Hz, 2 H), 1.48-1.35 (m, 4 H), 0.93 (t, J = 6.9 Hz, 3 H).

8-(Hexanoyloxy)-4-oxo-4*H*-chromen-7-yl 2,3,5-tri-*O*-acetyl-α-D-arabino

furanoside (13): A solution of **12** (7.64 g, 27.65 mmol) and glycosyl imidate **3** (17.86 g, 42.46 mmol) in dried CH_2Cl_2 (200 mL) was treated with newly activated 4 Å MS and stirred at rt for 15 min. $BF_3 \cdot OEt_2$ (2.8 mL, 2.80 mmol) was added dropwise to the solution at 0 °C, and the reaction mixture was stirred at rt for 3 h, and then Et_3N (5 mL) was added to quench the reaction. The solid was filtered off by passing the reaction through a celite pad and the solvent was removed in vacuum. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 2 : 1) to yield **13** as a yellows syrup (9.1g, 62%). R_f 0.53 (petroleum : EtOAc =1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 9.0 Hz, 1 H), 7.78 (d, *J* = 6.3 Hz, 1 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 6.30 (d, *J* = 6.3 Hz, 1 H), 5.79 (s, 1 H), 5.38 (s, 1 H), 5.11 (br s, 1 H), 4.47-4.35 (m, 2 H), 4.28 (dd, *J* =11.7 Hz, 4.5 Hz, 1 H), 2.68 (t, *J* = 7.8 Hz, 2 H), 2.16 (s, 3 H), 2.14 (s, 3 H), 2.11 (s, 3 H), 1.84 (q, *J* = 7.5 Hz, 2 H), 1.51-1.30 (m, 4 H), 0.96 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 170.5, 170.4, 169.9, 169.4, 154.8, 152.0, 149.9, 128.8, 123.6, 120.7, 113.8, 113.0, 104.5, 82.0, 81.1, 76.7, 62.7, 33.7, 31.2, 24.6, 22.2, 20.7, 20.6, 13.9; ESI-MS (m/z): 535.3 (M + H^+), 557.3 (M + Na^+); HRMS (MALDI) calcd for $C_{26}H_{30}O_{12}Na^+$ 557.1630, Found 557.1638.

3-Bromo-8-(hexanoyloxy)-4-oxo-4*H*-chromen-7-yl 2,3,5-tri-*O*-acetyl-α-D-arabinofuranoside (14): TMSBr (8.6 mL, 64.96 mmol) was added slowly to a solution of $PhI(OAc)_2$ (10.6 g, 32.71 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C, and the solution was stirred in an ice-bath for 45 min before the addition of **13** (5.8 g, 10.85 mmol) in CH_2Cl_2 (25 mL). The ice-bath was removed and the reaction mixture was allowed to warm up to rt and stayed 2 h. Pyridine (5.7 mL, 66.47 mmol) was then added, and the stirring was continued for an additional 1 h. The resulting mixture was diluted with CH_2Cl_2, and washed with saturated $Na_2S_2O_3$ and saturated NaCl. The organic layer was dried with anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 3 : 1 to 5 : 2) to yield **14** as a yellow syrup (4.5 g, 67%). R_f 0.85 (petroleum ether : EtOAc = 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 7.35 (d, *J* = 9.0 Hz, 1 H), 5.80 (s, 1 H), 5.38 (s, 1 H), 5.12 (d, *J* = 3.6 Hz, 1 H), 4.47-4.36 (m, 2 H), 4.28 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H), 2.68 (t, *J* = 7.5 Hz, 2 H), 2.16 (s, 3 H), 2.14 (s, 3 H), 2.11 (s, 3 H), 1.83 (q, *J* = 7.2 Hz, 2 H), 1.48-1.35 (m, 4 H), 0.96 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 170.4, 170.38, 169.9, 169.4, 153.2, 152.3, 149.6, 128.6, 124.2, 118.8, 114.5, 110.9, 104.5, 82.2, 81.1, 76.7, 62.7, 33.7, 31.2, 24.6, 22.2, 20.7, 20.62, 20.60, 13.9; ESI-MS (*m/z*): 613.1 ($M + H^+$), 635.2 ($M + Na^+$); HRMS (MALDI) calcd for $C_{26}H_{29}O_{12}BrNa^+$ 635.0735, Found: 635.0721.

3-Bromo-8-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside (15): The chromone derivative **14** (585 mg, 0.954 mmol) in MeOH/THF/H_2O (2 : 1 : 0.2, 50 mL) was treated with K_2CO_3 (527 mg, 3.82 mmol) at rt for 10 h. TLC indicated the completion of the reaction. Dowex-50 (H^+) was added to neutralize the mixture. The solvent was removed in vacuum. Flash chromatography of the residue on silica gel yielded **15** as a yellow solid (287 mg, 77%). R_f 0.41 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 74.7 (*c* 0.20, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.57 (s, 1 H), 7.56 (d, *J* = 9.0 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 5.72 (s, 1 H), 4.36 (d, *J* = 2.1 Hz, 1 H), 4.13 (dd, *J* = 9.0 Hz, 4.5 Hz, 1 H), 4.08 (m, 1 H), 3.75 (dd, *J* = 11.7 Hz, 3.6 Hz, 1 H), 3.70 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H); ESI-MS (*m/z*): 410.8 ($M + Na^+$).

Synthesis of 3-Bromo-5-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside (21)

1-(2,4,6-Trihydroxyphenyl)ethanone (16): A solution of phloroglucinol (25.0 g, 198 mmol) and Ac_2O (190 mL, 199.5 mmol) in $BF_3 \cdot OEt_2$ (75 mL) was stirred at rt for 34 h, before it was poured into 10% NaOAc (700 mL) and stirred overnight. The precipitate was filtered off, washed with water and dried to give the crude **16** (24 g) as a yellow solid. R_f 0.74 (CH_2Cl_2 : MeOH =5 : 1).

5,7-Dihydroxy-4*H*-chromen-4-one (17): Newly distilled $BF_3 \cdot OEt_2$ (50 mL, 0.54 mol) was added slowly to a solution of **16** (20.2 g, 0.12 mmol) in dried DMF (180 mL) in 1 h at rt. Then the reaction was transferred to an oil-bath of 50 ^{o}C before the addition of a solution of MsCl (32 mL, 0.4 mol) in dried DMF (72 mL, 0.9 mol). The mixture was stirred at 50 ^{o}C for 4 h, and then cooled and poured into 2 L ice-water. The black solid was filtered off and the filtrate was extracted with EtOAc. Evaporation of the solvent and purification of the residue by flash chromatography (CH_2Cl_2 : MeOH =10: 1) yielded yellow solid **17** (8.0 g, 37% for two steps). R_f 0.90 ($CHCl_3$: MeOH = 10: 1); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.07 (br s, 1 H), 10.92 (br s, 1 H), 8.18 (d, J = 6.0 Hz, 1 H), 6.38 (d, J = 2.1 Hz, 1 H), 6.28 (d, J = 6.0 Hz, 1 H), 6.21 (d, J = 2.1 Hz, 1 H).

7-Hydroxy-4-oxo-4*H*-chromen-5-yl hexanoate (18): A similar procedure to the synthesis of **12** was employed. Yield = 64%; R_f 0.21 (petroleum ether : EtOAc=3 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.97 (br s, 1 H), 7.67 (d, J = 9.0 Hz, 1 H), 7.78 (d, J = 2.4 Hz, 1 H), 6.59 (d, J = 2.4 Hz, 1 H), 6.09 (d, J = 9.0 Hz, 1 H), 2.71 (t, J = 7.5 Hz, 2 H), 1.80 (m, 2 H), 1.50-1.33 (m, 4 H), 0.94 (t, J = 6.9 Hz, 3 H).

5-(Hexanoyloxy)-4-oxo-4*H*-chromen-7-yl 2,3,5-tri-*O*-acetyl-α-D-arabinofuranoside (19): A similar procedure to the synthesis of **13** was employed. Yield = 89%. R_f 0.38 (petroleum ether : EtOAc=2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 6.0 Hz, 1 H), 7.00 (d, J = 2.1 Hz, 1 H), 6.72 (d, J = 2.1 Hz, 1 H), 6.16 (d, J =

6.0 Hz, 1 H), 5.77 (s, 1 H), 5.37 (s, 1 H), 5.11 (d, *J* = 4.5 Hz, 1 H), 4.47-4.35 (m, 2 H), 4.29 (dd, *J* = 11.4 Hz, 4.8Hz, 1 H), 2.71 (t, *J* = 7.8 Hz, 2 H), 2.16 (s, 3 H), 2.15 (s, 3 H), 2.12 (s, 3 H), 1.80-1.70 (m, 2 H), 1.45-1.30 (m, 4 H), 0.93 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 172.3, 170.5, 170.1, 169.5, 159.5, 158.7, 153.9, 150.8, 113.9, 113.5, 109.9, 103.8, 102.1, 82.2, 81.1, 76.7, 62.8, 34.2, 31.3, 24.1, 22.4, 20.73, 20.68, 20.65, 13.9; ESI-MS (m/z): 557.3 (M + Na^+); HRMS (MALDI) calcd for $C_{26}H_{30}O_{12}Na^+$ 557.1630, Found 557.1638.

3-Bromo-5-(hexanoyloxy)-4-oxo-4*H*-chromen-7-yl 2,3,5-tri-*O*-acetyl-α-D-arabinofuranoside (20): A similar procedure to the synthesis of **14** was employed. Yield = 63%. R$_f$ 0.55 (petroleum ether : EtOAc = 2 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.02 (d, *J* = 1.2 Hz, 1 H), 6.77 (d, *J* = 1.2 Hz, 1 H), 5.77 (s, 1 H), 5.38 (s, 1 H), 5.12 (d, *J* = 4.5 Hz, 1 H), 4.48-4.35 (m, 2 H), 4.27 (dd, *J* = 11.4 Hz, 4.8 Hz, 1 H), 2.75 (t, *J* = 7.5 Hz, 2 H), 2.16 (s, 3 H), 2.15 (s, 3 H), 2.12 (s, 3 H), 1.77 (q, *J* = 6.9 Hz, 2 H), 1.45-1.30 (m, 4 H), 0.93 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 170.5, 170.1, 169.9, 169.5, 159.8, 158.3, 152.5, 150.9, 111.6, 110.6, 103.9, 102.0, 82.3, 81.1, 76.6, 62.8, 57.9, 34.1, 31.3, 24.1, 22.4, 20.75, 20.70, 20.66, 13.9; ESI-MS (*m/z*): 635.2 (M + Na^+); HRMS (MALDI) calcd for $C_{26}H_{29}O_{12}BrNa^+$ 635.0735, Found: 635.0720.

3-Bromo-5-hydroxy-4-oxo-4*H*-chromen-7-yl α-D-arabinofuranoside (21): A similar procedure to the synthesis of **15** was employed. Yield = 42%. R$_f$ 0.47 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 117.6 (*c* 0.28, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.47 (s, 1 H), 6.70 (d, *J* = 1.8 Hz, 1 H), 6.54 (d, *J* = 1.8 Hz, 1 H), 5.65 (d, *J* = 1.5 Hz, 1 H), 4.30 (dd, *J* = 3.9, 1.5 Hz, 1 H), 4.08 (m, 1 H), 4.03 (dd, *J* = 6.0 Hz, 3.9 Hz, 1 H), 3.80 (dd, *J* = 12.0, 2.7 Hz, 1 H), 3.70 (dd, *J* = 12.0, 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.2, 165.0, 163.0, 159.3, 157.3, 108.9, 108.2, 107.2, 102.0, 96.5, 87.4, 83.9, 78.5, 63.0; ESI-MS (*m/z*): 410.8 ($M + Na^+$).

Suzuki-Miyaura coupling

General procedure A: $Pd(OAc)_2$ (1.5 mg, 0.0067 mmol), SPhos (8.0 mg, 0.0195 mmol), and K_2CO_3 (54 mg, 0.390 mmol) were added to a solution of 3-bromochromone **15** or **21** (50 mg, 0.129 mmol) and aryl boronic acid (0.195 mmol) in acetone-H_2O (1:1, 1.0 mL) under the protection of argon. The mixture was stirred in an oil-bath at 50 °C until TLC indicated the disappearance of the starting material (**15** or **21**). The reaction solution was then filtered through a silica pad (300~400 mesh) and the filtrate was concentrated in vacuum to give a residue, which was purified by preparative TLC (CH_2Cl_2 : MeOH = 8 : 1) to yield the coupling products. The yields are given in Tables 1 and 2.

General procedure B: $Pd(OAc)_2$ (1.5 mg, 0.0067 mmol), SPhos (8.0 mg, 0.0195 mmol, 0.15 eq.), and NaOAc (32 mg, 0.390 mmol) were added to a solution of 3-bromochromone **21** (50 mg, 0.129 mmol) and aryl boronic acid (0.195 mmol) in methanol (0.5 mL) under the protection of argon. The mixture was refluxed in an oil-bath until TLC indicated the disappearance of **21**. Similar workup procedure as given in the General procedure A provided the coupling products. The yields are given in Table 2.

8-Hydroxyisoflavon-7-yl α-D-arabinofuranoside (22a): R_f 0.29 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24} = 31.8$ (*c* 0.11, MeOH); ^1H NMR (300 MHz, CD_3OD): δ = 8.26 (s, 1 H), 7.62 (d, *J* = 9.0 Hz, 1 H), 7.52 (d, *J* = 6.3 Hz, 2 H), 7.43-7.35 (m, 3 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 5.73 (s, 1 H), 4.37 (br s, 1 H), 4.16 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.06 (m, 1 H), 3.73 (dd, *J* = 11.7 Hz, 3.6 Hz, 1 H), 3.68 (dd, *J* = 11.7 Hz, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.5, 155.9, 149.7, 148.3, 138.0, 133.6, 130.6, 129.7, 129.4, 126.1, 121.4, 116.8, 115.8, 109.1, 88.7, 83.0, 78.9, 63.3; ESI-MS (*m/z*): 387.2

(M + H$^+$), 409.2 (M + Na$^+$), 425.0 (M + K$^+$); HRMS (MALDI) calcd for $C_{20}H_{18}O_8Na^+$ 409.0894, Found: 409.0902.

8–Hydroxy-4'-methoxyisoflavon-7-yl α-D-arabinofuranoside (22b): R$_f$ 0.29 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 142.4 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.29 (s, 1 H), 7.66 (d, *J* = 8.7 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.7 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 5.77 (s, 1 H), 4.41 (br s, 1 H), 4.18 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.10 (m, 1 H), 3.85 (br s, 3 H), 3.77 (dd, *J* = 11.7 Hz, 3.6 Hz, 1 H), 3.73 (dd, J = 11.7 Hz, 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.8, 161.5, 155.4, 149.6, 148.4, 138.1, 131.7, 125.74, 125.71, 121.4, 116.7, 115.8, 115.2, 109.1, 88.8, 83.0, 78.9, 63.3, 56.1; ESI-MS (m/z): 417.0 (M + H$^+$), 439.0 (M + Na$^+$), 455.0 (M + K$^+$); HRMS (MALDI) calcd for $C_{21}H_{20}O_9Na^+$ 439.1000, Found: 439.0999.

8–Hydroxy-2'-methoxyisoflavon-7-yl α-D-arabinofuranoside (22c): R$_f$ 0.29 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 74.2 (*c* 0.12, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.54 (br s, 1 H), 8.13 (s, 1 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.28-7.19(m, 2 H), 7.05 (d, *J* = 8.7 Hz, 1 H), 6.99 (t, *J* = 7.8 Hz, 1 H), 5.68 (s, 1 H), 4.39 (br s, 1 H), 4.19 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.00 (m, 1 H), 3.77 (br s, 4 H), 3.70 (dd, *J* = 11.7 Hz, 5.4 Hz, 1 H); ESI-MS (*m/z*): 439.0 (M + Na$^+$); HRMS (MALDI) calcd for $C_{21}H_{20}O_9Na^+$ 439.1000, Found: 439.0990.

8-Hydroxy-3'-methoxyisoflavon-7-yl α-D-arabinofuranoside (22d): R$_f$ 0.29 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 27.6 (*c* 0.13, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.33 (s, 1 H), 7.54 (d, *J* = 9.0 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 9 Hz, 1 H), 7.16 (br s, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 6.97 (br d, *J* = 7.2 Hz, 1 H), 5.73 (s, 1 H), 4.40 (br s, 1 H), 4.19 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.05 (m, 1 H), 3.85 (s, 3 H), 3.83-3.65 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 179.1, 161.4, 156.1, 150.5, 145.9, 144.5, 135.2, 130.7, 125.6, 122.8, 121.7, 116.4, 116.2, 115.0, 113.8, 109.1, 88.5, 83.0, 78.9, 63.3, 56.1; ESI-MS (m/z): 417.2 (M + H$^+$), 439.2 (M + Na$^+$), 455.2 (M + K$^+$); HRMS (MALDI) calcd for $C_{21}H_{21}O_9^+$ 417.1180, Found: 417.1188.

8-Hydroxy-4’-methylisoflavon-7-yl α-D-arabinofuranoside (22e): R$_f$ 0.27 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 37.1 (*c* 0.17, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.18 (s, 1 H), 7.54 (d, *J* = 9.0 Hz, 1 H), 7.34 (d, *J* = 7.5 Hz, 2 H), 7.24 (d, *J* = 9.0 Hz, 1 H), 7.15 (d, *J* = 7.5 Hz, 2 H), 5.66 (s, 1 H), 4.30 (br s, 1 H), 4.08 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 3.98 (br s, 1 H), 3.66 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.62 (dd, *J* = 11.7 Hz, 4.8 Hz, 1 H), 2.28 (s, 3 H); ESI-MS (m/z): 401.0 (M + H$^+$), 423.0 (M + Na$^+$); HRMS (MALDI) calcd for $C_{21}H_{21}O_8^+$ 401.1231, Found: 401.1235.

8-Hydroxy-2’-methylisoflavon-7-yl α-D-arabinofuranoside (22f): R$_f$ 0.39 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 52.1 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.13 (s, 1 H), 7.40 (d, *J* = 8.7 Hz, 1 H), 7.34-7.16 (m, 5 H), 5.71 (s, 1 H), 4.39 (br s, 1 H), 4.20 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.03 (m, 1 H), 3.76 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.67 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H), 2.21 (s, 3 H) ; ESI-MS (m/z): 401.2 (M + H$^+$), 423.2 (M + Na$^+$), 439.0 (M + K$^+$); HRMS (MALDI) calcd for $C_{21}H_{20}O_8Na^+$ 423.1050, Found: 423.1058.

8-Hydroxy-3’-methylisoflavon-7-yl α-D-arabinofuranoside (22g): R$_f$ 0.35 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 17.7 (*c* 0.13, MeOH); ^{1}H NMR (300 MHz, CD_3O D): δ = 8.32 (s, 1 H), 7.78-7.63 (m, 2 H), 7.42-7.29 (m, 3 H), 7.22 (br s, 1 H), 5.79 (s, 1 H), 4.43 (br s, 1 H), 4.21 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.10 (m, 1 H), 3.78 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.71 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H), 2.41 (s, 3 H); ESI-MS (m/z): 401.2 (M + H$^+$), 423.2 (M + Na$^+$), 439.2 (M + K$^+$); HRMS (ESI) calcd for $C_{21}H_{20}O_8Na^+$ 423.1050, Found: 423.1051.

4’,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside (22h, A-76202)[10]

3’,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside (22i): R$_f$ 0.23 ($CHCl_3$:

MeOH = 8 : 1); $[\alpha]_D^{24}$ = 99.7 (*c* 0.08, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.31 (s, 1 H), 7.67 (d, *J* = 8.7 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.05 (br s, 1 H), 7.03 (d, *J* = 8.1 Hz, 1 H), 6.85 (br d, *J* = 6.6 Hz, 1 H), 5.79 (s, 1 H), 4.43 (br s, 1 H), 4.22 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.11 (m, 1 H), 3.79 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.74 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.6, 158.8, 155.7, 150.0, 148.7, 138.9, 134.9, 130.7, 126.2, 121.7, 117.7, 116.5, 116.4, 116.2, 109.4, 88.9, 83.0, 79.0, 63.4; ESI-MS (m/z): 403.0 (M + H^+), 425.0 (M + Na^+); HRMS (MALDI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1028.

4'-Fluoro-8–hydroxyisoflavon-7-yl α-D-arabinofuranoside (22j): R_f 0.42 ($CHCl_3$: MeOH = 8 : 1); $[\alpha]_D^{24}$ = 31.6 (*c* 0.16, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.34 (s, 1 H), 7.65-7.56 (m, 3 H), 7.34 (d, *J* = 9.0 Hz, 1 H), 7.19 (t, *J* = 8.4 Hz, 2 H), 5.77 (s, 1 H), 4.41 (br s, 1 H), 4.21 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.09 (m, 1 H), 3.78 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.73 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H); ESI-MS (m/z): 405.2 (M + H^+), 427.2 (M + Na^+); HRMS (ESI) calcd for $C_{20}H_{17}O_8FNa^+$ 427.0800, Found: 427.0795.

4'-(Dimethylamino)-8-hydroxyisoflavon-7-yl α-D-arabinofuranoside (22k): R_f 0.30 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 104.6 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.22 (s, 1 H), 7.43 (d, *J* = 8.4 Hz, 3 H), 7.25 (d, *J* = 9.0 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 5.69 (s, 1 H), 4.40 (br s, 1 H), 4.20 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.02 (m, 1 H), 3.77 (dd, *J* = 11.7 Hz, 3.0 Hz, 1 H), 3.71 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H), 2.96 (br s, 6 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 180.0, 155.0, 152.3, 150.6, 144.4, 131.1, 125.6, 122.1, 116.7, 124.0, 112.1, 109.1, 88.3, 83.0, 79.0, 63.4, 41.1; ESI-MS (m/z): 430.0 (M + H^+); HRMS (ESI) calcd for $C_{22}H_{23}O_8NNa^+$ 452.1316, Found: 452.1320.

4'-(*tert*-Butoxycarbonylamino)-8–hydroxyisoflavon-7-yl α-D-arabinofuranoside

(22l): R$_f$ 0.42 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 45.6 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.57 (s, 1 H), 8.28 (s, 1 H), 7.60 (d, *J* = 9.0 Hz, 1 H), 7.48 (br s, 4 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 5.75 (s, 1 H), 4.40 (br s, 1 H), 4.17 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H), 4.07 (m, 1 H), 3.79 (dd, *J* = 11.7 Hz, 3.9 Hz, 1 H), 3.71 (dd, *J* = 11.7 Hz, 5.1 Hz, 1 H), 1.53 (s, 9H); ESI-MS (m/z): 502.0 (M + H$^+$), 524.0 (M + Na$^+$); HRMS (MALDI) calcd for $C_{25}H_{27}O_{10}NNa^+$ 524.1527, Found: 524.1532.

8-Hydroxy-4’-(trifluoromethyl)isoflavon-7-yl α-D-arabinofuranoside (22m): R$_f$ 0.43 ($CHCl_3$: MeOH = 10 : 1); $[\alpha]_D^{24}$ = 37.5 (*c* 0.23, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 7.83-7.65 (m, 4 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 5.77 (s, 1 H), 4.42 (br s, 1 H), 4.21 (dd, *J* = 7.8 Hz, 4.5 Hz, 1 H), 4.09 (m, 1 H), 3.82-3.74 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.3, 156.4, 150.3, 149.1, 140.6, 138.1, 131.1, 126.4, 124.6, 121.7, 116.4, 115.1, 109.3, 88.9, 82.8, 79.0, 63.4, 31.0; ESI-MS (m/z): 455.0 (M + H$^+$), 477.0 (M + Na$^+$); HRMS (ESI) calcd for $C_{21}H_{17}O_8F_3Na^+$ 477.0768, Found: 477.0768.

8-Hydroxy-4’-(trimethylsilyl)isoflavon-7-yl α-D-arabinofuranoside (22n): R$_f$ 0.58 (CH_2Cl_2 : MeOH = 8 : 1); $[\alpha]_D^{24}$ = 49.1 (*c* 0.12, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.32 (s, 1 H), 7.71-7.46 (m, 5 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 5.76 (s, 1 H), 4.42 (br s, 1 H), 4.21 (dd, *J* = 8.7 Hz, 4.5 Hz, 1 H,), 4.07 (br s, 1 H), 3.86-3.64 (m, 2 H), 0.30 (s, 9 H); ESI-MS (m/z): 459.0 (M + H$^+$).

5-Hydroxyisoflavon-7-yl α-D-arabinofuranoside (23a): R$_f$ 0.42 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 86.7 (*c* 0.15, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.20 (s, 1 H), 7.56 (d, *J* = 6.6 Hz, 2 H), 7.48-7.34 (m, 3 H), 6.70 (br s, 1 H), 6.50 (br s, 1 H), 5.65 (s, 1 H), 4.29 (br s, 1 H), 4.13-3.96 (m, 2 H), 3.78 (dd, *J* = 12.0 Hz, 2.4 Hz, 1 H), 3.69 (dd, *J* = 12.0 Hz, 4.5 Hz, 1 H); ESI-MS (m/z): 387.0 (M + H$^+$), 409.0 (M + Na$^+$); HRMS (ESI) calcd for $C_{20}H_{19}O_8^+$ 387.1074, Found: 387.1075.

5-Hydroxy-4'-methoxyisoflavon-7-yl α-D-arabinofuranoside (23b): R$_f$ 0.48 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 68.6 (*c* 0.19, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.17 (s, 1 H), 7.50 (d, *J* = 7.2 Hz, 2 H), 6.99 (d, *J* = 7.2 Hz, 2 H), 6.69 (br s, 1 H), 6.50 (br s, 1 H), 5.67 (s, 1 H), 4.31 (br s, 1 H), 4.13-4.02 (m, 2 H), 3.84 (s, 3 H), 3.80 (dd, *J* = 12.0 Hz, 3.0 Hz, 1 H), 3.73 (dd, *J* = 12.0, 4.5 Hz, 1 H); ESI-MS (m/z): 417.0 (M + H$^+$), 439.0 (M + Na$^+$); HRMS (MALDI) calcd for $C_{21}H_{21}O_9^+$ 417.1180, Found: 417.1186.

5-Hydroxy-2'-methoxyisoflavon-7-yl α-D-arabinofuranoside (23c): R$_f$ 0.49 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 74.6 (*c* 0.19, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.28 (s, 1 H), 7.63 (t, *J* = 8.4 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 6.93 (d, *J* = 1.8 Hz, 1 H), 6.74 (d, *J* = 1.8 Hz, 1 H), 5.89 (s, 1 H), 4.53 (d, *J* = 2.1 Hz, 1 H), 4.35-4.22 (m, 2 H), 4.04 (dd, *J* = 12.0 Hz, 3.0 Hz, 1 H), 4.03 (s, 3 H), 3.93 (dd, *J* = 12.0 Hz, 4.5 Hz, 1 H); ESI-MS (*m/z*): 417.2 (M + H$^+$); HRMS (ESI) calcd for $C_{21}H_{21}O_9^+$ 417.1180, Found: 417.1190.

5-Hydroxy-3'-methoxyisoflavon-7-yl α-D-arabinofuranoside (23d): R$_f$ 0.47 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 89.2 (*c* 0.08, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.22 (br s, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.15 (br s, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 6.96 (d, *J* = 7.5 Hz, 1 H), 6.70 (d, *J* = 1.5 Hz, 1 H), 6.51 (d, *J* = 1.5 Hz, 1 H), 5.65 (br s, 1 H), 4.29 (d, *J* = 3.6 Hz, 1 H), 4.10-3.98 (m, 2 H), 3.82 (s, 3 H), 3.78 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.70 (dd, *J* = 12.0 Hz, 4.5 Hz); ESI-MS (m/z): 417.2 (M + H$^+$), 439.2 (M + Na$^+$); HRMS (ESI) calcd for $C_{21}H_{21}O_9^+$ 417.1180, Found: 417.1178.

5-Hydroxy-4'-methylisoflavon-7-yl α-D-arabinofuranoside (23e): R$_f$ 0.50 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 136.7 (*c* 0.13, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.16 (s, 1 H), 7.43 (d, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 6.68 (br s, 1 H), 6.49 (br s, 1 H), 5.64 (s, 1 H), 4.29 (br s, 1 H), 4.13-3.98 (m, 2 H), 4.06 (dd, *J* = 12.0 Hz, 3.0 Hz, 1 H), 3.98 (dd, *J* = 12.0 Hz, 4.5 Hz, 1 H), 2.37 (s, 3 H); ESI-MS (m/z): 401.1 (M + H$^+$), 423.1 (M + Na$^+$); HRMS (ESI) calcd for $C_{21}H_{21}O_8^+$ 401.1231, Found: 401.1232.

5-Hydroxy-3'-methylisoflavon-7-yl α-D-arabinofuranoside (23f): R$_f$ 0.49 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 97.6 (*c* 0.10, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.16 (s, 1 H), 7.40-7.30 (m, 3 H), 7.22 -7.18(d, *J* = 7.2 Hz, 1 H), 6.69 (br s, 1 H), 6.51 (br s, 1 H), 5.64 (br s, 1 H), 4.28 (br s, 1 H), 4.12-3.98 (m, 2 H), 3.84-3.63 (m, 2 H), 2.39 (s, 3 H); ESI-MS (m/z): 401.1 (M + H$^+$), 423.0 (M + Na$^+$); HRMS (ESI) calcd for $C_{21}H_{20}O_8Na^+$ 423.1050, Found: 423.1050.

4',5-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside (23g): R$_f$ 0.28 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 37.1 (*c* 0.15, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.15 (s, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 1.5 Hz, 1 H), 6.50 (d, *J* = 1.5 Hz, 1 H), 5.65 (br s, 1 H), 4.29 (d, *J* = 3.6 Hz, 1 H), 4.07 (m, 1 H), 4.02 (dd, *J* = 6.6 Hz, 3.9 Hz, 1 H), 3.78 (dd, *J* = 12.0, 2.7 Hz, 1 H), 3.70 (dd, *J* = 12.0, 4.5 Hz, 1 H); ESI-MS (*m/z*): 403.1 (M + H$^+$), 425.2 (M + Na$^+$); HRMS (ESI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1025.

3',5-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside (23h): R$_f$ 0.29 (CH_2Cl_2 : MeOH = 10 : 1); $[\alpha]_D^{24}$ = 49.2 (*c* 0.17, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 8.18 (s, 1 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 7.02 (br s, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 6.69 (br s, 1 H), 6.50 (br s, 1 H), 5.65 (s, 1 H), 4.29 (d, *J* = 3.0 Hz, 1 H), 4.07 (m, 1 H), 4.03 (dd, *J* = 6.6 Hz, 3.9 Hz, 1 H), 3.79 (dd, *J* = 12.0, 2.7 Hz, 1 H), 3.69 (dd, *J* = 12.0, 4.8 Hz, 1 H); ESI-MS (*m/z*): 403.1 (M + H$^+$); HRMS (MALDI) calcd for $C_{20}H_{19}O_9^+$ 403.1024, Found: 403.1030.

Acknowledgements

This work is supported by the Chinese Academy of Sciences (KGCX2-SW-213 and KGCX2-SW-209) and the National Natural Science Foundation of China (20321202).

References

[1] B. Imperiali, V. W.-F. Tai, *Carbohydrate-based Drug Discovery* (Ed.: C.-H. Wong), Wiley-VCH, Weinheim, **2003**, *1*, 281-301.

[2] J. Schweden, C. Borgmann, G. Legler, E. Bause, *Arch. Biochem. Biophys.* **1986**, *248*, 335-340.

[3] N. Sharon, H. Lis, *Sci. Am.* **1993**, *268*, 82-89.

[4] a) P. Hollander, X. Pi-Sunyer, R. E. Conif, *Diabetes Care* **1997**, *20*, 248-253; b) A. Mitrakou, N. Tountas, A. E. Raptis, R. J. Bauer, H. Shulz, S. A. Raptis, *Diabet. Med.* **1998**, *15*, 657-660; c) L. Scott, C. M. Spencer, *Drugs* **2000**, *59*, 521-549; d) A. Y. Y. Cheng, R. G. Josse, *Drug Discov. Today* **2004**, 201-206.

[5] C. P. Kordik, A. B. Reitz, *J. Med. Chem.* **1999**, *42*, 181-201.

[6] a) F. M. Platt, T. D. Butters, *Exp. Rev. Mol. Med.* **2000**, 1–18; b) T. D. Butters, R. A. Dwek, F. M. Platt, *Curr. Top. Med. Chem.* **2003**, *3*, 561–574; c) M. Takeuchi, K. Kamata, M. Yoshida, Y. Kameda, K. Matsui, *J. Biochem.* **1990**, *108*, 42–46; d) T. D. Butters, R. A. Dwek, F. M. Platt, *Glycobiology* **2005**, *15*, 43R–52R.

[7] a) M. J. Papandreou, R. Barbouche, R. Guieu, M. P. Kieny, E. Fenouillet, *Mol. Pharmacol.* **2002**, *61*, 186– 193; b) P. S. Sunkara, D. L. Taylor, M. S. Kang, T. L. Bowlin, P. S. Liu, A. S. Tyms, A. Sjoerdsma, *Lancet* **1989**, *333*, 1206; c) M. Dettenhofer, X.-F. Yu, *J. Biol. Chem.* **2001**, *276*, 5985–5991; d) G. S. Jacob, *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611.

[8] a) N. Asano, A. Kato, A. A. Watson, *Mini Rev. Med. Chem.* **2001**, *1*, 145–154; b) B. Ganem, *Acc. Chem. Res.* **1996**, *29*, 340–347; c) N. Asano, *Glycobiology* **2003**, *13*,

93R–104R; d) Y. Nishimura, *Curr. Top. Med. Chem.* **2003**, *3*, 575–591; e) T. A. Houston, J. T. Blanchfield, *Mini Rev. Med. Chem.* **2003**, *3*, 669–678.

[9] E. B. Melo, A. S. Gomes, I. Carvalho, *Tetrahedron* **2006**, *62*, 10277-10302.

[10] A. Takatsuki, M. Nakajima, O. Ando, *Jpn Kokai Tokkyo Kohou*, 96134091 (May 28, 1996).

[11] a) M. Shiozaki, *Tetrahedron: Asymmetry* **1999**, *10*, 1477–1482; b) Y. Watanabe, M. Shiozaki, R. Kamegai, *Carbohydr. Res.* **2001**, *335*, 283–289.

[12] M. Li, X. Han, B. Yu, *J. Org. Chem.* **2003**, *68*, 6842-6845.

[13] M. K. Gurjar, L. K. Reddy, S. Hotha, *J. Org. Chem.* **2001**, *66,* 4657-4660.

[14] L. V. Backinowsky, S. A. Nepogod'ev, A. S. Shashkov, N. K. Kochetkov, *Carbohydr. Res.* **1985**, *138*, 41–54.

[15] I. Chiu-Machado, J. C. Castro-Palomino, O. Madrazo-Alonso, C. Lopetegui-Palacios, V. Verez-Bencomo, *J. Carbohydr. Chem.* **1995**, *14*, 551-561.

[16] M. Wilstermann, G. Magnusson, *J. Org. Chem.* **1997,** *62,* 7961-7971.

[17] 2,3,5-Tri-*O*-acetyl-D-xylofuranosyl trichloroacetimidates (**6**) was prepared by condensation of 2,3,5-tri-*O*-acetyl-D-xylofuranose (W. J. Hennen, H. M. Sweers, Y. Wang, C.-H. Wong, *J. Org. Chem.* **1988**, *53*, 4939-4945) with CCl_3CN in the presence of DBU in CH_2Cl_2 (88%).

[18] (a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483. (b) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11-59.

[19] H. S. Rho, B.-S. Ko, Y.-S. Ju, *Synth. Commun.* **2001**, 31, 2101–2106.

[20] a) D. Zembower, H. Zhang, *J. Org. Chem.* **1998**, *63*, 9300-9305; b) X. Zheng, W. Meng, F. Qing, *Tetrahedron Lett.* **2004**, *45*, 8083-8085; c) X. Huang, E. Tang, W. M. Xu, J. Cao, *J. Comb. Chem.* **2005**, *7*, 802-805; d) W. Peng, X. Han, B. Yu, *Chin. J. Chem.* **2006**, *24*, 1154-1162.

[21] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876.