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TETRAHEDRON: *ASYMMETRY*

Synthesis of 4′,8-dihydroxyisoflavon-7-yl α-D-arabinofuranoside

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Abstract

4′,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside **1** (A-76202), which is a strong α-glucosidase I and II inhibitor, was synthesized by the glycosylation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl bromide **2** and the lithium salt of 4′,8-diallyloxy-7-hydroxyisoflavone **4**, and successive deprotection of allyl groups and benzoyl esters of the glycosylated product **5**.

1. Introduction

4′,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside **1** (A-76202) was isolated from *Rhodococcus* sp. SANK61694. It strongly inhibits α-glucosidases I and II, which exist in endoplasmic reticulum, and participates in the processing of secretory-, cell membrane- and virus surface-glycoproteins. The structure of A-76202[1] has been elucidated as a D-arabinose analogue **1** which contains a phenolic isoflavone as the aglycon. The synthesis of A-76202 is interesting because of its biological activity and also for developing the synthetic route for related compounds and is described here.

2. Results and discussion

The 4′ and 8 positions of 4′,7,8-trihydroxyisoflavone **3**[2] was protected by allyl bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeOH to give mainly 4′,8-diallyloxy-7-hydroxyisoflavone **3** (mp 125–126°C) in 41% yield after chromatographic purification from accompanying 8-allyloxy-4′,7-dihydroxyisoflavone, 7,8-diallyloxy-4′-hydroxyisoflavone and 4′,7,8-triallyloxyisoflavone. Treatment of **4** with butyl lithium in tetrahydrofuran (THF) generated the corresponding lithium salt, which was further reacted with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide **2**[3] in THF under reflux temperature to give **5** (26% from **4**, and 53% from **4** allowing for recovery of unreacted **4**), 2,3,5-tri-*O*-benzoyl-D-arabinofuranose (30% from **2**), and recovered **4** (51%). From this reaction, the product was only the

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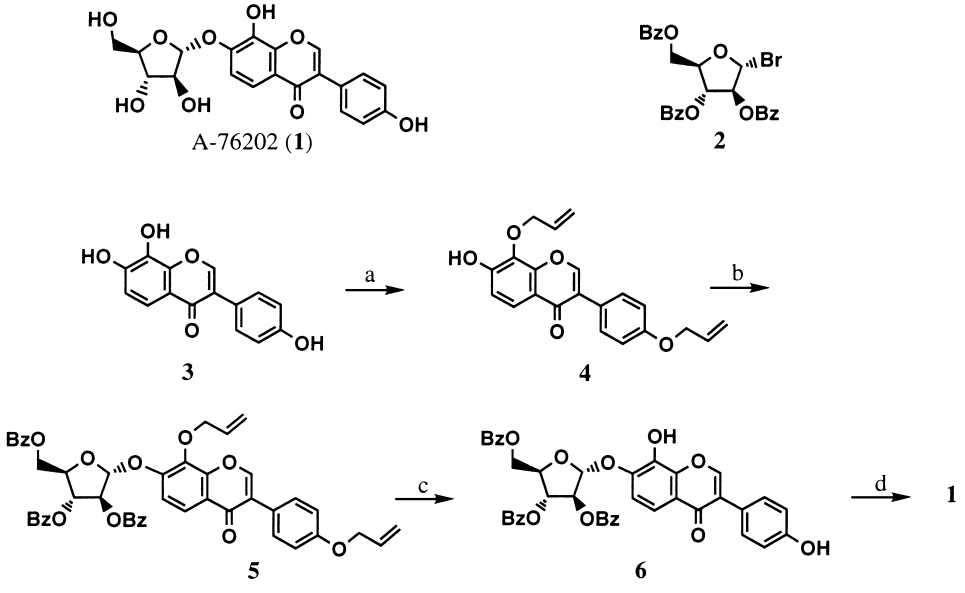
α-anomer without any β-anomer.[4] When the reaction of **4** with **2** in dichloromethane in the presence of silver carbonate (1 equiv.)–silver triflate (1 equiv.)–4Å molecular sieves (excess) according to the reported conditions[5] gave an inseparable mixture which contained **5** and three other compounds (from FAB MS data). The other procedure, which was employed for the coupling of the isoflavones and pyranosyl bromides by Wagner et al.,[6] was applied for this reaction. Treatment of a mixture of **2** and **4** in pyridine with silver carbonate led to recovery of the starting **4** without any coupling products (Scheme 1).

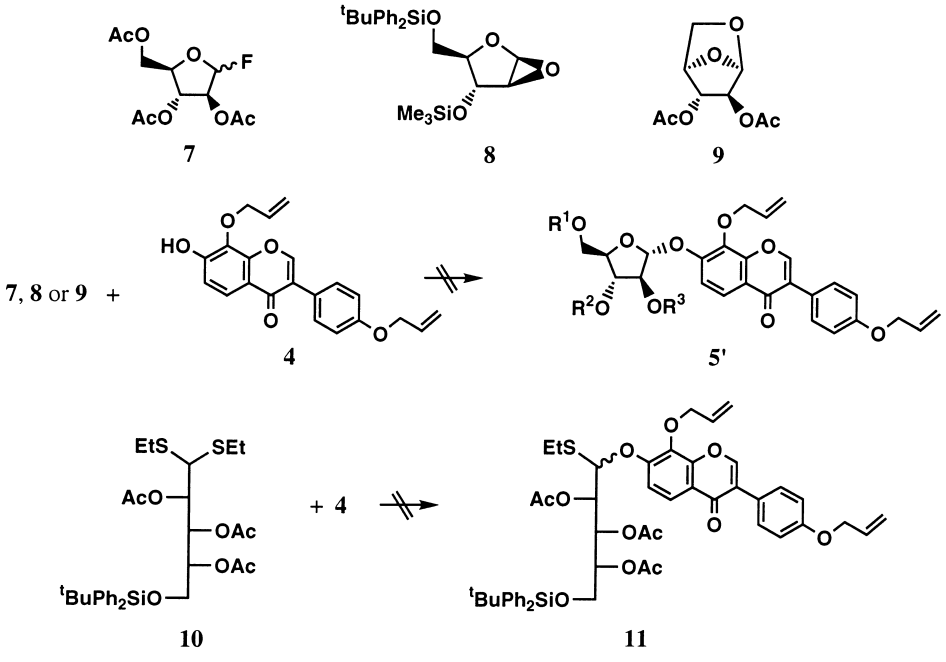


Scheme 1. Reagents and conditions: (a) allyl bromide, DBU, MeOH, rt then reflux 3 h, 41%; (b) *n*-BuLi, 2 THF rt, then reflux 6 h, 26% from **4** (recovery **4**, 51%; revised 53%); (c) $RhCl_3$ hydrate, EtOH, under N_2, reflux, 3 h, 78%; (d) 0.2 M NaOH aq. in MeOH, rt, 3 h, 76%

Deprotection of the allyl groups from **5** was performed by the treatment of $RhCl_3$ hydrate in EtOH at reflux to afford **6**. Saponification of the three benzoyl esters of **6** with 0.2 M NaOH aq. in MeOH gave **1** {($[\alpha]_D^{24}$ +115 (*c* 0.12, DMSO); natural A-76202: $[\alpha]_D^{24}$ +125 (*c* 0.12, DMSO)}, which was identical with natural A-76202 in the ^1H and ^{13}C NMR, IR, and FAB MS data.

A few alternative stereoselective routes to synthesize the equivalent compounds **5′** of the α-anomer **5** were attempted (Scheme 2). Treatment of 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl fluoride **7**[7,12] and **4** using 1.2 equivalents of bis(cyclopentadienyl)hafnium dichloride, 1.2 equivalents of silver trifluoromethanesulfonate and excess 4Å molecular sieves as Lewis acids in dichloromethane at 0–24°C under nitrogen according to Suzuki's method[8] gave an inseparable 3:1 mixture of α- and β-anomers (4′,8-diallyloxyisoflavon-7-yl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **5′** (R^1=R^2=R^3=Ac)) in extremely low yield (<2%). In this coupling reaction, the use of silver perchlorate–bis(cyclopentadienyl)zirconium dichloride–4Å molecular sieves[8] caused the degradation of compound **7**.

In another attempt to obtain the correct stereochemical 1,2-*trans* α-arabinoside, 1,2-anhydro-5-*O*-*tert*-butyldiphenylsilyl-3-*O*-trimethylsilyl-β-D-arabinofuranose **8**[9] was treated with **4** according to the reported procedure,[9b] however, the coupling compound **5′** (R^1=*tert*-butyldiphenylsilyl, R^2=trimethylsilyl, R^3=H) was not obtained. Also a solution of both 2,3-di-*O*-acetyl-1,5-anhydro-β-D-arabinofuranose **9**[10] and **4** in dichloromethane was treated with boron trifluoride diethyl etherate, trimethylsilyl trifluoromethanesulfonate, or titanium(IV) chloride under various conditions, however, no coupling compounds were detected only degradation of **9**. The other compound 2,3,4-tri-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-D-



Scheme 2.

arabinose diethyldithioacetal **10**, which was obtained easily by acetic anhydride–pyridine acetylation of 5-*O*-(*tert*-butyldiphenylsilyl)-D-arabinose diethyldithioacetal,[11] was treated with **4** using boron trifluoride diethyl etherate, mercury(II) chloride, or mercury(II) chloride–mercury(II) oxide under various conditions. These attempts did not yield any coupling compounds **11**.

Thus, in these attempts, the only successful coupling procedure was the reaction between the lithium salt of 4′,8-diallyloxy-7-hydroxyisoflavone and 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide.

3. Experimental

3.1. General

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR (270 and 400 MHz) spectra were recorded with JEOL JNM-270 and JEOL JNM-GSX 400 spectrometers using tetramethylsilane as an internal standard. IR absorption spectra were determined with an IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-700 mass spectrometer. Elemental analyses were performed by the Institute of Science and Technology, Inc. Separation of the compounds by column chromatography was carried out with silica gel 60 (230–400 mesh ASTM, E. Merck) under a slightly elevated pressure (1.2–1.5 atm) for easy elution. The quantity of silica gel used was 50–100 times the weight charged on the column. Detection involved spraying the chromatogram with a solution of 17% H_2SO_4 in water (w/w), containing ammonium molybdate (2.3%) and ceric sulfate (0.9%) (Hanessian dip), and heating the plate for several minutes at ca. 180°C. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and used immediately. Dichloromethane was dried by being passed through an ICN Alumina B-Super I.

3.2. Materials

3.2.1. 4′,8-Diallyloxy-7-hydroxyisoflavone **4**

To a solution of 4′,7,8-trihydroxyisoflavone **3** (270 mg, 1.00 mmol) in MeOH (2 ml) were added DBU (530 mg, 3.48 mmol) and allyl bromide (223 mg, 1.82 mmol). The mixture was stirred for 16 h at room temperature, acidified with 1 M HCl, diluted with EtOAc, washed with H_2O, then with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a mixture, which was chromatographed on a silica gel column. Elution with cyclohexane:EtOAc (1:1) gave 4′,7,8-triallyloxyisoflavone (25 mg, 6%), **4** (144 mg, 41%) as a semi-solid, 7,8-diallyloxy-4′-hydroxyisoflavone (53 mg, 13%), and 8-allyloxy-4′,7-dihydroxyisoflavone (104 mg, 35%). Physical data of 4′,7,8-triallyloxyisoflavone: R_f=0.877 (cyclohexane:EtOAc=2:3); 270 MHz ^{1}H NMR ($CDCl_3$) δ 4.56–4.74 (6H, m), 5.24–5.51 (6H, m), 6.01–6.22 (3H, m), 6.99 (2H, d, *J*=8.7 Hz), 7.04 (1H, d, *J*=9.1 Hz), 7.49 (2H, d, *J*=8.7 Hz), 7.99 (1H, s), 8.01 (1H, d, *J*=9.1 Hz). Physical data of **4**: mp 125–126°C (from hexane–EtOAc); R_f=0.745 (cyclohexane:EtOAc=2:3); IR ν_{max} (KBr) 3223, 1628, 1618, 1600, 1573, 1510, 1440 cm^{-1}; 270 MHz ^{1}H NMR ($CDCl_3$) δ 4.58 (2H, dm, *J*=5.3, ≤1 Hz), 4.74 (2H, d, *J*=6.1 Hz), 5.28–5.46 (4H, m), 6.01–6.19 (2H, m), 6.27 (1H, brs, OH), 6.99 (2H, d, *J*=8.9 Hz), 7.05 (1H, d, *J*=9.1 Hz), 7.49 (2H, d, *J*=8.9 Hz), 7.97 (1H, s), 7.98 (1H, d, *J*=9.1 Hz). FAB MS (positive) *m/z*: 351 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{21}H_{19}O_5$: 351.1232; found: 351.1219. Physical data of 7,8-diallyloxy-4′-hydroxyisoflavone: R_f=0.667 (cyclohexane:EtOAc=2:3); 270 MHz ^{1}H NMR ($CDCl_3$) δ 4.68–4.75 (4H, m), 5.24–5.51 (4H, m), 6.03–6.20 (2H, m), 6.89 (2H, d, *J*=8.5 Hz), 7.05 (1H, d, *J*=9.2 Hz), 7.44 (2H, d, *J*=8.5 Hz), 8.00 (1H, s), 8.01 (1H, d, *J*=9.2 Hz). FAB MS (positive) *m/z*: 351 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{21}H_{19}O_5$: 351.1232; found: 351.1209. Physical data of 8-allyloxy-4′,7-dihydroxyisoflavone: R_f=0.474 (cyclohexane:EtOAc=2:3); 270 MHz ^{1}H NMR ($CDCl_3$) δ 4.78 (2H, d, *J*=5.8 Hz), 5.37–5.44 (3H, m, containing OH), 6.14 (1H, m), 6.92 (2H, d, *J*=8.6 Hz), 7.10 (1H, d, *J*=8.7 Hz), 7.45 (2H, d, *J*=8.6 Hz), 8.00 (1H, s), 8.02 (1H, d, *J*=8.7 Hz).

Treatment of these compounds with acetic anhydride in pyridine gave the corresponding acetates which were further confirmed. Physical data of 7-acetoxy-4′,8-diallyloxyisoflavone: 270 MHz ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 4.57–4.60 (2H, m), 4.69 (2H, d, *J*=5.6 Hz), 5.27–5.48 (4H, m), 6.00–6.16 (2H, m), 7.00 (2H, d, *J*=8.6 Hz), 7.14 (1H, d, *J*=8.7 Hz), 7.49 (2H, d, *J*=8.6 Hz), 8.03 (1H, s), 8.05 (1H, d, *J*=8.7 Hz). FAB MS (positive) *m/z*: 393 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{23}H_{21}O_6$: 393.1339; found: 393.1341. Physical data of 4′-acetoxy-7,8-diallyloxyisoflavone: 270 MHz ^{1}H NMR ($CDCl_3$) δ 2.32 (3H, s), 4.69–4.78 (4H, m), 5.24–5.51 (4H, m), 6.03–6.20 (2H, m), 7.05 (1H, d, *J*=9.1 Hz), 7.17 (2H, d, *J*=8.6 Hz), 7.59 (1H, d, *J*=8.6 Hz), 8.01 (1H, d, *J*=9.1 Hz), 8.02 (1H, s). FAB MS (positive) *m/z*: 393 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{23}H_{21}O_6$: 393.1339; found: 393.1337. Physical data of 4′,7-diacetoxy-8-allyloxyoxyisoflavone: 270 MHz ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.38 (3H, s), 4.69 (2H, d, *J*=5.8 Hz), 5.27–5.45 (2H, m), 6.07 (1H, m), 7.16 (1H, d, *J*=8.6 Hz), 7.18 (2H, d, *J*=8.5 Hz), 7.59 (2H, d, *J*=8.5 Hz), 8.05 (1H, d, *J*=8.6 Hz), 8.06 (1H, s).

3.2.2. 4′,8-Diallyloxyisoflavon-7-yl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside **5**

To a solution of **4** (480 mg, 1.37 mmol) in THF (20 ml) was added *n*-BuLi (1.53 M *n*-hexane solution, 1.00 ml) at room temperature. After 5 min stirring, to this solution was added a solution of 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide **2** (864 mg, 1.64 mmol, 1.2 equiv.) in THF (10 ml). After 1.5 h stirring at room temperature, this solution was refluxed for 6 h, and diluted with EtOAc. The solution was washed with aq. $NaHCO_3$, then with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture, which was chromatographed on a silica gel column. Elution with cyclohexane:EtOAc (3:1) gave **5** [285 mg, 26% and 22% from **4** and **2**, respectively; and 53% and 31% from **4** and **2** allowing for

recovery of unreacted **4** and **2**, respectively; R_f=0.56 (cyclohexane:EtOAc=2:1)] as a powder, 2,3,5-tri-*O*-benzoyl-D-arabinofuranose [224 mg, 30% from **2**, R_f=0.49 (cyclohexane:EtOAc=2:1)] and recovery **4** [245 mg, 51%, R_f=0.38 (cyclohexane:EtOAc=2:1)]. Physical data of **5**: $[\alpha]_D^{24}$ +40 (*c* 0.22, $CHCl_3$); IR ν_{max} (KBr) 1726, 1646, 1604, 1568 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 4.58 (2H, d, *J*=5.4 Hz), 4.70–4.87 (5H, m), 5.18 (1H, d, *J*=10.3 Hz), 5.29–5.46 (3H, m), 5.73 (1H, d), 5.90 (1H, s), 6.04–6.12 (2H, m), 6.13 (1H, s), 6.99 (2H, d, *J*=8.5 Hz), 7.26–7.65 (12H, m), 8.01–8.16 (8H, m). FAB MS (positive) *m/z*: 795 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{47}H_{39}O_{12}$: 795.2441; found: 795.2444. Anal. calcd for $C_{47}H_{38}O_{12}$: C, 71.03; H, 4.82; found: C, 70.86; H, 4.99.

*3.2.3. 4′,8-Dihydroxyisoflavon-7-yl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside **6***

A solution of **5** (40 mg, 0.05 mmol) in anhydrous EtOH (4 ml) containing $RhCl_3$ hydrate (4 mg) was refluxed for 3 h under nitrogen. The resulting dark solution was concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with cyclohexane:EtOAc (1:1) gave **6** (28 mg, 78%) as a white powder. $[\alpha]_D^{24}$ +86 (*c* 0.05, $CHCl_3$); IR ν_{max} (KBr) 3410 (broad), 1726, 1603, 1575 cm^{-1}; 270 MHz ^1H NMR ($CDCl_3$) δ 4.70–4.92 (3H, m), 5.79 (1H, m), 5.93 (1H, d, *J*=1.0 Hz), 6.02 (1H, s), 6.63 (1H, bs, OH), 6.85 (2H, d, *J*=8.4 Hz), 7.26–7.64 (12H, m), 7.79 (1H, d, *J*=9.2 Hz), 7.98–8.11 (7H, m). FAB MS (positive) *m/z*: 715 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{41}H_{31}O_{12}$: 715.1815; found: 715.1811. Anal. calcd for $C_{41}H_{30}O_{12}$: C, 68.89; H, 4.23; found: C, 68.76; H, 4.51.

*3.2.4. 4′,8-Dihydroxyisoflavon-7-yl α-D-arabinofuranoside **1***

Compound **6** (124 mg, 0.17 mmol) in 0.2 M NaOH methanol solution (6.1 ml, 1.21 mmol, 7.0 equiv.) was stirred for 16 h at 24°C. The solution was concentrated in vacuo to one-third of the volume, acidified with 1 M HCl (1.3 ml), and diluted with EtOAc. The mixture was washed with H_2O, then with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a residue, which was chromatographed on a silica gel short column (silica gel, 6 g). Elution with EtOAc, and then EtOAc:MeOH (19:1) gave **1** (53 mg, 76%). $[\alpha]_D^{24}$ +115 (*c* 0.12, DMSO); [cf. natural A-76202: $[\alpha]_D^{24}$ +125 (*c* 0.12, DMSO)]; IR ν_{max} (KBr) 3329 (broad), 2930, 1626, 1600, 1573, 1515, 1451, 1396, 1336, 1283, 1211, 1176 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$:CD_3OD=1:1) δ 3.72 (1H, dd, *J*=3.2, 12.1 Hz), 3.80 (1H, dd, *J*=3.4, 12.1 Hz), 4.20 (1H, d, *J*=2.6 Hz), 4.28 (1H, m), 4.34 (1H, s), 5.77 (1H, s), 6.92 (2H, d, *J*=8.4 Hz), 7.25 (1H, d, *J*=9.1 Hz), 7.38 (2H, d, *J*=8.4 Hz), 7.73 (1H, d, *J*=9.1 Hz), 8.05 (1H, s); 100 MHz ^{13}C NMR (DMSO-d_6) δ 61.0, 76.5, 81.3, 85.8, 107.1, 114.4, 114.9, 115.0, 115.1, 119.6, 122.4, 123.2, 130.1, 136.0, 146.0, 147.5, 147.6, 153.1, 157.2, 175.1. FAB MS (positive) *m/z*: 403 $[M+H]^+$. High resolution FAB MS *m/z*: calcd for $C_{20}H_{19}O_9$: 403.1029; found: 403.1026. Anal. calcd for $C_{20}H_{18}O_9$: C, 59.69; H, 4.51; found: C, 59.60; H, 4.55. ^1H and ^{13}C NMR, IR, and FAB MS data of synthetic **1** were identical with those of natural A-76202.

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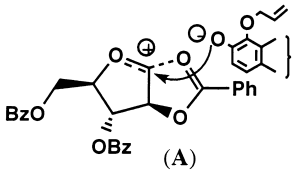
4. The configuration of **5** [1(*R*) (α-1,2-*trans*)] should come from α-side attack of the phenolic anion to the intermediate cation (**A**).



(**A**)

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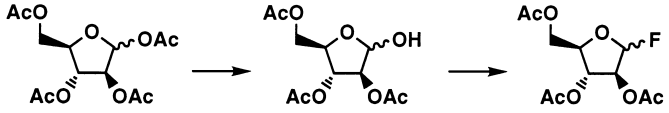
7. This compound was prepared as follows: 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose **12**[12] in CH_2Cl_2 was treated with 30% HBr in AcOH at 25°C, and successively aqueous saturated $NaHCO_3$ to yield 1,2,3-tri-*O*-acetyl-D-arabinofuranose **13** in 84% yield. A solution of **13** in CH_2Cl_2 was treated with diethylaminosulfur trifluoride for 15 min at ice cooling bath under nitrogen, and short column silica gel chromatography gave **7** in 73% as a viscose oil. Compound **7** is unstable at room temperature, and should be stored in a refrigerator. IR ν_{max} (film) 1748, 1373, 1226, 1064 cm^{-1}; 270 MHz ^1H NMR ($CDCl_3$) δ 2.11–2.15 (9H, m), 4.12–4.58 (3H, m), 5.00–5.44 (2H, m), 5.65–6.00 (1H, m). FAB MS (positive) *m/z*: 279 $[M+H]^+$, 301 $[M+Na]^+$. High resolution FAB MS *m/z*: calcd for $C_{11}H_{15}O_7FNa$: 301.0696; found: 301.0700. Anal. calcd for $C_{11}H_{15}O_7F$: C, 47.49; H, 5.43; F, 6.83; found: C, 47.39; H, 5.44; F, 6.39.



12 **13** **7**

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