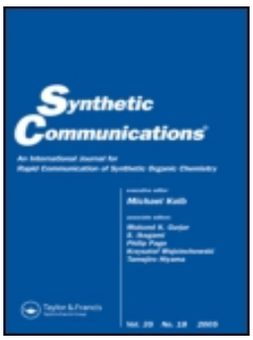


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Studies on the Regioselective Reductive Ringcleavage Reactions of 3,5-O-Arylidene- d-xylofuranosides

Ching-Yun Hsu & Chia-Chun Chen

To cite this article: Ching-Yun Hsu & Chia-Chun Chen (2003) Studies on the Regioselective Reductive Ringcleavage Reactions of 3,5-O-Arylidene- d-xylofuranosides, Synthetic Communications, 33:13, 2349-2363, DOI: 10.1081/SCC-120021517

To link to this article: http://dx.doi.org/10.1081/SCC-120021517

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 13, pp. 2349–2363, 2003

Studies on the Regioselective Reductive Ringcleavage Reactions of 3,5-*O*-Arylidene-D-xylofuranosides

Ching-Yun Hsu* and Chia-Chun Chen

Department of Chemical Engineering, Cheng Shiu Institute of Technology Kaohsiung, Taiwan, ROC

ABSTRACT

Reductive ring cleavage of 3,5-*O*-arylidene-D-xylofuranosides using $LiA1H_4$–$A1C1_3$ and $NaBH_3CN$–BF_3 proceeded regioselectively to provide secondary alcohol as the major product. The effect of the substitutents on the selectivity is examined.

Key Words: Regioselective reductive cleavage; Xylofuranosides; Benzylidene ketals; Projective groups; Hydride reducing agents.

*Correspondence: Ching-Yun Hsu, Department of Chemical Engineering, Cheng Shiu Institute of Technology Kaohsiung, Taiwan, 833 ROC; E-mail: erichsu@cc.csit.edu.tw.

DOI: 10.1081/SCC-120021517 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

INTRODUCTION

Recent advances made in the field of oligosaccharide synthesis can be attributed to the improved methods for the construction of the glycosidic bond, whose success depends on the selective protection and deprotection of sugar hydroxyl groups.[1] Benzylidene acetal is one of the extensively used protective groups, which provides selective protection of the 4- and 6-hydroxyl groups of gluco, manno, and galactopyranoses and other related sugars.[2,3] Methodologies for the regioselective reductive cleavage of the benzylidene acetal, allowing selective formation of benzyl ether at either the C_4 or C_6 hydroxyl moieties enhanced the utility of this protective group.[4,5]

RESULTS AND DISCUSSION

Though regioselective reduction of benzylidene acetals of pyranoses is extensively studied, selective deprotection of this function is less explored in furanose derivatives.[6] $LiA1H_4$-$A1C1_3$[7,8] and $NaBH_3CN$-BF_3[5] were quite often used as reagents to cleave the acetal function. In the case of 4,6-*O*-benzylidene hexopyranosides, the direction of the ring opening depends on the bulkiness of the C_3-substituent.[6,8–10] Although there are couple reports that dealt with the reductive ring opening of 3,5-*O*-benzylidene-D-xylofuranoside, only one furanosyl sugar was studied.[11] We have carried out a detailed study of the regioselective ring opening reactions of 3,5-*O*-benzylidene-D-xylofuranosides **1** and results are presented in this article.

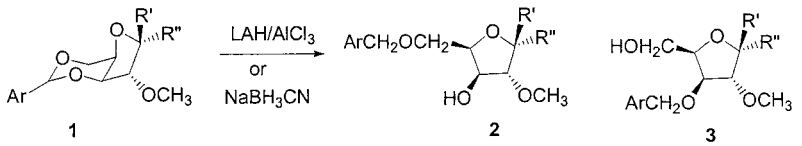
When either anomer of 3,5-*O*-benzylidene-D-xylofuranoside **la** was treated with $NaBH_3CN$-BF_3 or $LiA1H_4$-$A1C1_3$ in THF, the corresponding 5-*O*-benzyl-D-xylofuranoside **2a** was obtained as the major product (Sch. 1). The reductive cleavage was highly regioselective and only trace amount of 3-*O*-benzyl-D-xylofuranoside **3a** was formed. The yield of the product was relatively more when $NaBH_3CN$-BF_3 was used as the reagent.

To study the effect of the substituents on the regioselectivity of the ring opening,3,5-*O*-arylidene-D-xylofuranosides were subjected to reduction under similar experimental conditions. Benzylidene acetals containing electron donating substituents such as 4′-methoxy benzylidene and 2′,4′-dimethoxy benzylidene derivatives of D-xylofuranosides, **1b** and **1c** on treatment with $NaBH_3CN$-BF_3 or $LiAlH_4$-$A1C1_3$ in THF furnished the corresponding 5-*O*-benzyl-D-xylofuranosides **2b** and **2c** respectively as the major products in these reactions. However, the selectivity was

significantly low when compared to simple benzyl derivative. On the other hand, benzylidene acetals of furanosides with electron withdrawing substituents in the benzene ring such as 2′,6′-difluorobenzylidene and 2′,6′-dichlorobenzylidene acetals, **1d** and **1e**, afforded a single product **4** in each case. However, the ^{1}H NMR spectrum of **4** was devoid of the C_1 anomeric proton signal corresponding to xylofuranoside (5.36 ppm). Compound **4** was characterized as diol based on its spectral data. Thus **1d** and **1e** underwent initial reductive cleavage of benzylidene moiety to 5-*O*-benzyl derivative which suffered subsequent furanose ring cleavage to yield 1, 2-diols **4a** and **4b** respectively. Though the reaction was very slow, the selectivity was good in these cases.

Table 1. Ratio and yields of secondary (**2**) and primary alcohols (**3**).

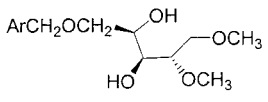
Compound	Reagent	Product ratio (2°OH:1°OH)	Yield (%)
1a α	$LAH/AlCl_3$	26:1	69
	$NaBH_3CN/BF_3$	41:1	86
1a β	$LAH/AlCl_3$	38:1	70
	$NaBH_3CN/BF_3$	31:1	88
1b α	$LAH/AlC1_3$	6:1	83
	$NaBH_3CN/BF_3$	4:1	80
1b β	$LAH/AlCl_3$	5:1	91
	$NaBH_3CN/BF_3$	3:1	78
1c α	$LAH/AlCl_3$	3:1	73
	$NaBH_3CN/BF_3$	4:3	78
1c β	$LAH/AlCl_3$	2:1	70
	$NaBH_3CN/BF_3$	7:6	83



1 2 3

α-anomer R' = H, R" = OCH_3; β-anomer R' = OCH_3, R" = H

Ar = a) phenyl, b) 4-methoxy phenyl, c) 2,4-dimethoxy phenyl, d) 2,6-dichloro phenyl, e) 2,6-difluoro phenyl



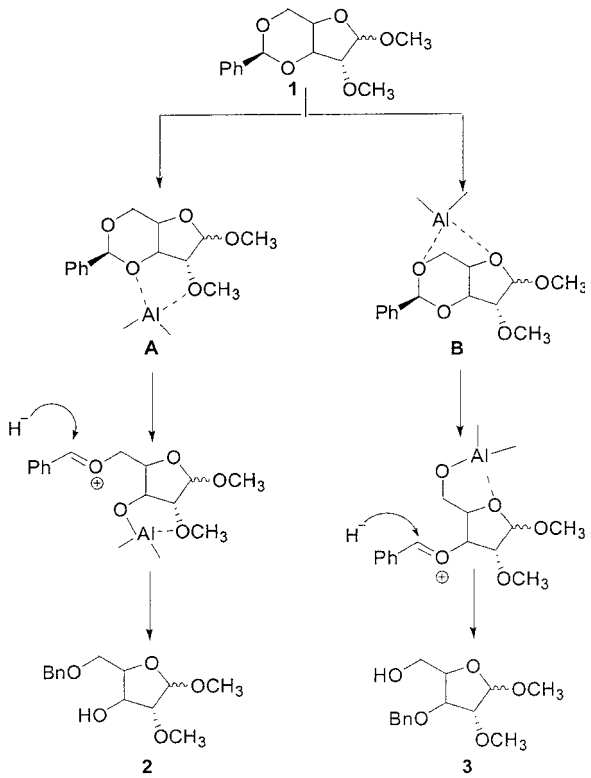
4

Scheme 1.

Thus electron donating groups in the benzylidene ring diminished the regioselectivity while presence of an electron withdrawing group led to enhanced selectivity, although reaction did not stop with the opening of arylidene acetal ring in the latter case.

The mixture of the isomeric alcohols **2** and **3** could be separated by using HPLC, and ^{1}H NMR helped in the differentiation of primary and secondary alcoholic products. Thus in moderately dilute solution, OH proton of primary and secondary alcohols appeared as triplet and doublet respectively. Esterification of the hydroxyl group using acetyl chloride under basic conditions also served in distinguishing the isomeric products which was based on the relative downfield shift in signal positions of proton(s) attached to the hydroxyl group containing carbon.

The possible mechanistic pathways leading to both primary and secondary alcohols are depicted in Sch. 2. Chelation of the oxygen



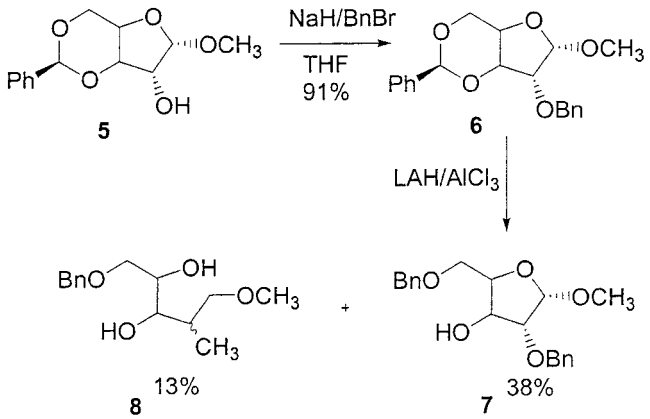
Scheme 2.

atoms of substrate with the electron deficient A1 of the reagent leads to the intermediates **A** and **B**. Intermediate A in which C_2 oxygen is coordinated to the electron deficient A1 leads to secondary alcohol **2** while primary alcohol **3** results from intermediate **B**.

Formation of **2** as the major product in these reductive ring cleavage reactions indicated the prominent role played by the C_2 oxygen in chelation with Al and this was proved by ^{13}C NMR study carried out at low temperatures. Thus, when an equimolar reaction of **1a** and trimethylaluminium hexane solution was studied by ^{13}C NMR at $-78^{\circ}C$ in 1:1 CD_2Cl_2 and $CDCl_3$ mixture as the solvent, a significant shift was observed in the signals at 108.4 (CH), 88.6 (CH), 72.8 (CH), 56.0 (CH_3) corresponding to C_2, C_3, C_7, and C_2-methoxy carbons of **1a** respectively. Shift in these signals may be obviously attributed to the participation of the C_2 oxygen in the chelation which will affect the environment of these carbons.

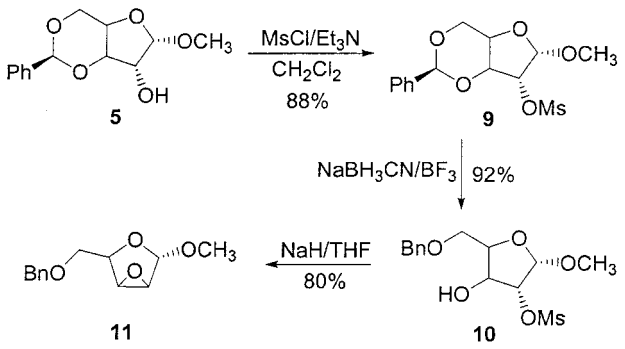
Subsequently we have modified the oxygen function at C_2 in the substrate to find out its effect on the extent of chelation with the reagent. Reaction of the 2-hydroxy compound **5** with benzyl bromide in the presence of NaH afforded the corresponding benzyle derivative **6** which on treatment with $LAH/AlCl_3$ afforded the secondary alcohol **7** along with the corresponding open chain vicinal diol **8** as the minor product (Sch. 3). Thus, in spite of the presence of a relatively bulkier benzyl substituent, the C_2 oxygen could participate in chelation.

In order to study the effect of an electron withdrawing group on the ability of the C_2 oxygen to participate in chelation, a mesyl group was

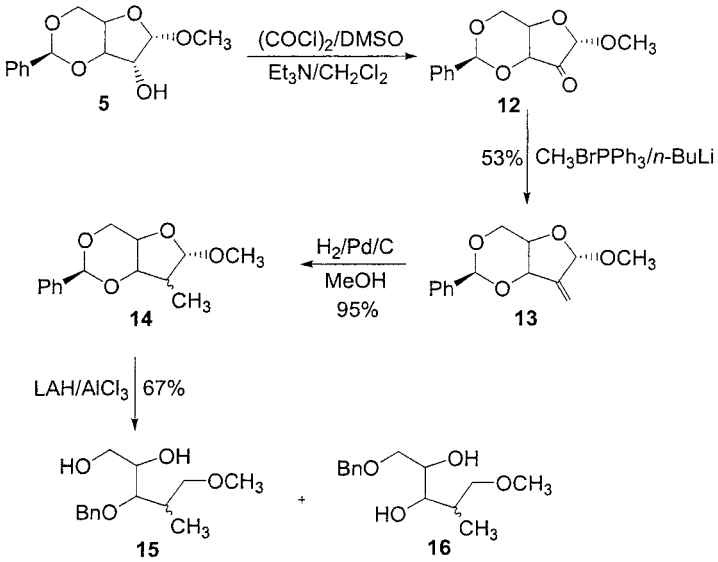


5 6 8 7

Scheme 3.



Scheme 4.



Scheme 5.

introduced on it. Thus reaction of the methyl furanoside **5** with mesyl chloride in the presence of triethylamine in dichloromethane furnished the corresponding mesylate **9** as a white solid. Treatment of **9** with two equiv. of $BF_3{\cdot}Et_2O$ at 0°C followed by the addition of a THF solution of $NaBH_3CN$ yielded the secondary alcohol **10** as the sole product (Sch. 4). Formation of the epoxide **11** from **10** in the presence of NaH through an

intramolecular substitution of mesyl group proved the assigned structure of **10**.

Finally it was planned to examine the regioselectivity of the reductive ring cleavage in the absence of C_2 oxygen and C_2 OH group of **5** was replaced by a methyl group. Swern oxidation of the alcohol **5** yielded ketone **12** in 87% yield. As ketone was prone to undergo epimerization readily, it was as such used in the subsequent laboratory operation with out further chromatographic purification. Thus Wittig reaction of the ketone **12** with CH_3BrPPh_3/BuLi at 0°C yielded alkene **13** which on catalytic hydrogenation afforded **14** as an inseparable mixture of α, β isomers in 10:1 ratio.

Reductive cleavage of **14** using LAH/$AlCl_3$ proceeded very slowly and afforded a mixture of open chain diols **15** and **16** corresponding to primary and secondary alcohols, respectively in 1:1 ratio (Sch. 5). Thus no selectivity was observed in the absence of C_2 oxygen.

In conclusion, reductive ring opening of acetals of xylofuranosides with mixed hydride reagents, LiA-H_4–$AlCl_3$ and $NaBH_3CN$–BF_3 proceeded regioselectively to provide secondary alcohol as the major product. Electron donating substituents in the arylidene moiety decreased the selectivity, while electron withdrawing groups enhanced the selectivity, though reduction led to furanose ring opening in the latter case. The role of the C_2 oxygen in providing the regioselectivity was studied by modifying the oxygen functionality at C_2 of the substrate.

EXPERIMENTAL SECTION

All the melting points were determined on a Buchi 512 melting point apparatus and are uncorrected. Infra red spectra were recorded on Perkin Elmer 781 and Bomern B-100 Infrared Spectrophotometers. ^{1}H NMR spectra were run on a Bruker AM-400 NMR spectrometer. Low Resolution Mass spectra and High Resolution Mass Spectra were measured on Jeol TMS-D-100 and Jeol TMS-HX spectrometers, respectively. Elemental analyses were performed on a Heraeus CHN-O-Rapid Analyzer. Specific rotations were determined on Jasco DIP-360 polarimeter.

General Procedure for the Reductive Cleavage of 3,5-*O*-Arylidene-2-*O*-methyl-α(β)2-*O*-D-xylofuranoses (1a–e)

To a solution of $AlCl_3$ (0.88 b, 6.60 mmol) in anhydrous ether (8 mL) at 0°C was added 1M solution of LAH (1.70 mL, 1.70 mmol, THF) and

the reaction mixture was stirred for 20 min. A solution of compound **1** (3.30 mmol) in of ether (3 mL) was added slowly to the above reagent solution and the reaction mixture was warmed to room temperature and stirred for 4 h.

In case of xylofuranoses **1d** and **1e**, the reaction mixture was heated at 55°C for 50 h. The reaction was quenched with saturated NaCl solution (10 mL) and the mixture was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes). Xylofuranoses **1a–c** yielded a mixture of corresponding alcohols 2 and 3 in each case, which was separated by HPLC using hexane/EtOAc/isopropanol (2:4:1) as the mobile phase. Compounds **1d** and **1e** afforded the diols **4a** and **4b**, respectively.

Compound 2a. $[\alpha]_D^{20}$ 18.2 (*c* 2.5, $CHC1_3$). IR ($CHC1_3$): 3600–3200 (OH), 2890, 1480, 1170, 1110 cm^{-1}. ^1H NMR ($CDC1_3$, 400 MHz): δ 7.39–7.28 (m, 5H), 4.97 (d, 1H, $J = 4.4$ Hz.), 4.62, 4.57 (ABq, 2H, $J = 12.0$ Hz), 4.44 (m, 1H), 4.29 (m, 1H), 3.74 (m, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.17 (d, OH, $J = 8$ Hz). ^{13}C NMR ($CDC1_3$, 100 MHz): δ 137.3 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 100.4 (CH), 87.1 (CH), 76.0 (CH), 75.4 (CH), 73.8 (CH_2), 69.2 (CH_2), 58.0 (CH_3), 55.1 (CH_3). HRMS (EI, 70 eV): Calcd. for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1318.

Compound 3a. $[\alpha]_D^{20}$ −26.73 (*c* 2.0, $CHC1_3$). IR ($CHC1_3$): 3600–3300 (OH), 2940, 1510, 1200, 1120 cm^{-1}. ^1H NMR ($CDC1_3$, 400 MHz): δ 7.37–7.29 (m, 5H), 4.84 (d, 1H, $J = 1.6$ Hz), 4.70, 4.54 (ABq, 2H, $J = 12$ Hz), 4.31–4.26 (m, 1H), 4.10 (dd, 1H, $J = 6.8$, 4.0 Hz), 3. 87 (dd, 1H, $J = 3.6$, 2.0 Hz), 3.97 (1H), 3.42 (s, 3), 3.37 (s, 3H), 2.58 (br, OH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 107.6 (CH), 89.1 (CH), 82.6 (CH), 80.6 (CH), 72.5 (CH_2), 62.2 (CH_2), 57.8 (CH_3), 55.6 (CH_3). MS (12eV, *m*/*z*): 237 (M^+-31, 4), 177 (52), 117 (20), 91 (100). HRMS (EI, 70 eV). Calcd. for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1299.

Compound 2b. $[\alpha]_D^{20}$ 93 (*c* 0.5, $CHCl_3$); IR ($CHC1_3$) 3700–3150, 2940, 1620, 1515, 1260, 1040 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, 2H, $J = 8.8$ Hz), 6.87 (d, 2H, $J = 8.8$ Hz), 4.95 (d, 1H, $J = 4.4$ Hz), 4.54, 4.46 (ABq, 2H, $J = 11.6$ Hz), 4.42 (m, 1H), 4.26 (dt, 1H, $J = 7.2$, 3.6 Hz), 3.79 (s, 3H), 3.72–3.69 (m, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.14 (d, OH, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5 (C), 130.0 (CH), 129.5 (C), 114.0 (CH), 100.5 (CH), 87.5 (CH), 76.5 (CH), 75.5 (CH), 73.5 (CH), 68.5 (CH_2), 58.5 (CH_2), 55.5(CH_2), 55.4 (CH_2). MS (12 eV, *m*/*z*) 298 (M^+, 6), 266 (17), 179 (41), 164 (100). HRMS (EI, 70eV). Calcd. for $C_{15}H_{22}O_6$: 298.1433. Found: 298.1425.

Compound 3b. $[\alpha]_D^{20}$ −2.9 (*c*. 1, $CHCl_3$). IR ($CHCl_3$): 3600–3200, 2920, 1610, 1510, 1250, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, 2H, $J = 8.4$ Hz), 6.88 (d, 2H, $J = 8.4$ Hz), 4.83 (d, 1H, $J = 1.6$ Hz), 4.64, 4.46 (ABq, 2H, $J = 11.6$ Hz), 4.26 (m, 1H), 4.08 (dd, 1H, $J = 4.4$, 3.6 Hz), 3.86 (d, 1H, $J = 3.6$ Hz), 3.08, (m, 3H), 3.76 (m, 2H), 3.42 (m, 3H), 3.37 (m, 3H). MS (12 eV, *m*/*z*): 298 (M^+, 1), 235 (10), 151 (15), 121 (100). HRMS (EI, 70 eV). Calcd. for $C_{15}H_{22}O_6$: 298.1404. Found: 298.1398.

Compound 2c. $[\alpha]_D^{20}$ −54(*c* 1, $CHCl_3$). IR ($CHCl_3$): 3550–3400 (OH), 3020, 1615, 1510, 1220 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ 7.2 (d, 1H, $J = 8.8$ Hz), 6.44–6.42 (m, 2H), 4.85 (s, 1H), 4.53, 4.47 (ABq, 2H, $J = 11.2$ Hz), 4.34 (dt, 1H, $J = 11.2$, 5.6 Hz), 4.19 (dd, 1H, $J = 6.0$, 6.0 Hz), 3.92–3.69 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.39 (s, 3H), 3.35 (s, 3H), 3.28 (d, OH, $J = 8.0$ Hz). MS (12 eV, *m*/*z*): 328 (M^+, 78), 296 (87), 167 (81), 166 (100), 151 (89). HRMS (EI, 70 eV). Calcd. for $C_{16}H_{24}O_7$: 328.1522. Found: 328.1526.

Compound 3c. $[\alpha]_D^{20}$ −51.9 (*c* 1, $CHCl_3$). IR ($CHCl_3$): 3600–3400 (OH), 3020, 2940, 1620, 1510, 1300, 1220 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.15 (d, 1H, $J = 8.0$ Hz), 6.44 (dd, 1H, $J = 8.0$, 2.4 Hz), 6.41 (d, 1H, $J = 2.4$ Hz), 4.94 (d, 1H, $J = 4.4$ Hz), 4.66, 4.50 (ABq, 2H, $J = 10.8$ Hz), 4.32 (dd, 1H, $J = 6.8$, 7.2 Hz), 4.17 (m, 1H), 3.88 (dd, 1H, $J = 6.0$, 4.0 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.69 (dd, 2H, $J = 6.8$, 4.8 Hz), 3.45 (s, 3H), 3.41 (s, 3H), 2.89 (t, OH, $J = 6.8$ Hz). MS (12 eV, *m*/*z*): 328 (M^+, 17), 296 (13), 265 (21), 167 (31), 151 (100). HRMS (EI, 70 eV). Calcd. for $C_{16}H_{24}O_7$: 328.1522. Found: 328.1528.

Compound 4a. Yield 50%; $[\alpha]_D^{20}$ −13.23 (*c* 5, $CHCl_3$): IR (neat). 3600–3200 (OH), 2940, 1540, 1440, 1200 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, 1H, $J = 7.6$ Hz), 7.17 (d, 1H, $J = 7.6$ Hz), 7.15 (d, 1H, $J = 7.6$ Hz), 4.82, 4.79 (ABq, 2H, $J = 10.8$ Hz), 3.88 (bs, 1H), 3.75-3.55 (m, 6H), 3.41 (s, 3H), 3.34 (s, 3H), 3.06 (d, OH, $J = 4.0$ Hz), 2.84 (d, OH,. $J = 5.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.8 (C), 133.0 (C), 130.0 (CH), 128.4 (CH), 81.0 (CH), 72.3 (CH_2), 71.2 (CH_2), 71.0 (CH), 69.9 (CH), 67.6 (CH_2), 59.3 (CH_3), 58.3(CH_3). MS (12 eV, *m*/*z*): 305 (M^+-33, 8), 303 (M^+-35, 9), 249 (27), 247 (45), 177 (64), 175 (100), 87 (78). MS (FAB, 70 eV): 339.

Compound 4b. Yield 56%; $[\alpha]_D^{20}$ −4.80 (*c* 5, $CHC1_3$): IR (neat). 3600–3200 (OH), 2950, 1630, 1605, 1480, 1240, 1100 cm^{-1}. ^1H NMR ($CDC1_3$, 400 MHz): δ 7.23–7.19 (m. 1H), 6.85-6.80 (m, 2H), 4.58 (s, 2H), 3.82 (bs, 1H), 3.66 (bs, 1H), 3.60–3.48 (m, 4H), 3.39–3.37 (m, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.20 (bs, OH), 2.94 (bs, OH). ^{13}C NMR ($CDC1_3$, 100 MHz), δ 163 (C), 160.5 (C), 130.1 (CH), 113.4 (C), 111.1 (CH), 80.8 (CH), 71.9 (CH_2), 71.1 (CH_2), 70.8 (CH), 69.8 (CH), 60.3 (CH_{20}), 59 (CH_3), 58.1 (CH_3); Mass (12 eV, *m*/*z*): 261 (M^+-45, 25), 255

(18), 171 (31), 127 (100), 88 (81). MS (FAB, 70 eV): 307. Anal. calcd. for $C_{14}H_{16}F_2O_5$: C, 55.63; H, 5.23. Found: C, 55.65; H, 5.27.

Preparation of Methyl 3,5-*O*-Benzylidene-2-*O*-benzyl-α-D-xylofuranose (6)

NaH (60%, 0.64 g, 16 mmol) was washed with hexane (3 × 10 mL), dried in vacuo and THF (10 mL) was added to it under N_2 atmosphere. A solution of alcohol **5** (2.5 g, 9.92 mmol) in THF (10 mL) was added slowly to the above mixture and stirred vigorously for 15 min. Benzyl bromide (1.43 mL, 11.9 mmol) was added and reaction mixture was stirred at room temperature for 6 h. Reaction was quenched with saturated NaCl solution (20 mL) and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried (Na_2S0_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 4:1) to frunish compound **6** (3.08 g, 91%) as a white solid. M.p. 114°C. $[\alpha]_D^{20}$ −74.96 (*c* 5, $CHCl_3$). IR ($CHCl_3$): 3030, 1230, 940, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.30 (m, 10H), 5.43 (s, 1H), 5.28 (d, 1H, $J = 4.4$ Hz), 4.75, 4.64 (ABq, 2H, $J = 12.0$ Hz), 4.43 (d, 1H, $J = 2.8$ Hz), 4.41 (d, 1H, $J = 13.6$ Hz), 4.15–4.10 (m, 3H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 137.7 (C), 137.5 (C),129.0 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 126.0 (CH), 104.4 (CH), 99.2 (CH), 83.3 (CH), 80.0 (CH), 73.2 (CH), 70.7 (CH), 67.0 (CH_2), 56.5 (CH_3). HRMS (EI, 70 eV). Calcd. for $C_{20}H_{22}O_5$: 342.1467. Found: 342.1477. Anal. calcd. for $C_{20}H_{22}O_5$: C, 70.17; H, 6.43. Found: C, 69.96; H, 6.52.

Reductive Cleavage of 3,5-*O*-Benzylidene-2-*O*-benzyl-α-D-xylofuranose (6)

To a solution of $AlCl_3$ (1.76 g, 13.2 mmol) in anhydrous ether (16 mL) at 0°C was added 1M solution of LAH (3.4 mL, 3.4 mmol, THF) and the reaction mixture was stirred for 20 min. A solution of compound **6** (2.12 g, 6.20 mmol) in 5 mL of ether was added slowly to the above reagent solution and the reaction mixture was warmed to room temperature and stirred for 10 h. The reaction was quenched with saturated NaCl solution (10 mL) and mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried (Na_2S0_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:3) to provide alcohols **7** and **8**.

Compound 7. Yield 38%; $[\alpha]_D^{20}$ −35 (*c* 1, $CHCl_3$). IR ($CHCl_3$): 3600–3400 (OH), 3020, 2940, 1470, 960 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.25 (m, 5H), 4.78 (d, 1H, $J = 4.4$ Hz), 4.70, 4.67 (ABq, 2H, $J = 14.4$ Hz), 4.57, 4.51 (ABq, 2H, $J = 14.8$ Hz), 4.50(m, 1H), 4.28 (m, 1H), 3.86 (dd, 1H, $J = 6.0$, 4.4 Hz), 3.73 (dd, 1H, $J = 3.2$, 2.0 Hz), 3.37 (s, 3H), 2.98 (d, OH, $J = 8.0$ Hz). ^{13}C NMR (CDC13, 100 MHz): δ 138 (C), 137.5 (C, 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 101 (CH), 85.1 (CH), 76.0 (CH), 75.7 (CH), 74.0 (CH_2), 72.5 (CH_2), 69.4 (CH_2), 55.5 (CH_3). Mass (12 eV, *m*/*z*): 312 (M^+-32,6),193 (34), 163 (61),91 (100).

Compound 8: Yield 13%; $[\alpha]_D^{20}$ −40 (*c* 1, $CHCl_3$). IR ($CHCl_3$): 3600–3300 (OH), 3020, 2940, 1460, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.27 (m, 5H), 4.75, 4.55 (ABq, 2H, $J = 11.6$ Hz), 4.53, 4.51 (ABq, 2H, $J = 11.6$ Hz), 3.92 (bs, 1H), 3.77 (dd, 1H, $J = 4.4$, 2.4 Hz), 3.69–3.51 (m, 5H), 3.37 (s, 3H), 3.11 (d, OH, $J = 3.6$ Hz), 2.83 (d, OH, $J = 5.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 137.9 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 78.9 (CH), 73.5 (CH_2), 72.6 (CH_2), 72.0 (CH_2), 71.8 (CH_2), 71.1 (CH), 70.1 (CH), 59.3 (CH_3). MS (FAB, 70 eV): 347.

Preparation of Methyl 3,5-*O*-Benzylidene-2-*O*-mesyl-α-D-xylofuranose (9)

To a solution of alcohol **5** (1.60 g, 6.35 mmol) and triethylamine (1.80 mL, 13.7 mmol) in dry dichloromethane at 0°C was added mesyl chloride (0.54 mL, 6.98 mmol) and the reaction mixture was stirred at room temperature for 8 h. The reaction was quenched with 5% HCl (10 mL) and the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried (Na_2S0_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:6) to provide compound **9** (1.84 g, 88%) as a white solid. M.p. 116°C. $[\alpha]_D^{20}$ −115.87 (c 3.2, $CHCl_3$). IR ($CHCl_3$): 3020, 1450, 1350, 1210, 1180, 1075, 1020 cm^{-1}. ^1H NMR (CDCl3, 400 MHz): δ 7.48–7.44 (m, 2H), 7.39-7.34 (m, 3H), 5.47 (s, 1H), 5.41 (d, 1H, $J = 3.$ 6 Hz), 4.61 (d, 1H, $J = 2.0$ Hz), 4.42 (dd, 1H, $J = 13.2$, 1.2 Hz), 4.17 (bs, 1H), 4.12 (dd, 1H, $J = 13.6$, 2.0 Hz), 3.54 (s, 3H), 3.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 137.2 (C), 129.2 (CH), 128.3 (CH), 126.0 (CH), 103.4 (CH), 99.3 (CH), 81.9 (CH), 75.2 (CH), 71.2 (CH), 66.9 (CH_2), 57.0 (CH_3), 38.7 (CH_3). MS (12 eV, *m*/*z*): 330 (M^+, 42), 329 (M^+-1, 36), 251 (63), 191 (42), 121 (100). HRMS (EI, 70 eV). Calcd. for $C_{14}H_{18}O_7S$: 330.0725. Found: 330.0740. Anal. calcd. for $C_{14}H_{18}O_7S$: C, 50.91; H, 5.45; S, 9.70. Found: C, 50.46; H, 5.40; S, 9.86.

Reductive Cleavage of 3,5-*O*-Benzylidene-2-*O*-mesyl-α-D-xylofuranose (9)

To a solution of BF3·Et_20 (1.60 mL, 1.60 mmol) in THF (5 mL) at 0°C was added compound **9** and the reaction mixture was stirred for 10 min. A solution of $NaBH_3CN$ (0.12 g, 1.92 mmol) dissolved in THF (10 mL) was added slowly to the above mixture and the contents were stirred at room temperature for 40 h. Reaction mixture was poured in to saturated $NaHCO_3$ solution (20 mL) and was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:2) to provide secondary alcohol **10** (0.13 g, 92%). M.p. 134°C. $[\alpha]_D^{20}$ −128.4 (*c* 9.2, $CHCl_3$). IR ($CHCl_3$): 3680–3300 (OH), 3030, 2950, 1365, 1220, 1185 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.28 (m, 5H), 5.01 (d, 1H, $J = 4.4$ Hz), 4.83 (dd, 1H, $J = 6.4$, 4.4 Hz), 4.61, 4.55 (ABq, 2H, $J = 12$ Hz), 4.59–4.57 (m, 1H), 4.30–4.28 (m, 1H), 3.74, 3.73 (ABq, 2H, $J = 1.6$ Hz), 3.41(s, 3H), 3.34 (d, OH, $J = 8.4$ Hz), 3.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 137.0 (C), 128.6 (CH), 128.0 (CH), 127.7 (CH), 99.6 (CH), 84.1 (CH), 75.3 (CH), 74.0 (CH_2), 73.9 (CH), 68.9 (CH_2), 55.4 (CH_3), 58.5 (CH_3). MS (12 eV, *m*/*z*): 332 (M^+, 5), 221 (18), 193 (26), 91 (56), 87 (100). HRMS (EI, 70 eV). Calcd. for $C_{14}H_{20}O_7S$: 332.0905. Found: 332.0917.

Preparation of Methyl 5-Benzyl-2,3-anhydro-α-D-xylofuranose (11)

NaH (60%, 0.08 g, 1.93 mmol) was washed with hexane (3×10 mL), dried in vacuo and THF (10 mL) was added to it under N2 atmosphere. A solution of alcohol **10** (0.16 g, 0.48 mmol) in THF (5 mL) was added slowly to the above mixture and stirred for 4 h. The reaction was quenched with saturated NaCl solution (5 mL) and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:6) to furnish epoxide **11** (0.091 g, 80%). $[\alpha]_D^{20}$ 24.11 (*c* 0.9, $CHC1_3$). IR ($CHCl_3$): 3680–3300 (OH), 3020, 1523, 1450, 1353, 1215 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.25 (m, 5H), 4.93 (s, 1H), 4.60, 4.56 (ABq, 2H, $J = 12$ Hz), 4.19 (dd, 1H, $J = 6.4$, 6.4 Hz), 3.74 (d, 1H, $J = 2.8$ Hz), 3.65–4.62 (m, 3H), 3.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.8 (C), 128(CH), 127.8 (CH), 127.7 (CH), 102.3 (CH), 75.1 (CH), 73.7 (CH_2), 68.5 (CH_2), 56.2 (CH), 55.6 (CH), 54.3 (CH_2), 58.5 (CH_3). MS (FAB, *m*/*z*) 235.

Swern Oxidation of Methyl 3,5-D-Benzylidene-α(β)-D-xylofuranose (5)

To a solution of oxalyl chloride (3.00 mL, 34.2 mmol) in CH_2Cl_2 (20 mL) under N_2 atmosphere at −78°C was added DMSO (5.30 mL, 68.4 mmol) and the mixture was stirred for 5 min. A solution of alcohol **5** (4.30 g, 17.1 mmol) in CH_2Cl_2 (10 mL) was slowly added to the above reagent and the reaction mixture was stirred at −78°C for 1h. The reaction was quenched with triethylamine (14.3 mL, 102 mmol) and warmed to room temperature. Ether (100 mL) was added and the precipitate was filtered off. The filtrate was diluted with H_2O (30 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:3) to furnish ketone **12** (3.70 g, 87%). IR ($CHCl_3$): 3010 (OH), 1725 (C = 0), 1220, 1045 cm^{-1}. ^1H NMR ($CDC1_3$, 400 MHz): δ 7.50–7.45 (m, 2H), 7.37–7.33 (m, 3H), 5.52 (d, 1H, $J = 5.2$ Hz), 5.00 (d, 1H, $J = 4.4$ Hz), 4.51–4.06 (m, 4H), 3.56 (s, 3H). MS (12 eV, m/z): 249 (M^+-1, 5), 162(95), 145 (15), 105 (100).

Preparation of Methyl 3,5-*O*-Benzylidene-2-deoxy-2-*C*-methylene-α-D-xylofuranose (13)

At −78°C, CH_3BrPPh_3 (15.9 g, 45.0 mmol) was dissolved in THF (25 mL) under N_2 atmosphere and BuLi (2.2 M, 19.0 mL, 41.80 mmol) was slowly added to this solution. The reaction mixture was warmed to 0°C and stirred for 30 min, then was lowered to −78°C and a solution of **12** (3.55 g, 14.2 mmol) in THF (10 mL) was slowly added. The reaction mixture was stirred at room temperature for 24 h, and quenched with saturated NaCl solution (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:5) to furnish alkene **13** (1.93 g, 55%). M.p. 135°C. $[\alpha]_D^{20}$ 177.5 (*c* 2, $CHC1_3$). IR ($CHCl_3$): 3020, 1515, 1215, 1050, 925: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.47 (dd, 1H, $J = 8.0$, 2.0 Hz), 7.36–7.31 (m, 3H), 5.63 (d, 1H, $J = 1.6$ Hz), 5.55 (s, 1H), 5.49 (s, 2H), 4.70 (d, 1H, $J = 2.0$ Hz), 4.47 (d, 1H, $J = 13.2$ Hz), 4.19 (dd, 1H, $J = 13.2$ Hz), 3.98 (d, 1H, $J = 2.0$ Hz), 3.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.8 (C), 137.7 (CH), 129.0 (CH), 128.2 (CH), 126.2 (CH), 116.7 (CH_2), 103.9 (C), 99.2 (CH), 77.1 (CH), 72.0 (CH), 66.9 (CH_2), 55.6 (CH_3). MS (12 eV, m/z): 248 (M^+, 8), 247 (M^+-1, 100), 171 (46), 149 (42), 99 (100). (HRMS: EI, 70 eV) Calcd. for $C_{14}H_{16}O_4$: 248.1011. Found: 248.1006.

Preparation of Methyl 3,5-*O*-Benzylidene-2-*C*-methyl-2-deoxy-α-D-xylofuranose (14)

A solution of alkene (1.05 g, 1.23 mmol) and Pd-C (10%, 0.05 g) in MeOH (20 mL) was subjected to hydrogenation at 1 atm pressure for 5 h. The reaction mixture was filtered through celite and the precipitate was washed with methanol (2×5 mL). The combined methanolic solution was dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:4) to furnish **14** (1.01 g, 95%) as a white solid. M.p. 74°C. IR ($CHCl_3$): 3020, 1520, 1420, 1210, 930 cm^{-1}. ^1H NMR ($CDCL_3$, 400 MHz): 7.50–7.46 (m, 2H), 7.36–7.31 (m, 3H), 5.44 (s, 1H), 4.95 (d, 1H, $J = 5.6$ Hz), 4.3 8 (d, 1H, $J = 13.2$ Hz), 4.26 (dd, 1H, $J = 4.0$, 2.0 Hz), 4.09 (dd, 1H, $J = 13.2$, 2.4 Hz), 4.00 (m, 1H), 3.44 (s, 3H), 2.34–2.25 (m, 2H), 1.24–1.10 (m, 2H). MS (12 eV, m/z): 248 (M^+, 57), 250 (M^+-l, 39), 190 (21), 144 (48), 101 (100). HRMS (EI, 70 eV). Calcd. for $C_{14}H_{18}O_4$: 250.1209. Found: 250.1207.

Reductive Cleavage of Methyl 3,5-*O*-Benzylidene-2-*C*-methyl-2-deoxy-α-D-xylofuranose (14)

To a solution of LAH (1 M, 1.70 mL, 1.70 mmol, THF) in THF (5 mL), was added a suspension of $AlCl_3$ ($0.56 \pm$ g, 4.20 mmol) in THF (5 mL) at 0°C under N_2 atmosphere and the reagent mixture was stirred for 20 min. A solution of compound **14** (0.51 g, 2.10 mmol) in 5 mL of THF was added slowly to the above reagent solution and the reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched with saturated NaCl solution (10 mL) and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried (Na_2S0_4) and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes 1:2) to furnish alcohols **15** and **16**.

Compound 15. Yield 0.17 g, 34%. IR ($CHCl_3$): 3393, 2909, 1496, 1454, 1391, 1079; ^1H NMR ($CDCl_3$, 400 MHz), 7.41–7.29 (m, 5H), 4.64, 4.52 (ABq, 2H, $J = 11.2$ Hz), 3.75 (bs, 1H), 3.61 (m 2H), 3.51-3.35 (m, 4H), 3.30 (s, 3H), 2.85 (bs, OH), 2.15 (m, 1H), 1.71 (bs, OH), 1.02 (d, 3H, $J = 7.2$ Hz). MS (FAB, 70 eV): 255.

Compound 16. Yield 0.18 g, 33%. IR ($CHCl_3$): 3600–3400, 3020, 2920, 1230, 1050; ^1H NMR ($CDCl_3$, 400 MHz): 7.38–7.26 (m, 5H), 4.55, 4.53 (ABq, 2H, $J = 13.2$ Hz), 3.73 (bs, OH), 3.64–3.33 (m, 6H), 3.31 (s, 3H), 3.21 (bs, OH), 2.55–1.89 (m, 1H), 0.96 (d, 3H, $J = 7.2$ Hz). HRMS (EI, 70 eV). Calcd. for $C_{14}H_{23}O_4$: 255.1612. Found. 255.1604.

ACKNOWLEDGMENT

We thank the National Science Council of the Republic of China for the Financial support. (NSC 85-2113-M-230-0027). We also thank our research students—Li-Wen Wang, Ti-Chung Huang, and Hsiao-Ting Huang.

REFERENCES

1. Sakagami, M.; Hamana, H. Tetrahedron Lett. **2000**, *41*, 5547.
2. Garegg, P. J. Pure Appl. Chem. **1984**, 845.
3. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997; 53–65.
4. Garegg, P.J.; Hultberg, H. Carbohydrate Res. **1981**, *93*, C10.
5. Garegg, P.J.; Hultberg, H.; Wallin, S. Carbohydrate Res. **1982**, *108*, 97.
6. Liptak, A.; Neszmelyi, A.; Kovac, P.; Hirsch, J. Tetrahedron **1981**, *37*, 2379.
7. Bhattacharjee, S.S.; Gorin, P.A. J. Can. J. Chem. **1969**, *47*, 1195.
8. Liptak, A. Tetrahedron Lett. **1976**, *16*, 3551.
9. Liptak, A.; Jodal, I.; Nanasi, P. Carbohydrate Res. **1975**, *44*, 1.
10. Liptak, A.; Fugedi, P.; Nanasi, P. Carbohydrate Res. **1978**, *65*, 209.
11. (a) Marwood, R.D.; Shuto, S.; Jenkins, D.J.; Potter, B.V.L. Chem. Commun. **2000**, 219; (b) Marwood, R.D.; Jenkins, D.J.; Correa, V.; Taylor, C.W.; Potter, B.V.L. J. Med. Chem. **2000**, *43*, 4278.

Received in the Netherlands October 24, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016