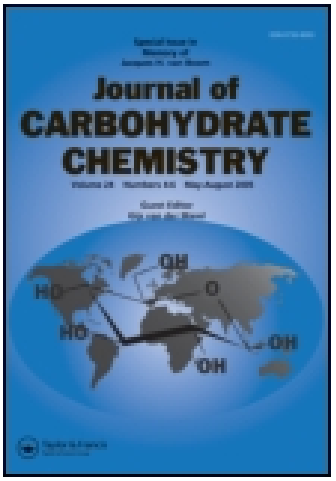
This article was downloaded by: [York University Libraries]
On: 20 June 2014, At: 06:33
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Formation of C-Glycosides by Ferrier Reaction

Eusebius Wieczorek [a] & Joachim Thiem [a]
[a] University of Hamburg, Faculty of Science, Department of Chemistry, Martin-Luther-King-Platz 6 , D-20146 , Hamburg , Germany
Published online: 03 Dec 2013.

To cite this article: Eusebius Wieczorek & Joachim Thiem (2013) Formation of C-Glycosides by Ferrier Reaction, Journal of Carbohydrate Chemistry, 32:8-9, 502-512, DOI: 10.1080/07328303.2013.860160

To link to this article: http://dx.doi.org/10.1080/07328303.2013.860160

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Journal of Carbohydrate Chemistry, 32:502–512, 2013
Copyright © Taylor & Francis Group, LLC
ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328303.2013.860160

Taylor & Francis
Taylor & Francis Group

Formation of *C*-Glycosides by Ferrier Reaction

Eusebius Wieczorek and Joachim Thiem

University of Hamburg, Faculty of Science, Department of Chemistry, Martin-Luther-King-Platz 6, D-20146, Hamburg, Germany

Peracetylated glycals were treated with terminal alkyne derivatives under Lewis acid catalysis to result in the formation of the pure α- or β- anomerically substituted hex-2-enopyranosides carrying 2(*E*)-halogenated olefins.

Keywords Glycals; *C*-Glycosylation; Alkyne nucleophiles; Allylic rearrangement

Downloaded by [York University Libraries] at 06:33 20 June 2014

INTRODUCTION

Formation of carbohydrate surrogates and mimetics is attractive due to structural as well as conformational similarities to natural components occurring in many complex biopathways.[1,2] In particular, *C*-glycosylation proved to be an attractive approach, and reports on such syntheses are abundant[3,4] and were compiled several times.[5–12] Ferrier et al.[13] first reacted glycal structures with nucleophiles to arrive at 2,3-unsaturated compounds; it was the seminal work of Robin J. Ferrier to elaborate this reaction about 50 years ago.[14] A number of reviews by him[15–18] and others[19,20] gave evidence of the advantageous use of this reaction to construct a large number of complex carbohydrate-derived components. As a show of appreciation of the then-called Ferrier reaction [21–23] and to the author, who recently passed away, this short contribution reports on some findings in the use of *C*-nucleophiles for formation of *C*-glycosides. This subject was recently reviewed[24] and compiled some 40 papers about Ferrier *C*-glycosylation reactions within the last 20 years.

Dedicated to the memory of Prof. Karsten Krohn
Received September 4, 2013; accepted October 24, 2013.
Address correspondence to Joachim Thiem, University of Hamburg, Faculty of Science, Department of Chemistry, 20146, Hamburg, Germany. E-mail: thiem@chemie.uni-hamburg.de

Table 1: Assignment of alkene isomers

Compound	(*Z*) δ calculated	(*E*) δ calculated	δ observed
2	6.39	6.08	6.05
3	6.91	6.29	6.30
6	6.91	6.30	6.28
7	6.39	6.08	5.96
8	5.31	5.46	5.48

Downloaded by [York University Libraries] at 06:33 20 June 2014

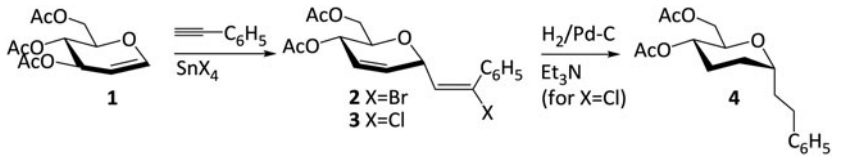
RESULTS AND DISCUSSION

Previously it could be shown that application of propargyl silanes to Ferrier conditions resulted in formation of alkynylated hex-2-enopyranosyl structures.[25–32] Thus, surprisingly, by reaction of tri-*O*-acetyl-D-glucal (**1**) with phenyl acetylene in the presence of SnX_4 at -45°C, the formation of 2-halide substituted (*E*) styryl hex 2-enopyranosides **2** and **3** was observed. Their α-anomerity was evident from the ^{1}H NMR data. The shift assignments of alkene protons were calculated according to the rules of Pascual et al.:

$$\delta(\mathrm{H}) = 5.28 + \mathrm{S_{gem}} + \mathrm{S_{cis}} + \mathrm{S_{trans}}\ [\mathrm{ppm}]$$

with S_{gem}, S_{cis}, and S_{trans} as empirical substituent increments.[33–35] The data in Table 1 clearly show formation of (*E*) isomers exclusively.

Catalytic hydrogenation of the chloro derivative **3** on 10% Pd/C in the presence of triethylamine gave exclusively the α component **4**, thus substantiating the anomer assignment (Scheme 1).

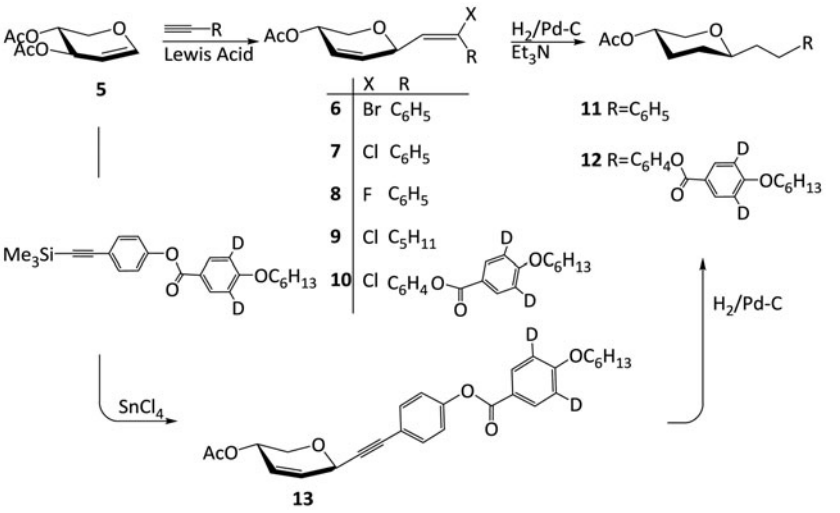


Scheme 1: Ferrier C-Glycosylation of D-Glucal.

In a corresponding reaction, di-*O*-acetyl-D-xylal (**5**) was treated at -45°C with phenyl acetylene in the presence of $SnBr_4$, $SnCl_4$, and $BF_3{}^*Et_2O$. In keeping with the above results the corresponding 2-halo-substituted and (*E*)-configured styryl ß-hex-2-enopyranosides **6**, **7**, and **8** could be obtained in average to acceptable yields. Hydrogenation of the bromide **6** gave clearly the pure de-halogenated ß-anomer **11** in $^4C_1$(D) conformation, thus approving the structural assignment.

By reaction of hept-1-yne **5,** the corresponding ß-C-glycoside **9** could be obtained in fair yield. In connection with studies toward liquid crystalline properties, the reaction of **5** was also performed with a typically 4-substituted phenyl acetylene *p*-alkoxybenzoate to give under corresponding conditions in the presence of $SnCl_4$ the ß-*C*-glycoside **10** in 67% yield.

It was interesting to react **5** also with the trimethylsilyl-substituted phenyl acetylene compound under similar conditions with $SnCl_4$ at −45°C. In this case 93% of the ß-*C*-alkynylated structure **13** resulted, as evident from the characteristic triple-bond carbon signals at 89.63 and 88.15 in the ^{13}C NMR spectra. This outcome is in accord with the previously observed formation as mentioned above[24–32] but deviates clearly from the presented finding. The mesogenic compound **13** showed a smectic A phase at 89.5°C and decomposed at 100°C. As expected, both compounds **10** (in the presence of triethylamine) and **13** could be hydrogenated with 10% Pd/C to give the saturated ß-*C*-glycoside **12** in good yields. The liquid crystalline derivative **12** melted at 85.2°C and transferred into a cholesteric phase at 121.5°C (Scheme 2).



Scheme 2: Ferrier C-Glycosylation of D-Xylal.

CONCLUSION

In this contribution the Ferrier *C*-glycosylation could be shown to operate with alkynyl components and the reported Lewis acids, giving anomerically pure (*E*)-configured 2-halo hex-2-enopyranosides exclusively. Thus, this approach differs substantially from the previously reported reaction with alkynyl silanes, which was also proven by formation of liquid crystalline components following both approaches.

Downloaded by [York University Libraries] at 06:33 20 June 2014

EXPERIMENTAL

Solvents were dried according to standard methods. TLC was performed on precoated aluminium plates (silica gel 60 F254, Merck 5554), charring with 10% H_2SO_4 in ethanol for visualization. For column chromatography silica gel 60, 230–400 mesh, 40–63 μm (Merck) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400 (400 MHz for ^{1}H, 100.67 MHz for ^{13}C) at 300 K. Chemical shifts were calibrated to solvent residual peaks.[19] The signals were assigned by H, H-COSY, HSQC, and HMBC experiments. Optical rotations were measured using a Perkin-Elmer Polarimeter 243 (589 nm) at 20°C.

Downloaded by [York University Libraries] at 06:33 20 June 2014

General Procedure for Ferrier *C*-Glycosylation (GP 1)

The peracetylated glycal (1 eq.) and the alkyne component (1.2 eq.) are cooled to –45°C in anhydrous dichloromethane. The respective stannic tetrahalide catalyst (0.5 eq.) is added, and after complete transformation (about 10 min), the reaction is quenched by addition of saturated aqueous sodium hydrogen carbonate. The organic phase is dried ($MgSO_4$) and concentrated and the residue purified by column chromatography.

General Procedure for Catalytic Hydrogenation (GP 2)

The compound dissolved in methanol or methanol/ethyl acetate (1:1) is treated with palladium on charcoal (10%) and hydrogenated under normal pressure for 10 h. The catalyst is filtered over Celite, the solvent removed in vacuum, and the residue purified by column chromatography.

(*E*)-1-(4, 6-Di-*O*-acetyl-2, 3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-bromo-2-phenyl-ethene(2)

Tri-*O*-acetyl-D-glucal (**1**, 100 mg, 0.37 mmol), phenyl acetylene (60 μL, 0.54 mmol), and a 1 M solution of $SnBr_4$ in dichloromethane (50 μL) are treated according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 6:1 to give **2** as slightly yellow syrup (65 mg, 45%). $[\alpha]_D^{20} = 34.5$ (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.28–7.44 (m, 5H, phenyl), 6.30 (d, 1H, $J_{1,1'} = 9.2$ Hz, H-1′-ethene), 5.77 (ddd, 1H, $J_{1,3} = 2.0$, $J_{2,3} = 10.2$, $J_{3,4} = 3.5$ Hz, H-3), 5.72 (dd, 1H, $J_{1,2} = 1.5$, $J_{2,3} = 10.2$ Hz, H-2), 5.09 (dd, 1H, $J_{3,4} = 3.5$, $J_{4,5} = 7.1$ Hz, H-4), 4.57 (ddd, 1H, $J_{1,1'} = 9.2$, $J_{1,2} = 1.5$, $J_{1,3} = 2.0$ Hz, H-1), 4.14 (dd, 1H, $J_{5,6a} = 6.1$, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b} = 3.1$, $J_{6a,6b} = 12.2$ Hz, H-6b), 3.93 (ddd, 1H, $J_{4,5} = 7.1$, $J_{5,6a} = 6.1$, $J_{5,6b} = 3.1$ Hz, H-5), 2.04 and 2.02 (each s, each 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.2, 169.9 (each *C*=O), 132.2, 130.2, 129.5, 128.9, 128.4(2), 128.0, 127.9, 126.1, 124.3 (C-phenyl, C-2, C-3, C-1′and C-2′-ethene), 69.8 (C-1), 69.6

(C-5), 64.1 (C-4), 62.5 (C-6), 20.6, 20.4 (CO*CH*$_3$). Calc for $C_{18}H_{19}O_5Br$ (395.3): C 54.70, H 4.85, Br 20.25; found: C 55.25, H 4.80, Br 18.95.

(*E*)-1-(4, 6-Di-*O*-acetyl-2, 3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-chloro-2-phenyl-ethene(3)

Tri-*O*-acetyl-D-glucal (**1**, 200 mg, 0.73 mmol), phenyl acetylene (120 μL, 1.08 mmol), and a 1 M solution of $SnCl_4$ in dichloromethane (100 μL) are treated according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 6:1 to give **3** as yellow syrup (103 mg, 40%). $[\alpha]_D^{20} = 32.0$ (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.29–7.43 (m, 5H, phenyl), 6.05 (d, 1H, $J_{1,1'} = 10.2$ Hz, H-1′-ethene), 5.74 (m, 2H, H-2, H-3), 5.10 (dd, 1H, $J_{3,4} = 3.2$, $J_{4,5} = 7.1$ Hz, H-4), 4.57 (dd, 1H, $J_{1,1'} = 10.2$, $J_{1,2} = 1.0$ Hz, H-1), 4.15 (dd, 1H, $J_{5,6a} = 5.6$, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.08 (dd, 1H, $J_{5,6b} = 3.1$, $J_{6a,6b} = 12.2$ Hz, H-6b), 3.94 (ddd, 1H, $J_{4,5} = 7.1$, $J_{5,6a} = 5.6$, $J_{5,6b} = 3.1$ Hz, H-5), 2.04 and 2.01 (each s, each 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.3, 169.9 (each *C*=O), 136.8, 135.7, 130.6, 129.0, 128.2, 128.0, 127.8, 126.1, 125.3, 124.3 (C-phenyl, C-2, C-3, C-1′and C-2′-ethene), 69.6 (C-1), 69.1 (C-5), 64.1 (C-4), 62.5 (C-6), 20.6, 20.4 (CO*CH*$_3$). Calc for $C_{18}H_{19}O_5Cl$ (350.8): C 61.63, H 5.46, Cl 10.11; found: C 59.90, H 6.07, Cl 9.12.

1-(4, 6-Di-O-acetyl-2, 3-dideoxy-α-D-*erythro*-hexopyranosyl)-2-phenyl-ethane(4)

Compound **3** (60 mg, 0.17 mmol) is hydrogenated according to GP 2 in the presence of triethyl amine (0.1 mL) and the resulting material is purified by flash chromatography with petroleum ether/ethyl acetate 3:1 to give 23 mg (42%) of **4** as yellow syrup. $[\alpha]_D^{20} = 4.0$ (c = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.13–7.32 (m, 5H, phenyl), 4.74 (m, 1H, H-4), 4.23 (dd, 1H, $J_{5,6a} = 5.6$, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.16 (dd, 1H, $J_{5,6b} = 2.5$, $J_{6a,6b} = 12.2$ Hz, H-6b), 3.51 (m, 1H, H-1), 2.58–2.81 (m, 2H, H-2a′-, H-2b′-ethane), 1.52–2.02 (m, 6H, H-2ax, H-2eq, H-3ax, H-3eq, H-1a′-, H1b′-ethane) 2.08 and 2.10 (each s, each 3H, OAc).

(*E*)-1-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl) -2-bromo-2-phenyl-ethene(6)

Di-*O*-acetyl-D-xylal (**5**, 200 mg, 1.0 mmol), phenyl acetylene (135 μL, 1.22 mmol), and a 1 M solution of $SnBr_4$ in dichloromethane (200 μL) are treated according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 3:1 to give **6** as yellow syrup (171 mg, 53%). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.28–7.45 (m, 5H, phenyl), 6.28 (d, 1H, $J_{1,1'}$ = 9.7 Hz, H-1′-ethene), 5.92

Downloaded by [York University Libraries] at 06:33 20 June 2014

(ddd, 1H, $J_{1,3}$ = 2.0, $J_{2,3}$ = 10.7, $J_{3,4}$ = 3.5 Hz, H-3), 5.88 (dd, 1H, $J_{1,2}$ = 2.5, $J_{2,3}$ = 10.7 Hz, H-2), 5.16 (m, 1H, H-4), 4.57 (ddd, 1H, $J_{1,1'}$ = 9.7, $J_{1,2}$ = 1.5, $J_{1,3}$ = 2.0 Hz, H-1), 4.11 (dd, 1H, $J_{4,5e}$ = 4.1, $J_{5a,5e}$ = 12.2 Hz, H-5e), 3.65 (dd, 1H, $J_{4,5a}$=4.6, $J_{5a,5e}$ = 12.2 Hz, H-5a), 2.05 (s, 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.2 (*C* = O), 132.2, 130.4(2), 129.2(2), 128.8, 128.2, 127.0, 124.3(2) (C-phenyl, C-2, C-3, C-1′and C-2′-ethene), 70.9 (C-1), 64.4 (C-5), 64.1 (C-4), 21.0 (CO*CH*$_3$).

Downloaded by [York University Libraries] at 06:33 20 June 2014

(*E*)-1-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl) -2- chloro-2-phenyl-ethene(7)

Di-*O*-acetyl-D-xylal (**5**, 200 mg, 1.0 mmol), phenyl acetylene (135 μL, 1.22 mmol), and a 1 M solution of $SnCl_4$ in dichloromethane (200 μL) are treated according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 3:1 to give **7** as yellow syrup (140 mg, 50%). $[\alpha]_D^{20}$ = 147.0 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.28–7.42 (m, 5H, phenyl), 5.96 (d, 1H, $J_{1,1'}$ = 10.2 Hz, H-1′-ethene), 5.86 (ddd, 1H, $J_{1,3}$ = 2.0, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.6 Hz, H-3), 5.79 (ddd, 1H, $J_{1,2}$ = 2.5, $J_{2,3}$ = 10.7, $J_{2,4}$ = 1.0 Hz, H-2), 5.00 (m, 1H, H-4), 4.56 (ddd, 1H, $J_{1,1'}$ = 10.2, $J_{1,2}$ = 2.5, $J_{1,3}$ = 2.0 Hz, H-1), 4.05 (dd, 1H, $J_{4,5e}$ = 4.1, $J_{5a,5e}$ = 12.2 Hz, H-5e), 3.59 (dd, 1H, $J_{4,5a}$ = 4.6, $J_{5a,5e}$ = 12.2 Hz, H-5a), 1.98 (s, 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.1 (*C*=O), 136.8, 135.8, 132.1, 128.9, 128.7, 128.3, 127.9, 126.1, 125.8, 123.7 (C-phenyl, C-2, C-3, C-1′and C-2′-ethene), 69.9 (C-1), 64.1 (C-5), 63.8 (C-4), 20.6 (CO*CH*$_3$). Calc for $C_{15}H_{15}O_3Cl$ (278.7): C 64.64, H 5.42, Cl 12.72; found: C 63.72, H 5.40, Cl 11.60.

(*E*)-1-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl) -2-fluoro-2-phenyl-ethene(8)

Di-*O*-acetyl-D-xylal (**5**, 55 mg, 0.27 mmol) and phenyl acetylene (35 μL, 0.32 mmol) are treated with BF_3*Et_2O (10 μL) in anhydrous dichloromethane according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 8:1 to give **8** as yellow syrup (20 mg, 28%). $[\alpha]_D^{20}$ = 123.6 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22–7.42 (m, 5H, phenyl), 5.89 (dd, 1H, $J_{1,2}$ = 2.0, $J_{2,3}$ = 10.2 Hz, H-2), 5.85 (ddd, 1H, $J_{1,3}$ = 1.5, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.1 Hz, H-3), 5.48 (d, 1H, $J_{1,1'}$ = 9.7 Hz, H-1′-ethene), 5.11 (m, 1H, H-4), 4.69 (ddd, 1H, $J_{1,1'}$ = 9.7, $J_{1,2}$ = 2.0, $J_{1,3}$ = 1.5 Hz, H-1), 4.06 (dd, 1H, $J_{4,5e}$ = 4.1, $J_{5a,5e}$ = 11.7 Hz, H-5e), 3.60 (dd, 1H, $J_{4,5a}$ = 4.6, $J_{5a,5e}$ = 11.7 Hz, H-5a), 1.99 (s, 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.6 (*C*=O), 133.5, 133.2, 130.81, 129.3, 128.6, 128.3, 128.0, 126.2, 124.9, 123.9 (C-phenyl, C-2, C-3, C-1′and C-2′-ethene), 69.3 (C-1), 64.5 (C-5), 63.3 (C-4), 21.0 (CO*CH*$_3$).

Downloaded by [York University Libraries] at 06:33 20 June 2014

(*E*)-1-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl)-2- chloro-hept-1-ene (9)

Di-*O*-acetyl-D-xylal (**5**, 200 mg, 1.0 mmol), 1-heptyne (160 μL, 1.22 mmol), and a 1 M solution of $SnCl_4$ in dichloromethane (100 μL) are treated according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 3:1 to give **9** as yellow syrup (103 mg, 38%). $[\alpha]_D^{20} = 176.0$ (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 5.87 (ddd, 1H, $J_{1,3} = 1.5$, $J_{2,3} = 10.2$, $J_{3,4} = 4.1$ Hz, H-3), 5.79 (dd, 1H, $J_{1,2} = 2.0$, $J_{2,3} = 10.2$ Hz, H-2), 5.61 (d, 1H, $J_{1,1'} = 9.2$ Hz, H-1′-heptene), 5.09 (m, 1H, H-4), 4.74 (ddd, 1H, $J_{1,1'} = 9.2$, $J_{1,2} = 2.0$, $J_{1,3} = 1.5$ Hz, H-1), 4.00 (dd, 1H, $J_{4,5e} = 4.1$, $J_{5a,5e} = 12.2$ Hz, H-5e), 3.59 (dd, 1H, $J_{4,5a} = 5.1$, $J_{5a,5e} = 12.2$ Hz, H-5a), 2.26 (m, 2H, H-3a′,b′-heptene) 2.10 (s, 3H, OAc), 1.51 (m, 2H, 4a′,b′-heptene), 1.24 (m, 4H, H-5a′,b′, H-6a′,b′-heptene). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.2 (*C*=O), 132.8, 132.8, 124.8, 124.0 (C-2, C-3, C-1′and C-2′-heptene), 69.6 (C-1), 64.5 (C-5), 64.3 (C-4), 34.2, 30.9, 27.1, 22.4 (C-3′, C-4′, C-5′, C-6′-heptene), 21.1 (CO*CH*$_3$). Calc for $C_{14}H_{21}O_3Cl$ (272.8): C 61.65, H 7.76, Cl 13.00; found: C 62.09, H 7.84, Cl 13.03.

(*E*)-1′-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl -2′- chloro-2′- (phenyl-4‴-hexyloxy-dideuterobenzoyl)-ethene (10)

Di-*O*-acetyl-D-xylal (**5**, 25 mg, 0.12 mmol) and 4-ethynyl-phenyl-4′-hexyloxy-dideutero benzoate (45 mg, 0.14 mmol) dissolved in dichloromethane (10 mL) are treated with a 1 M solution of $SnCl_4$ in dichloromethane (30 μL) according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 3:1 to give **10** as yellow syrup (40 mg, 67%). $[\alpha]_D^{20} = -4.5$ (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$) δ: 8.05 (m, 2H, H-2‴-, H-6‴-aryl), 7.48 (m, 2H, H-2″-, H-6″-aryl), 7.15 (m, 2H, H-3″-, H-5″-aryl), 5.97 (d, 1H, $J_{1,1'} = 10.2$ Hz, H-1′-ethene), 5.87 (ddd, 1H, $J_{1,3} = 2.0$, $J_{2,3} = 10.2$, $J_{3,4} = 4.0$ Hz, H-3), 5.80 (ddd, 1H, $J_{1,2} = 2.6$, $J_{2,3} = 10.2$, $J_{2,4} = 1.0$ Hz, H-2), 5.12 (m, 1H, H-4), 4.60 (ddd, 1H, $J_{1,1'} = 10.2$, $J_{1,2} = 2.6$, $J_{1,3} = 2.0$ Hz, H-1), 4.06 (dd, 1H, $J_{4,5e} = 4.1$, $J_{5a,5e} = 11.7$ Hz, H-5e), 3.98 (t, 2H, OCH_2), 3.60 (dd, 1H, $J_{4,5a} = 5.1$, $J_{5a,5e} = 11.7$ Hz, H-5a), 1.98 (s, 3H, OAc), 1.26–1.80 (m, 8H, 4 CH_2), 0.85 (t, 3H, CH_3). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.1 (*C*=O), 121.4–136.8 (C-aryl, C-2, C-3, C-1′and C-2′-ethene), 69.8 (C-1), 68.0 (O*C*H$_2$), 64.5 (C-5), 64.2 (C-4), 31.1, 28.6, 25.2, 22.1 (4 *C*H2), 20.6 (CO*CH*$_3$), 13.6 (CH_3). Calc for $C_{28}H_{30}O_6Cl$ (499.0): C 67.40, H 6.26, Cl 7.10; found: C 67.99, H 6.23, Cl 6.03.

1-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pentopyranosyl)-2-phenyl-ethane (11)

Compound **6** (100 mg, 0.31 mmol) is hydrogenated according to GP 2 in the presence of triethyl amine (0.1 mL) and the resulting material

is purified by flash chromatography with petroleum ether/ethyl acetate 10:1 to give 42 mg (55%) of **11** as yellow syrup. $[\alpha]_D^{20} = 79.5$ (c = 0.6, $CHCl_3$). ^1H NMR (400 MHz,$CDCl_3$) δ: 7.32–7.48 (m, 5H, phenyl), 4.95 (m, 1H, H-4), 4.22 (dd, 1H, $J_{4,5e} = 5.1$, $J_{5a,5e} = 10.7$ Hz, H-5e), 3.41 (m, 1H, H.1), 3.37 (dd,1H, $J_{4,5a} = 10.2$, $J_{5a,5e} = 10.7$ Hz, H-5a), 2.94 (m, 1H, H-2a′-ethane), 2.84 (m, 1H, H-2b′-ethane), 2.33 (m, 1H, H-2eq), 1.60–2.06 (m, 5H, H-2ax, H-3ax, H-3eq, H-1a′-, H1b′-ethane) 2.21 (s, 3H, OAc). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.1 (*C*=O), 141.9, 128.3(2), 128.2(2), 125.7 (C-phenyl), 76.3 (C-1), 69.1, 63.0 (C-5), 68.3 (C-4), 37.1 (C-1′-ethane), 31.7 (C-2′-ethane), 30.1, 29.0 (C-2, C-3), 21. (CO*CH*$_3$. Calc for $C_{15}H_{20}O_3$ (248.3): C 72.55, H 8.12; found: C 71.98, H 7.94.

1′-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pentopyranosyl)-2′-(phenyl-4‴-hexyloxy-dideuterobenzoyl)-ethane (12)

(A) Compound **10** (100 mg, 0.2 mmol) is hydrogenated according to GP 2 in the presence of triethyl amine (0.1 mL) and the resulting material is purified by flash chromatography with petroleum ether/ethyl acetate 6:1 to give 52 mg (55%) of **12**.

(B) Compound **13** (250 mg, 0.54 mmol) is hydrogenated according to GP 2 and purified by flash chromatography as above to give 159 mg (63%) of **12** as a colorless solid. $[\alpha]_D^{20} = -12.0$ (c = 0.2, $CHCl_3$). K 85.2 – Ch 121.5 – I. ^1H NMR (400 MHz,$CDCl_3$) δ: 8.09 (m, 2H, H-2‴-, H-6‴-aryl), 7.20 (m, 2H, H-2″-, H-6″-aryl), 7.08 (m,2H, H-3″-, H-5″-aryl), 4.77 (m, 1H, H-4), 4.01–4.07 (m, 3H, H-5e, H-1a′-, H-1b′-hexane), 3.23 (m, 1H, H-1), 3.20 (dd, 1H, $J_{4,5a} = 10.2$, $J_{5a,5e} = 10.7$ Hz, H-5a), 2.78 (m, 1H, H-2a′-ethane), 2.68 (m, 1H, H-2a′-ethane), 2.15 (m,1H H-2eq), 2.02 (s, 3H, OAc), 1.30–1.89 (m, 13H, H-2ax, H-3ax, H-3eq, H-1a′-H-1b′-ethane, H-2ab″-, H-3ab″-, H-4ab″-, H-5ab″-hexane), 0.92 (t, 3H, CH_3). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.2 (*C*=O), 121.1–131.7 (C-aryl), 75.8 (C-1), 68.8 (C-4), 67.9, 68.0 (C-5, O*C*H$_2$-hexane), 36.7, 31.1 (C-1′-, C-2′-ethane) 30.8, 29.8, 28.7, 28.6, 25.2, 22.1 (C-2, C-3, 5 CH_2-hexane), 20.7 (CO*CH*$_3$), 13.6 (CH_3).

1′-(4-*O*-Acetyl-2, 3-dideoxy-β-D-*glycero*-pent-2-enopyranosyl-2′- (phenyl-4‴-hexyloxy-dideuterobenzoyl)-ethyne (13)

Di-*O*-acetyl-xylal (**5**, 120 mg, 0.6 mmol) and 4-trimethylsylyl-ethynyl-phenyl -4′-hexyloxy-dideutero benzoate (250 mg, 0.63 mmol) dissolved in dichloromethane (10 mL) are treated with a 1 M solution of stannic tetrachloride in dichloromethane (30 μL) according to GP 1. Purification was by flash chromatography in petroleum ether/ethyl acetate 3:1 to give **13** as colorless crystals (260 mg, 93%). $[\alpha]_D^{20} = -2.7$ (c = 0.5, $CHCl_3$); K 104.2 - S_A 89.1 - I. ^1H NMR (400 MHz,$CDCl_3$) δ: 8.05 (m, 2H, H-2‴-, H-6‴-aryl), 7.44 (m, 2H, H-2″-, H-6″-aryl), 7.12 (m, 2H, H-3″-, H-5″-aryl), 6.07 (dd, 1H, $J_{1,2} =$

Downloaded by [York University Libraries] at 06:33 20 June 2014

3.6, $J_{2,3}$ = 10.2 Hz, H-2), 5.94 (ddd, 1H, $J_{1,3}$ = 2.0, $J_{2,3}$ = 10.2, $J_{3,4}$ = 5.6 Hz, H-3), 4.60 (dd, 1H, $J_{1,2}$ = 3.6, $J_{1,3}$ = 2.0 Hz, H-1), 5.01 (m, 1H, H-4), 4.20 (dd, 1H, $J_{4,5a}$ = 3.1, $J_{5a,5e}$ = 12.2 Hz, H-5a), 3.98 (t, 2H, OCH_2), 3.87 (dd, 1H, $J_{4,5e}$ = 1.0, $J_{5a,5e}$ = 12.2 Hz, H-5e), 2.02 (s, 3H, OAc), 1.76 (mc, 2H,OCH_2CH_2), 1.25–1.53 (m, 6H, 3 CH_2), 0.85 (t, 3H, CH_3). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ: 170.1 (C = O), 121.5–132.6 (C-aryl, C-2, C-3), 89.6, 88.2 (C-1′- C-2′-ethyne), 67.9 (OCH_2), 63.9 (C-5), 63.5, 63.0 (C-1, C-4), 31.1, 28.6, 25.2, 22.1 (4 CH_2), 20.7 ($COCH_3$), 13.6 (CH_3). Calc for $C_{28}H_{30}O_6$ (462.5): C 72.71, H 6.54; found: C 72.87, H 6.50.

Downloaded by [York University Libraries] at 06:33 20 June 2014

REFERENCES

1. Sears, P.; Wong, C.-H. Carbohydrate mimetics: a new strategy for tackling the problem of carbohydrate-mediated biological recognition. *Angew. Chem. Int. Ed.* **1999**, *38*, 2301–2324.

2. Koester, D.C.; Holkenbrink, A.; Werz, D.B. Recent advances in the synthesis of carbohydrate mimetics. *Synthesis* **2010**, 3217–3242.

3. Koester, D.C.; Leibeling, M.; Neufeld, R.; Werz, D.B. A Pd-catalyzed approach to (1→6)-linked *C*-glycosides. *Org. Lett.* **2010**, *12*, 3934–3937.

4. Koester, D.C.; Kriemen, E.; Werz, D.B. Flexible synthesis of 2-deoxy-C-glycosides and (1→2)-, (1→3) - , and (1→4) - linked C- glycosides. *Angew. Chem. Int. Ed.* **2013**, *52*, 2985–2989.

5. Nicotra, F.; Panza, L. Synthesis of *C*-glycosides and *C*-disaccharides. *Trends Org. Chem.* **1995**, *5*, 223–230.

6. Levy, D.E.; Tang, C. *The Chemistry of C-Glycosides*. Pergamon: Elsevier Science Ltd: Oxford, 1995 .

7. Nicotra, F. Synthesis of *C*-glycosides of biological interest. *Top. Curr. Chem.* **1997**, *187*, 55–83.

8. Gyorgydeak, Z.; Pelyvas, I.F. *C*-glycosylation. In *Glycoscience: Chemistry and Chemical Biology*. Fraser-Reid, B.O.; Tatsuta, K.; Thiem, J., Eds.; Springer: Berlin; **2001**, *1*, 691–747.

9. Levy, D.E. Strategies towards *C*-glycosides. In *Organic Chemistry of Sugars*. Levy, D.E.; Fuegedi, P., Eds.; **2006**, 269–348.

10. Kishore, N.; Mishra, B.B.; Tripathi, V.; Tiwari, V.K. Naturally occurring bioactive *C*-glycosides. *Trends Carbohydr. Res.* **2011**, *3*, 1–12.

11. Santos, R.G.; Jesus, A.R.; Caio, J.M.; Rauter, A.P. Fries-type reactions for the *C*-glycosylation of phenols. *Curr. Org. Chem.* **2011**, *15*, 128–148.

12. Rauter, A.P.; Lopes, R.G.; Martins, A. *C*-Glycosylflavonoids: identification, bioactivity, and synthesis. *Nat. Prod. Commun.* **2007**, *2*, 1175–1196.

13. Ferrier, R.J.; Overend, W.G.; Ryan, A.E. The reaction between 3,4,6-tri-*O*-acetyl-D-glucal and *p*-nitrophenol. *J. Chem. Soc.* **1962**, 3667–3670.

14. Ferrier, R.J. Unsaturated carbohydrates. II. Three reactions leading to unsaturated glycopyranosides. *J. Chem. Soc.* **1964**, 5443–5449.

15. Ferrier, R.J. Unsaturated sugars. *Advan. Carbohydr. Chem. Biochem.* **1969**, *24*, 199–266.

16. Ferrier, R.J. Substitution with allylic rearrangement reactions of glycal derivatives. *Top. Curr. Chem.* **2001**, *215*, 153–175.

17. Ferrier, R.J.; Hoberg, J.O. Synthesis and reactions of unsaturated sugars. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 55–119.

18. Ferrier, R.J.; Zubkov, O.A. Transformation of glycals into 2,3-unsaturated glycosyl derivatives. *Org. Reactions* **2003**, *62*, 569–736.

19. Priebe, W.; Grynkiewicz, G. Formation and reaction of glycal derivatives. In *Glycoscience: Chemistry and Chemical Biology.* Fraser-Reid, B.O.; Tatsuta, K.; Thiem, J., Eds. Springer: Berlin, **2001**, *1*, 749–783.

20. Gómez, A.M.; Cristóbal-López, J. Recent strategies for the preparation of *C*-1 glycals. *Carbohydr. Chem.* **2009**, *35*, 290–310.

21. Ciment, D.M.; Ferrier, R.J. Unsaturated carbohydrates. IV. Allylic rearrangement reactions of 3,4,6-tri-*O*-acetyl-D-galactal. *J. Chem. Soc.* **1966**, 441–445.

22. Ferrier, R.J.; Prasad, N. Unsaturated carbohydrates. IX. Synthesis of 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides from tri-*O*-acetyl-D-glucal. *J. Chem. Soc. C* **1969**, 570–575.

23. Ferrier, R.J.; Prasad, N. Unsaturated carbohydrates. XI. Isomerization and dimerization of tri-*O*-acetyl-D-glucal. *J. Chem. Soc. C* **1969**, 581–586.

24. Ansari, A.A.; Lahiri, R.; Vankar, Y.D. The carbon-Ferrier rearrangement: an approach towards the synthesis of *C*-glycosides. *ARKIVOC* **2013**, 316–362.

25. Nicolaou, K.C.; Hwang, C.K.; Duggan, M.E. Stereospecific synthesis of 1, 1- dialkylglycosides. *J. Chem. Soc., Chem. Commun.* **1986**, 925–926.

26. Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. Synthesis of *C*- glycosyl compounds from 3, 4, 6- tri- *O*- acetyl- 1, 5- anhydro- D- *arabino*-hex- 1- enitol and allyltrimethylsilane and bis(trimethylsilyl) acetylene. *Carbohydr. Res.* **1987**, *171*, 193–199.

27. Tsukiyama, T.; Isobe, M. *C*- Glycosidation with silylacetylenes to D- glucals. *Tetrahedron Lett.* **1992**, *33*, 7911–7914.

28. Hosokawa, S.; Kirschbaum, B.; Isobe, M. 1, 4- Anti induction in *C*- glycosylation of pentose glycals. *Tetrahedron Lett.* **1998**, *39*, 1917–1920.

29. Yadav, J.S.; Reddy, B.V.S.; Raju, A.K.; Rao, C.V. Indium tribromide- catalyzed highly stereoselective synthesis of alkynylsugars. *Tetrahedron Lett.* **2002**, *43*, 5437–5440.

30. Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. Iodine catalyzes C- glycosidation of D- glucal with silylacetylene. *Tetrahedron Lett.* **2003**, *44*, 6211–6215.

31. Isobe, M.; Phoosaha, W.; Saeeng, R.; Kira, K.; Yenjai, C. Different *C*- glycosidation products of glucal with alkynyl or propargyl silanes under acidic conditions. *Org. Lett.* **2003**, *5*, 4883–4885.

32. Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Russo, B.; Tagarelli, A. $Er(OTf)_3$ as new efficient catalyst for the stereoselective synthesis of *C*- pseudoglycals. *Synthesis* **2006**, 332–338.

33. Pascual, C.; Meier, J.; Simon, W. Rule for the estimation of the chemical proton shift in double bonds. *Helv. Chim. Acta* **1965**, *49*, 164–168.

Downloaded by [York University Libraries] at 06:33 20 June 2014

34. Matter, U.E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. Estimation of the chemical shifts of olefinic protons using additive increments. II. Compilation of additive increments for 43 functional groups. *Tetrahedron* **1969**, *25*, 691–697.

35. Matter, U.E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. Estimation of the chemical shifts of olefinic protons using additive increments. III. Examples of utility in N.M.R. studies and the identification of some structural features responsible for deviations from additivity. *Tetrahedron* **1969**, *25*, 2023–2034.

Downloaded by [York University Libraries] at 06:33 20 June 2014