Synthesis of *C*-Glucoside *endo*-Glycals from *C*-Glucosyl Vinyl Sulfones

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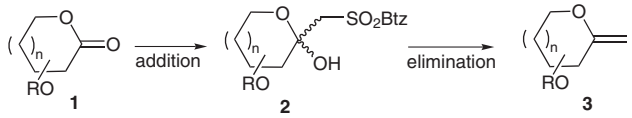
Received 12 December 2005

Abstract: The synthesis and the reactivity of *C*-glucosyl vinyl sulfones in two steps from benzylated gluconolactone and benzothiazolylsulfones derivatives is reported.

Key words: vinyl sulfones, *C*-glycosides, *exo*-glycals, *ipso* substitution

C-Glycosides, sugar analogues in which the anomeric oxygen atom is replaced by a carbon, have attracted a great interest either for the preparation of biologically interesting molecules[1] or because of their stability against enzyme hydrolysis.[2] Within this field, the particular case of *exo*-glycals[3] have attracted the attention of synthetic chemists for their application as glycosidase inhibitors[4] or valuable intermediates.[5] Nevertheless, while the preparation of methylene *exo*-glycals is well documented,[3] the synthesis of substituted or functionalized *exo*-glycals has been less thoroughly addressed in the literature.

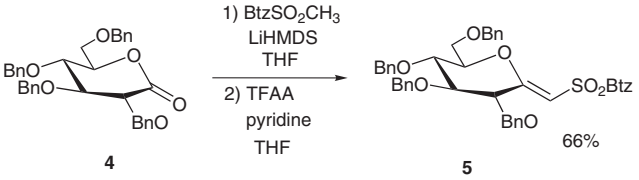
In our ongoing projects devoted to the preparation of *C*-glycosides,[6] we recently reported the synthesis of methylene *exo*-glycals using a modified Julia olefination.[7] This method proceeds through an addition–elimination sequence starting from sugar-derived lactones (Scheme 1). We showed that the α-heteroarylsulfonyl hemiketal intermediate could be isolated in good yield, and that the sulfonic acid elimination reaction was best performed under basic catalysis by an amine.



Scheme 1 Julia olefination of sugar-derived lactones; Btz: benzothiazolyl

In the current work, we investigate whether the same hemiketal intermediate can be used for the synthesis of *C*-glucosyl vinyl sulfones by dehydration.

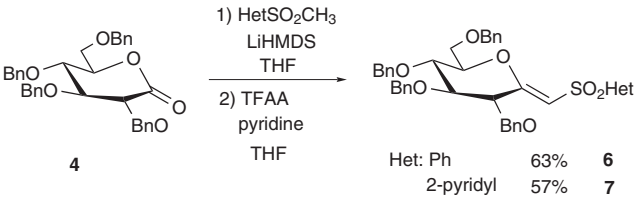
Several methods have been described in the literature for the dehydration of α-hydroxysulfones in acidic[8] or basic[9] media. In our case, the procedure using pyridine and trifluoroacetic anhydride was found to be the most efficient.[10] Thus, coupling of the lithium salt of the sulfone



Scheme 2 Synthesis of *C*-glucosyl vinyl sulfone

and treatment of the isolated hemiketal intermediate with pyridine and trifluoroacetic anhydride lead selectively to the *Z* isomer in a good yield (Scheme 2).[11]

Encouraged by these results, we have shown that the methodology could be applied to other heterocyclic systems. The phenyl and 2-pyridyl derivatives were obtained in 63% and 57% yields, respectively, (Scheme 3). Thus, the sequence takes place under mild conditions to afford the expected compounds in good yield regardless of the nature of the heterocyclic moiety (Tables 1– 3).



Scheme 3 Extension of the sequence to other heterocyclic systems

We then explored the *ipso* substitution of the heteroaromatic moiety (Scheme 4 and Table 4). Indeed, heteroaryl sulfones, particularly benzothiazol-2-yl sulfone, are prone to nucleophilic *ipso* substitution. This reaction proceeds through a Meisenheimer complex to lead to a sulfinate, which could be subsequently quenched by an electrophilic partner.[12]

For our first investigations on the *ipso* substitution, we attempted the reaction with methyl iodide as electrophile and sodium methoxide as nucleophile as described by Rollin et al.[13] We observed a base-catalyzed migration of the double bond prior to the transsulfonylation process. Under optimized conditions, the use of an excess of the base (5 equiv) was necessary in order to increase the reaction rate to avoid side-reactions. Furthermore, we found that the tetrahydrofuran–methanol ratio was critical for the success of the transsulfonylation process. After considerable experimentation, we determined that a 1:1 volumetric ratio was optimal in order to assure the solubility

SYNTHESIS 2006, No. 9, pp 1499–1503
Advanced online publication: 07.04.2006
DOI: 10.1055/s-2006-926422; Art ID: P18705SS

Table 1 *C*-Glycoside *exo*-Glycal Derivatives **5**, **6** and **7**

Entry	Compound	Molecular formula	HRMS	Yield (%)	$[\alpha]_D$ (*c* 1 g/100 mL)	IR (cm^{-1})
1	**5**	$C_{42}H_{39}NO_7S_2$	*m*/*z* calcd for $C_{42}H_{40}NO_7S_2$: 734.2246; found: 734.2248	66	+47	1143, 1318
2	**6**	$C_{41}H_{40}O_7S$	*m*/*z* calcd for $C_{41}H_{41}O_7S$: 677.2573; found: 677.2570	63	+67	1146, 1305
3	**7**	$C_{40}H_{39}NO_7S$	*m*/*z* calcd for $C_{40}H_{40}NO_7S$: 678.2525: found: 678.2523	57	+55	1167, 1313

Table 2 ^{1}H NMR Data for Compounds **5**, **6** and **7** [δ, *J*]

Compound	H-2	H-3	H-4	H-5	H-6	H-7	OBn	Het
5	3.95 (d, *J* = 5.1 Hz)	3.81 (m)	3.81 (m)	4.14 (br d, *J* = 8.4 Hz)	3.79 (dd, *J* = 3.3, 11.4 Hz), 3.72 (dd, *J* = 2.1 Hz),	6.06 (s)	4.33–4.62 (m), 7.03–7.26 (m)	7.03–7.26 (m), 7.41 (td, *J* = 1.5, 8.1 Hz), 7.48 (td, *J* = 1.8 Hz), 7.74 (dd)
6	3.90 (d, *J* = 5.4 Hz)	3.75 (m)	3.75 (m)	3.97 (br d, *J* = 8.7 Hz)	3.75 (m)	6.03 (s)	4.52–4.73 (m), 7.18–7.38 (m)	7.18–7.38 (m), 7.52 (t, *J* = 7.5 Hz), 8.01 (d, *J* = 7.8 Hz)
7	3.93 (d, *J* = 5.4 Hz)	3.77 (m)	3.77 (m)	3.98 (br d, *J* = 9.3 Hz)	3.62 (m)	6.13 (s)	4.46–4.73 (m), 7.16–7.38 (m)	7.18–7.38 (m), 7.60 (t, *J* = 7.5 Hz), 8.10 (d, *J* = 7.8 Hz), 8.65 (d, *J* = 4.2 Hz)

Table 3 ^{13}C NMR Data for Compounds **5**, **6** and **7** (δ)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	O*C*H_2Ph	OCH$_2$*Ph*	Het
5	166.0	77.5	82.8	76.9	79.9	68.3	108.3	73.4, 74.0, 74.1, 74.4	127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.9, 129.0, 129.1, 137.0, 137.9, 138.0, 138.4	122.6, 125.7, 128.2, 128.7, 137.3, 152.9, 169.2
6	162.0	77.7	83.2	77.0	79.1	68.3	112.1	73.4, 74.0, 74.1, 74.4	128.0, 128.2, 128.3, 128.4, 128.5, 128.7, 128.9, 129.1, 137.1, 138.0, 138.3	128.4, 128.9, 133.3, 143.2
7	163.0	77.5	83.1	76.9	79.0	68.4	109.5	73.4, 74.0, 74.1, 74.4	127.1, 128.2, 128.3, 128.4, 128.6, 128.8, 128.9, 129.1	122.9, 128.3, 138.0, 150.2

Table 4 Introduced Substituents through *Ipso* Substitution

Compound	R
8a	Me
8b	$CH_2CH{=}CH_2$
8c	CH_2Ph
8d	CH_2COOMe
8e	$(CH_2)_2CH{=}CH_2$
8f	$(CH_2)_8Br$
8g	$(CH_2)_4Me$
8h	CH_2COPh

of the sulfinate intermediate. Thus, the reaction furnishes a new class of *C*-glycoside *endo*-glycals in good yield (81%).

A series of reactions was performed varying the electrophilic partner (Scheme 5). Gratifyingly, all substrates tested during our studies gave the expected products with moderate to good yields (Tables 5– 7).

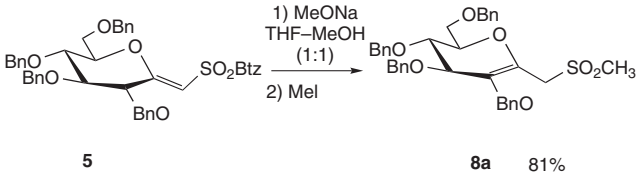
As expected, an increase in length of the alkyl halide resulted in lower yields (Table 5, entries 1 and 7). The reaction gave the expected compound either with iodo or bromo reagents (Table 5, entries 1 and 2). The reaction conditions are compatible with a large range of functional group such as double bond, ester, ketone, halides and aromatic rings.

Table 5 *C*-Glycoside *endo*-Glycal Derivatives **8**

Entry	Compound	Molecular formula	HRMS	Yield (%)	$[\alpha]_D$ (*c* 1 g/100 mL)	IR (cm^{-1})
1	**8a**	$C_{36}H_{38}O_7S$	*m*/*z* calcd for $C_{36}H_{38}NaO_7S$: 637.2236; found: 637.2233	81	–9	1140, 1312
2	**8b**	$C_{38}H_{40}O_7S$	*m*/*z* calcd for $C_{38}H_{40}NaO_7S$: 663.2392; found: 663.2393	75	–15	1135, 1319
3	**8c**	$C_{42}H_{42}O_7S$	*m*/*z* calcd for $C_{42}H_{42}NaO_7S$: 713.2549; found: 663.2557	63	–24	1121, 1317
4	**8d**	$C_{38}H_{40}O_9S$	*m*/*z* calcd for $C_{38}H_{40}NaO_9S$: 695.2291; found: 695.2293	68	–13	1105, 1330
5	**8e**	$C_{39}H_{42}O_7S$	*m*/*z* calcd for $C_{39}H_{42}NaO_7S$: 677.2549; found: 677.2542	39	–20	1133, 1312
6	**8f**	$C_{43}H_{51}BrO_7S$	Not determined	40	–18	1133, 1313
7	**8g**	$C_{40}H_{46}O_7S$	*m*/*z* calcd for $C_{40}H_{46}NaO_7S$: 693.2862; found: 693.2867	51	–19	1134, 1316
8	**8h**	$C_{43}H_{42}O_8S$	*m*/*z* calcd for $C_{43}H_{42}NaO_8S$: 741.2498; found: 741.2487	43	–29	1128, 1327

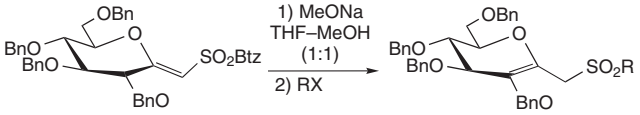
Table 6 ^{1}H NMR Data for Compounds **8a**–**h** [δ, *J* (Hz)]

Compound	H-3	H-4	H-5	H-6	CH_2	OCH_2Ph	OCH_2Ph	R
8a	4.27 (d, *J* = 3.6 Hz)	3.90 (m)	4.35 (m, *J* = 3.6, 7.2 Hz)	3.63 (dd, *J* = 3.6, 10.8 Hz), 3.90 (m)	3.90 (m)	4.50 (m), 4.63 (2 × d, *J* = 12.3 Hz), 4.80 (2 × d, *J* = 11.1 Hz)	7.23–7.44 (m)	2.94 (s)
8b	4.35 (m)	3.94 (m)	4.35 (m)	3.68 (dd, *J* = 3.3, 10.8 Hz), 3.94 (m)	3.94 (m)	4.55 (m), 4.68 (2 × d, *J* = 12.0 Hz), 4.86 (2 × d, *J* = 11.8 Hz)	7.22–7.43 (m)	3.94 (m), 5.45 (2× d, *J* = 11.4, 17.4 Hz), 5.90 (m)
8c	4.33 (d, *J* = 3.6 Hz)	3.92 (t, *J* = 4.2 Hz)	4.39 (m)	3.69 (dd, *J* = 3.3, 10.8 Hz), 3.95 (dd, *J* = 7.5 Hz)	3.80 (2×d, *J* = 15.0 Hz)	4.52 (m), 4.67 (2 × d, *J* = 12.3 Hz), 4.83 (2 × d, *J* = 11.4 Hz)	7.24–7.43 (m)	4.28 (d, *J* = 13.8 Hz), 4.45 (d), 7.24–7.43 (m)
8d	4.27 (m)	3.88 (m)	4.27 (m, *J* = 3.6, 7.2 Hz)	3.59 (dd, *J* = 3.3, 10.5 Hz), 3.88 (m)	3.65 (d, *J* = 12.2 Hz), 4.27 (m)	4.52 (m), 4.66 (2 × d, *J* = 11.7 Hz, 4.84 (2 × d, *J* = 11.4 Hz)	7.25–7.39 (m)	3.71 (s), 4.05 (d, *J* = 14.7 Hz), 4.27 (m)
8e	4.34 (m)	3.92 (m)	4.34 (m)	3.67 (dd, *J* = 3.6, 10.8 Hz), 3.92 (m)	3.92 (m)	4.54 (m), 4.67 (2 × d, *J* = 12.2 Hz), 4.85 (2 × d, *J* = 11.7 Hz)	7.23–7.38 (m)	2.94 (m), 3.21 (m), 5.03 (m), 5.71 (m)
8f	4.29 (d, *J* = 3.6 Hz)	3.89 (m)	4.33 (m)	3.64 (dd, *J* = 3.3, 10.5 Hz), 3.89 (m)	3.89 (m)	4.51 (m), 4.64 (2 × d, *J* = 12.0 Hz), 4.82 (2 × d, *J* = 11.1 Hz)	7.24–7.37 (m)	1.21–1.44 (m), 1.79 (m), 3.08 (m), 3.38 (t, *J* = 6.6 Hz)
8g	4.33 (d, *J* = 3.6 Hz)	3.91 (m)	4.33 (m)	3.68 (dd, *J* = 3.3, 10.5 Hz), 3.91 (m)	3.91 (m)	4.54 (m), 4.67 (2 × d, *J* = 12.3 Hz), 4.85 (2 × d, *J* = 11.1 Hz)	7.28–7.40 (m)	1.27 (m), 1.79 (m), 3.10 (m)
8h	4.23 (d, *J* = 2.7 Hz)	3.84 (t, *J* = 3.9 Hz)	4.30 (m)	3.58 (dd, *J* = 2.4, 10.5 Hz), 3.99 (dd, *J* = 10.5 Hz)	4.30 (m)	4.50 (m), 4.58 (2 × d, *J* = 12.0 Hz), 4.82 (s)	7.23–7.38 (m)	4.50 (m), 4.98 (d, *J* = 16.2 Hz), 7.23–7.38 (m), 7.55 (t, *J* = 7.5 Hz), 7.63 (d, *J* = 8.1 Hz)



5 8a 81%

Scheme 4 *Ipso* substitution



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Scheme 5 Screening of the electrophilic partner

In summary, we have demonstrated an access to activated glycals. This coupling–dehydratation sequence leads to anomeric vinyl sulfones. These molecules can be subsequently transformed into a new class of *C*-glycoside *endo*-glycals through transsulfonylation process.

We are currently investigating the use of the anomeric sulfone group as phosphate mimic[14] to design new potential inhibitors of glycogen phosphorylase and glucosyltransferase.

All reactions were conducted under argon atmosphere. All common reagents were used as obtained from commercial suppliers without further purification. Tetrahydrofuran was distilled over Na/Benzophenone. Flash column chromatography was carried out with silica gel (36–63 mesh). Specific optical rotations were measured with a Perkin Elmer (model 141) polarimeter using a 10-cm cell. NMR spectra were recorded on a Bruker Avance DRX 300 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. MS data were recorded on a ThermoFinnigan MAT 95 XL spectrometer. IR spectra were recorded on a Perkin Elmer FT apparatus.

Anomeric Vinyl Sulfone Synthesis; General Procedure

In a 50 mL round-bottomed flask under argon, 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (1.137 g, 2.11 mmol) and 2-methanesulfonylbenzothiazole (540 mg, 1.2 equiv) were dissolved in freshly distilled THF (10 mL) at –78 °C. Then a 1 M solution of LiHMDS in THF (5.072 mL, 2.4 equiv) was added dropwise over 10 min. Stirring was maintained during 30 min and then, the reaction mixture was quenched by addition of AcOH (0.362 mL, 3 equiv). After hydrolysis, the mixture was extracted with EtOAc (2 ×), dried over Na_2SO_4 and evaporated. The residue was dissolved in anhydrous THF (10 mL), and TFAA (1.655 mL, 8 equiv) and pyridine (2.421 mL, 20 equiv) were added dropwise. Stirring was maintained for 16 h at r.t. and then the reaction was hydrolyzed with a sat. solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (2 ×), dried over Na_2SO_4, concentrated by rotary evaporation and purified by flash chromatography to afford the desired product (yield: 1.022 g, 66%).

Table 7 ^{13}C NMR Data for Compounds **8a–h** (δ)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	CH_2	OCH_2*Ph*	O*C*H_2Ph	R
8a	136.7	136.1	73.4	73.2	76.7	68.2	54.8	128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 137.4, 137.9, 138.1, 138.2	71.4, 72.6, 73.7, 74.8	42.5
8b	137.0	136.5	73.8	73.3	76.9	68.3	51.1	128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 137.4, 138.0, 138.2	71.2, 72.7, 73.8, 75.0	58.8, 125.4, 125.5
8c	137.3	136.7	74.0	73.5	77.1	68.5	50.8	128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 137.3, 138.0, 138.1, 138.2	71.2, 72.8, 73.8, 75.0	60.6, 128.0, 129.2, 131.6
8d	136.6	136.5	73.6	73.3	76.8	68.2	53.2	128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 137.3, 137.9, 138.1, 138.2	71.3, 72.6, 73.7, 74.9	53.4, 58.3, 164.1
8e	136.8	136.3	73.6	73.2	76.8	68.2	53.4	128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 137.4, 138.0, 138.1, 138.2	71.3, 72.7, 73.8, 74.8	26.6, 53.2, 117.3, 134.7
8f	136.9	136.2	73.6	73.2	76.8	68.3	52.8	128.1, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 137.5, 138.0, 138.1, 138.3	71.3, 72.6, 73.7, 74.9	22.3, 28.4, 28.7, 28.8, 29.3, 33.1, 34.3, 54.2
8g	137.0	136.2	73.7	73.2	76.8	68.3	52.9	128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 137.5, 138.0, 138.1, 138.3	71.3, 72.7, 73.7, 74.9	14.2, 22.0, 22.6, 30.9, 54.3
8h	136.3	136.2	73.3	73.3	76.6	68.3	53.7	128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 129.1, 137.3, 137.9, 138.1, 138.3	71.4, 72.4, 73.8, 75.1	60.9, 129.2, 134.4, 136.8, 189.7

***Ipso*-Substitution Reaction; General Procedure**

In a 25-mL round-bottomed flask under argon, vinyl sulfone (0.112 g, 0.153 mmol) was dissolved in a THF–MeOH mixture (2 mL, 1:1) at r.t. Then sodium methanolate (42 mg, 5 equiv) was added. Stirring was maintained for 30 min and then iodomethane (95 μL, 10 equiv) was added. The mixture was refluxed for 30 min. After cooling, the mixture was hydrolyzed, extracted with EtOAc (2 ×), dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography to afford the desired product (yield: 76 mg, 81%).

Acknowledgment

The authors would like to thank Dr. D. Bouchu for HRMS analysis and Dr. B. Fenet for NMR experiments.

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