Synthesis of Methylene Exoglycals Using a Modified Julia Olefination

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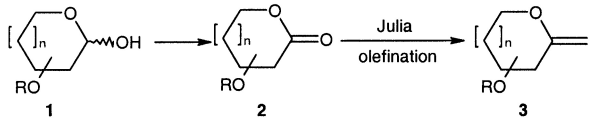
Abstract: A new route to exomethylene sugars is reported. The use of a two-step coupling–elimination procedure allows successful Julia olefination of sugar-derived lactones.

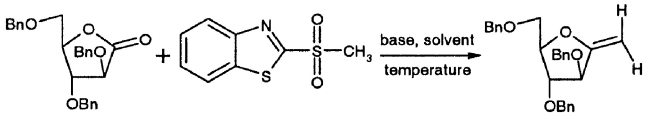
Key words: glycals, olefination, carbohydrate, alkenes, lactones

Methylene exoglycals[1] **3** (Scheme 1) are known to be glycosidase inhibitors[2] as well as valuable intermediates for the synthesis of *C*-glycosides,[3] *C*-disaccharides, [4] and natural products.[5] A number of procedures have been published for the preparation of such compounds: indirect methods based on elimination reactions,[6] olefination of sugars by the Tebbe reagent[7] or dimethyltitanocene,[8] Ramberg–Backlund rearrangement of glycosyl sulfones,[9] and recently Bamford–Stevens reaction of anhydroaldose tosylhydrazone.[10] The use of the Tebbe reagent is an efficient method, yet the sensitivity and cost of this reagent, as well as functional group compatibility considerations call nonetheless for alternative procedures. Our plan was to extend the modified Julia olefination conditions to sugar lactones as shown in Scheme 2. There are many published procedures for the conversion of reducing sugars into lactones, and the Julia olefination[11] has been used extensively in the last decade for the construction of C=C bonds present in many natural products.[12] Generally, this type of reaction is carried out using a heteroarylsulfone and an aldehyde. This reaction has recently been extended to ketones[13] and hemiacetals[14] but to our knowledge, Julia olefination has not been achieved with lactones.



Scheme 1 Julia olefination of sugar derived lactones

In this paper, we report the first example of a modified Julia olefination using a sugar-derived lactone to prepare methylene exoglycals. In order to optimise the reaction conditions, we first explored the coupling between methylbenzothiazoylsulfone and tri-*O*-benzyl-D-arabinolactone.



Scheme 2

This study is described in Table 1. We investigated the nature of the base, the solvent (toluene or THF), the temperature (–85 °C to r.t.) and the order of addition (Barbier or premetalation).

– None of the desired compounds is detected when the sulfone is premetalated (entries 1, 3 and 5).

– The reaction affords the methylene exoglycal in low to moderate yields under Barbier conditions, at low temperature (entries 2, 4 and 8).

– Best results using the standard modified Julia procedure (35%) were obtained with LiHMDS as base (entry 2 vs. 8) and THF as solvent (entry 2 vs. 4).

The observation that the expected α-heteroarylsulfonyl hemiketal intermediate was formed cleanly, yet reverted to starting material upon warming, led us to try a two-step

Table 1 Coupling between Methylbenzothiazoylsulfone and Tri-*O*-benzyl-D-arabinolactone

Entry	Base	Solvent	Temp. (°C)	Addition[a]	Yield (%)
1	KHMDS	Toluene	r.t.	Premetal.	–
2	LDA	THF	–78	Barbier	18
3	LDA	THF	–78	Premetal.	–
4	LDA	Toluene	–85	Barbier	7
5	LDA	Toluene	0	Premetal.	–
6	LiHMDS	THF	0	Barbier	–
7	LDA	THF	0	Barbier	–
8	LiHMDS	THF	–78	Barbier	35
9	1) LiHMDS 2) NaOH	THF THF	–78 r.t.	Barbier	21
10	1) LiHMDS 2) DBU	THF THF	–78 r.t.	Barbier	66

[a] Barbier: base added to a mixture of sulfone and lactone. Premetalate: base added to sulfone and then lactone added.

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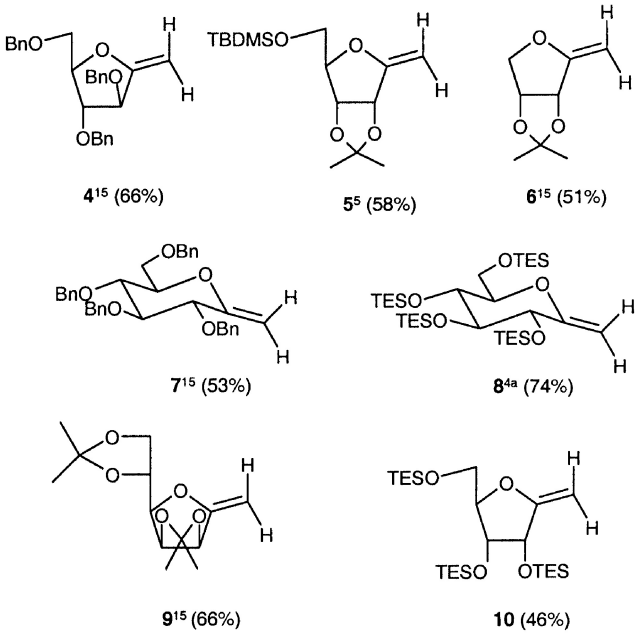
sequence (entries 9 and 10). The first step consists in the addition of the sulfone on the lactone using LiHMDS in THF at –78 °C, providing the intermediate in 78% yield. Attempted conversion into the desired exoglycal by basic treatment in THF using a strong base such as sodium hydroxide gave a low yield (21%), along with a significant amount of the starting lactone. On the other hand, treatment of the crude intermediate after aqueous work up with DBU led to the glycal in 66% overall yield for the two steps.

To evaluate the scope and limitations of this method, we performed the modified Julia olefination between sulfone and a variety of sugar-derived lactones under the optimised reaction conditions (Scheme 3).



Scheme 3 Synthesis of methylene exoglycals in diverse sugar series[16]

Generally, the reaction affords the methylene exoglycal with reasonable yields (46–74%). Pyranose and furanose rings were successfully employed. The reaction was shown to occur with diverse sugar series (D-arabino, D-gluco, D-ribo, D-manno and D-erythro) and several types of protective groups (benzyl ether, silyl ether and isopropylidene). Only a *t*-butyldimethylsilyl protecting group on the C2-hydroxyl group was found to interfere with the reaction.

In summary, we demonstrated that the Julia olefination can be extended to sugar derived lactones to lead to methylene exoglycals in good yields. We are currently extending the ester Julia olefination methodology to a range of sulfones, readily prepared through a two-step process from commercially available and inexpensive reagents, in order to furnish substituted exoglycals which are also of interest.

Synthesis of 4; Typical Experiments

In a 10 mL round bottom flask under argon, 100 mg (0.239 mmol) of tri-*O*-benzyl-D-arabinolactone and 61 mg (1.2 equiv) of 2-methanesulfonylbenzothiazole were dissolved in 1 mL of freshly distilled THF at –78 °C, then a 1 M solution of LiHMDS in THF (574 μL, 2.4 equiv) was added drop-wise over 10 min. Stirring was maintained during 30 min, and then the reaction mixture was quenched by addition of 3 equiv of HOAc (43 μL). After hydrolysis, the mixture was extracted with EtOAc (2 ×), dried over Na_2SO_4 and evaporated. The residue was dissolved in dry THF (5 mL), and 2 equiv of DBU (71 μL) was added. Stirring was maintained during 1 h, the mixture was concentrated by rotary evaporation and purified by flash chromatography to afford the desired product (66 mg) with 66% yield.

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(16) All compounds were characterised by NMR spectroscopy and HRMS. Data were identical to those reported in the literature.
Data for compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39 (d, 1 H, *J* = 4.3 Hz, H-2), 4.23 (s, 1 H, H-1′a), 4.05 (m, 2 H, H-3 and H-4), 3.95 (s, 1 H, H-1′b), 3.71 (dd, 1 H, *J* = 3.2 Hz, *J* = 11.5 Hz, H-5a), 3.63 (dd, 1 H, *J* = 3.4 Hz, H-5b), 0.90 (m, 27 H, CH_3), 0.59 (m, 18 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.7, 5.2, 5.5, 7.1, 7.2, 7.3, 62.4, 72.7, 73.0, 82.6, 85.9, 163.4. IR: 1678 cm^{-1} (C=C). $[\alpha]_D$ +15 (*c* 1, $CHCl_3$). HRMS (CI-MS): *m*/*z* calcd for $C_{24}H_{52}O_4Si_3$ $[M + H]^+$: 489.3252; found: 489.3257