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Synthesis of enol ethers from lactones using modified Julia olefination reagents: application to the preparation of tri- and tetrasubstituted exoglycals

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Abstract

A new route to substituted exoglycals from the corresponding lactones is described. The enol ethers synthesis via a modified Julia olefination of sugar-derived lactones is extended to substituted benzothiazolyl sulfones to furnish tri- and tetrasubstituted exoglycals.

Keywords: Julia olefination; Exoglycals; Lactones; Enol ethers

The synthesis of functionalized tri- and tetrasubstituted enol ethers by olefination of lactones represents a long-standing challenge in organic chemistry due to the low electrophilicity of esters and lactones. The use of metal carbenoids such as Tebbe reagents is most effective, but is usually limited to the preparation of unsubstituted enol ethers.[1] Conventional methods such as the Wittig reaction have generally been unsuccessful, although some improvements have been reported by the use of non-classical reagents.[2] In the specific case of exoglycals,[3] a number of procedures have been published for the preparation of unsubstituted methylene exoglycals: methods based on elimination reactions,[4] olefination of sugar lactones with the Tebbe reagent[5] or dimethyltitanocene,[6] Ramberg–Backlund rearrangement of glycosyl sulfones[7] and recently a Bamford–Stevens reaction of anhydroaldose tosylhydrazone.[8] Only a few of these methods can be used to obtain tri- and tetrasubstituted exoglycals. Wittig olefination has been employed to prepare dichloro,[9] difluoro,[10] dithio[11] and carbomethoxy[12] alkenes, and an example of trimethylsilyl substituted exoglycals obtained by reaction with tris(trimethylsilyl) titanacyclobutene has been described.[13] However, these methodologies are not general. A general route is provided by the Ramberg–Backlund rearrangement,[7] although this sequence requires a somewhat lengthy preparation of the substituted glycosyl sulfones. Finally, other available routes are much less direct.[14]

We have recently demonstrated that the use of Julia olefination reagents can be extended to the synthesis of methylene exoglycals from sugar-derived lactones.[15] The modified Julia olefination[16] has emerged as a powerful tool for olefin synthesis, through its application in total synthesis of natural products.[17] This reaction has been extended to the preparation of vinyl ethers,[18] fluoro alkenes[19] and α,β-unsaturated esters.[20] In this Letter, we report the extension of our enol ether synthesis using modified Julia reagents to the preparation of tri- and tetrasubstituted exoglycals (Fig. 1).

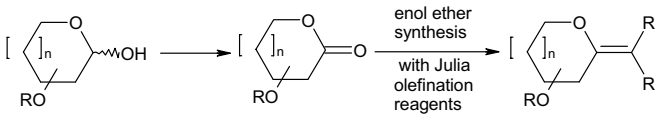

Fig. 1. Julia olefination of sugar-derived lactones.

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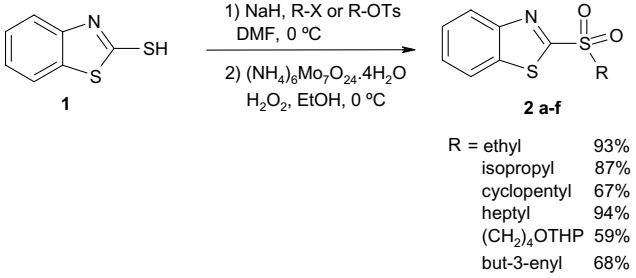


Scheme 1. Preparation of the benzothiazolyl sulfones.

Benzothiazolyl sulfones **2** were prepared from inexpensive and odourless 2-mercaptobenzothiazole through a two-step process involving S-alkylation and S-oxidation (Scheme 1).[20]

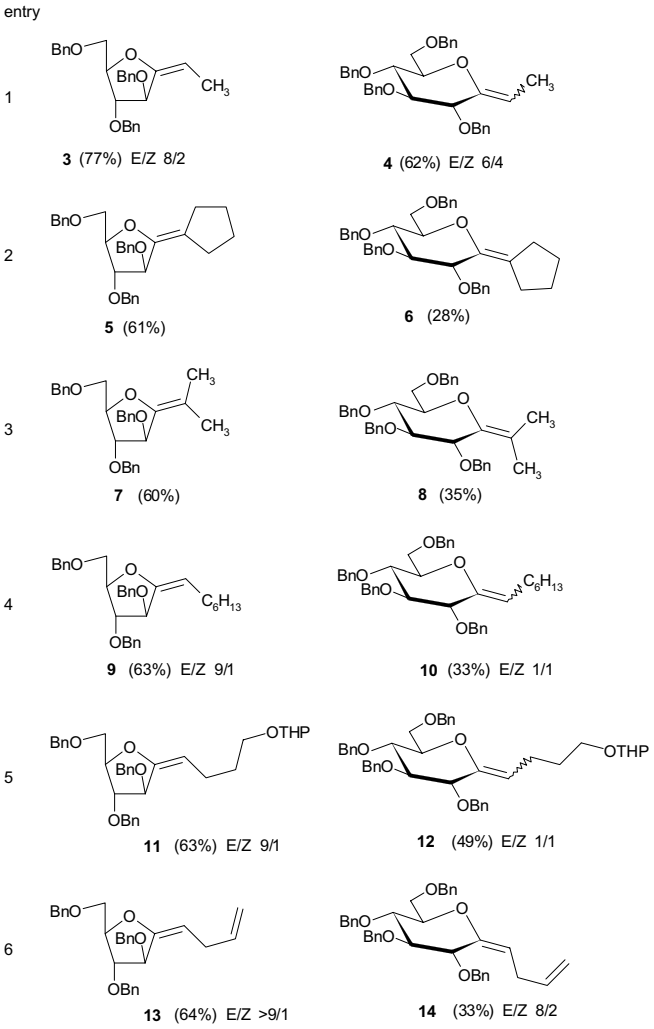
We chose the readily available 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone and 2,3,5-tri-*O*-benzyl-D-arabinonolactone as starting materials to determine the influence of the ring size of the sugar on the olefination reaction.

Our previous results showed that the enol ether synthesis requires that the coupling be done under Barbier conditions, presumably due to self-condensation reactions of the lithiated sulfones, and that a two-step procedure be used in which the elimination step is catalyzed by DBU.[15] Treating a mixture of carbohydrate lactone and benzothiazolylsulfone with LiHMDS at −78 °C and treating the resulting isolated hemiacetal with DBU afforded the corresponding exoglycals in reasonable yields (28–77%).[21] The reaction was successful with both pyranose and furanose ring sugars, even if in most cases D-arabino exoglycals were obtained in better yields. We also showed that functionalized benzothiazolyl sulfones can be used for the enol ether synthesis (Scheme 2, entries 5 and 6).

In the case of the methyl-substituted compounds **3** and **4**, the two diastereoisomers were separated to determine the alkene stereochemistry by NOE experiments. A correlation was observed from H-4 to the methyl group in the case of the *E* isomer, and to the H-2 proton in the *Z* isomer (Fig. 2). For compounds **9**–**14**, the *E*/*Z* stereochemistry was determined by analogy to compounds **3** and **4**, and the ratio was measured by integration of selected NMR peaks after isolation of the *E*/*Z* mixture by column chromatography. The observed *E*/*Z* selectivity is usually better in the D-arabino series (>8/2) than in the D-gluco series (1/1 to 8/2). However, it should be noted that the exoglycals are prone to isomerization and the *E* isomer in the D-gluco series is highly hindered due to the substituent on the pyranose ring. Additional studies are therefore underway to fully address the stereochemical issue.

The introduction of aromatic rings (phenyl) or electron-withdrawing groups (esters, nitriles and ketones) on the double bond has so far been unsuccessful using this methodology, presumably due to the low reactivity of the relevant alpha-lithiated sulfone.

In summary, we have demonstrated that the enol ether synthesis can be extended to the preparation of tri- and tetrasubstituted exoglycals in good yields from carbohydrate lactones. We are currently studying the reactivity of these substituted exoglycals for the preparation of various families of biologically relevant compounds.



Scheme 2. Synthesis of tri- and tetrasubstituted exoglycals.

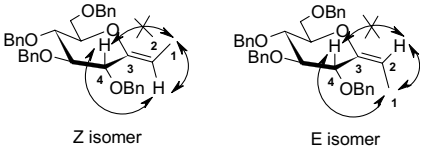


Fig. 2. Determination of the stereochemistry for compound **4** (*E* and *Z* isomer) by NOE experiments.

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21. *Typical procedure*: In a 10 mL round-bottomed flask under argon, 100 mg (0.239 mmol) of 2,3,5-tri-*O*-benzyl-D-arabinonolactone and 61 mg (1.2 equiv) of 2-ethanesulfonylbenzothiazole 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 dropwise over 10 min. Stirring was maintained during 30 min and then, the reaction mixture was quenched by the addition of 3 equiv of acetic acid (43 μL). After hydrolysis, the mixture is extracted with ethyl acetate (×2), dried over sodium sulfate and evaporated. The residue is dissolved in dry THF (2 mL) and 2 equiv of DBU (71 μL) were added. Stirring was maintained during 1 h, the mixture was concentrated by rotary evaporation and purified by flash chromatography to afford compound **3** (66 mg) in 77% yield. *Selected data*: Compound **3** (*Z* isomer): ^{1}H NMR (CD_3COCD_3, 300 MHz): $\delta = 1.60$ (d, 3H, $J = 6.8$ Hz, CH_3), 3.64 (d, 2H, $J = 6.4$ Hz, H-7), 4.10 (t, 1H, $J = 2.1$ Hz, H-5), 4.32 (br s, 1H, H-4), 4.43 (td, 1H, H-6), 4.49–4.55 (m, 7H, $3CH_2$ and H-2), 7.27–7.37 (m, 15H, Har). ^{13}C NMR (CD_3COCD_3, 75 MHz): $\delta = 10.5$, 70.9, 71.0, 71.9, 73.6, 82.3, 83.3, 84.7, 97.0, 128.3, 128.5, 128.6, 128.9, 129.1, 129.2, 139.1, 139.3, 139.5, 154.9. (*E* isomer): ^{1}H NMR (CD_3COCD_3, 300 MHz): $\delta = 1.59$ (d, 3H, $J = 7.2$ Hz, CH_3), 3.58 (dd, 1H, $J = 7.2$ Hz, $J = 9.8$ Hz, H-7b), 3.62 (dd, 1H, $J = 6.4$ Hz, H-7a), 4.18 (br s, 1H, H-5), 4.39 (td, 1H, $J = 6.6$ Hz, $J = 1.0$ Hz, H-6), 4.48–4.63 (m, 7H, $3CH_2$ and H-4), 4.93 (q, 1H, H-2), 7.29–7.34 (m, 15H, Har). ^{13}C NMR (CD_3COCD_3, 75 MHz): $\delta = 12.3$, 70.7, 71.3, 71.6, 73.6, 79.5, 82.7, 84.2, 97.3, 128.3, 128.4, 128.6, 129.0, 129.1, 139.0, 139.1, 139.3, 155.9. HRMS (EI): *m*/*z* [$M^{+\cdot}$] calcd for $C_{28}H_{30}O_4$: 430.2144; found: 430.2145. Compound **4** (*Z* isomer): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.72$ (d, 3H, $J = 4.2$ Hz, CH_3), 3.72 (t, 1H, $J = 4.2$ Hz, H-5), 3.75–3.82 (m, 3H, H-7, H-8b and H-6), 3.85 (dd, 1H, $J = 6.3$ Hz, $J = 0.9$ Hz, H-8a), 3.96 (d, 1H, $J = 4.2$ Hz, H-4), 4.56–4.90 (m, 8H, $4CH_2$), 5.06 (q, 1H, $J = 4.2$ Hz, H-2), 7.20–7.41 (m, 20H, Har). (*E* isomer): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.57$ (d, 3H, $J = 4.2$ Hz, CH_3), 3.69–3.77 (m, 3H, H-8 and H-6), 3.94 (dd, 1H, $J = 3.0$ Hz, $J = 1.5$ Hz, H-5), 4.28 (ddd, 1H, $J = 1.2$ Hz, $J = 2.4$ Hz, $J = 6.0$ Hz, H-7), 4.40 (d, 1H, $J = 1.5$ Hz, H-4), 4.42–4.71 (m, 8H, $4CH_2$), 5.33 (q, 1H, $J = 4.5$ Hz, H-2), 7.20–7.37 (m, 20H, Har). HRMS (ESI): *m*/*z* [$M+Na^+$] calcd for $C_{38}H_{40}O_5Na$: 573.2617; found: 573.2618. Compound **7**: ^{1}H NMR (CD_3COCD_3, 300 MHz): $\delta = 1.64$ and 1.66 (2s, 6H, $2CH_3$), 3.60 (dd, 1H, $J = 7.5$ Hz, $J = 9.8$ Hz, H-7b), 3.65 (dd, 1H, $J = 6.2$ Hz, H-7a), 4.20 (s, 1H, H-5), 4.44 (t, 1H, $J = 6.9$ Hz, H-6), 4.50–4.66 (m, 7H, $3CH_2$ and H-4), 7.29–7.39 (m, 15H, Har). ^{13}C NMR (CD_3COCD_3, 75 MHz): $\delta = 17.2$, 19.2, 71.0, 71.2, 71.7, 73.6, 80.2, 83.1, 84.2, 105.9 128.3, 128.4, 128.5, 128.6, 129.1, 129.2, 139.2, 139.3, 139.5, 149.8. HRMS (EI): *m*/*z* [$M^{+\cdot}$] calcd for $C_{29}H_{32}O_4$: 444.2301; found: 444.2304.