*Preparing C-Linked Disaccharides*

# A Simplified Ramberg–Bäcklund Approach to Novel C-Glycosides and C-Linked Disaccharides**

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*Dedicated to Dr. Alan H. Haines*

In recent years, there has been increasing interest in the preparation and properties of C-disaccharides. Their hydrolytic stability and potential enzyme-inhibitory properties make such compounds attractive as unnatural mimetics and therefore as synthetic targets.[1] As a result, a number of methodologies have been developed for the synthesis of this class of compound.[2,3] As part of an ongoing program[3,4] to investigate applications of the Ramberg–Bäcklund Reaction (RBR),[5] we recently reported a RBR approach to C-linked disaccharides and employed it to prepare C-isotrehalose, C-homoisotrehalose, and methyl C-gentiobioside.[3] However, the route involved the initial preparation of protected monosaccharides and their subsequent conversion into thioglycosides and then thioglycoside dioxides and was therefore rather lengthy. Herein we report the rapid synthesis of a range of novel C-glycosides and C-disaccharides which commences from readily available protected monosaccharides **1** and involves a tandem Horner–Wadsworth–Emmons (HWE)/conjugate-addition C-glycosidation followed by a tandem halogenation–RBR sequence, utilizing Meyers variant of the RBR[6] (Scheme 1). Thus, the plan was to prepare glycosylsulfonylmethyl-HWE reagents **2** and then carry out the condensation giving the vinyl sulfone intermediate **3** which would be expected[7] to undergo conjugate cyclization in situ to produce sulfone **4**. Subsequent Meyers-type in situ α-sulfonyl halogenation followed by tandem RBR should then produce alkene **5** which could be elaborated/deprotected to provide a range of novel C-disaccharides.

Proof-of-principle studies were carried out using the benzylsulfonylphosphonate reagent **6**[8] and diisopropylidene mannofuranose **7** (Scheme 2). We were delighted to find that the HWE/conjugate-addition process proceeded in a reasonable 64% unoptimized yield using sodium hydride in THF giving the C-glycoside **8** stereoselectively as the β-isomer ($J_{1,2} = 3.6$ Hz). Sulfone **8** was next subjected to the halogenation-RBR sequence. The standard Meyers conditions[6a] only gave a 48% yield of **9** but use of the supported KOH-$CBr_2F_2$

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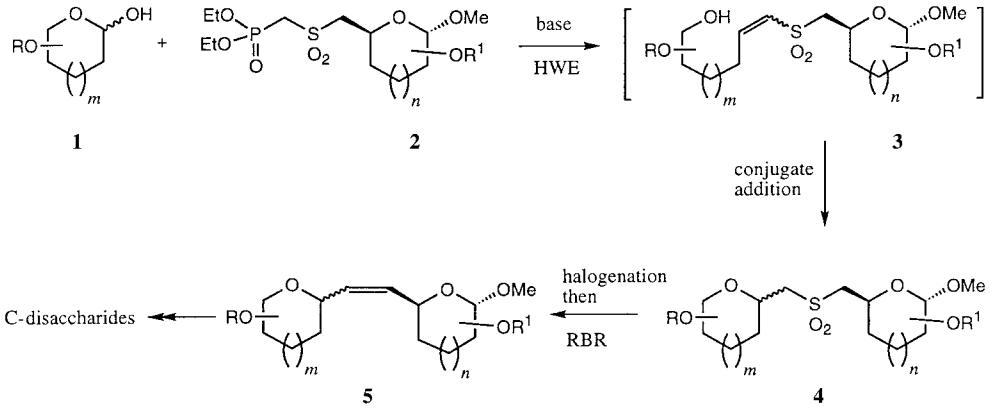
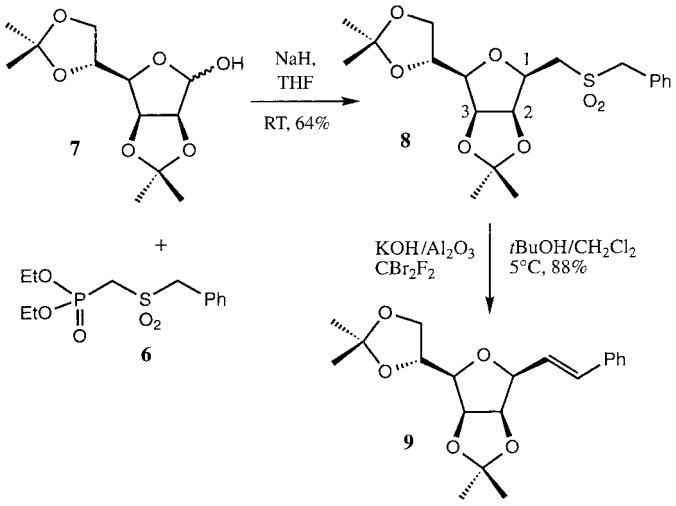



***Scheme 1.*** Summary of overall transformation ($m,n = 0,1$).

conditions devised by Chan et al.[6b] produced alkene **9** in 88% yield, exclusively as the 1,2-*cis*-diastereomer with the β-anomeric configuration, and the *E*-geometry ($J_{vinyl} = 16.0$ Hz). The thermodynamic preference for the 1,2-*cis*-relationship in 2,3-*O*-isopropylidene derivatives of furanosyl C-glycosides has precedent.[7,9]



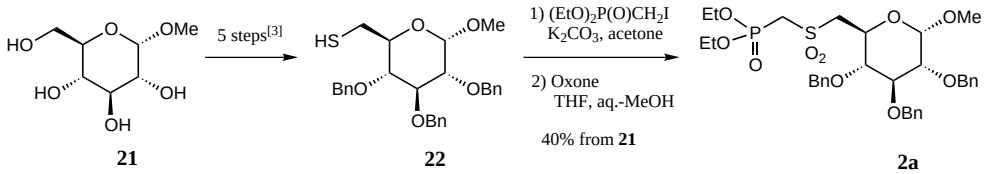

***Scheme 2.*** Proof-of-principle studies using benzylsulfonylphosphonate **6**.

The multiple roles of the sulfonyl group in this sequence are noteworthy: it provides the stabilizing group needed for the HWE reaction, the activating group which facilitates the conjugate addition, and the key functionality for the RBR—and its removal does not require a separate step, it is lost in a cheleotropic manner during the key carbon–carbon bond forming reaction.

We extended these studies to ribose derivatives and investigated the compatibility of a range of protecting groups (Table 1). As can be seen, benzyl (Bn), acetonide, and *tert*-butyldimethylsilyl (TBS) protecting groups were all accommodated within this methodology. Noteworthy is that epimerization at the anomeric position occurs under these conditions: this is most apparent in the conversion of the 1,2-*trans*-system **18** into the predominantly 1,2-*cis*-C-glycoside **20** ($J_{1,2} = 6.0$ Hz for **20α**, 4.0 Hz for **20β**; the larger coupling constants for the *cis*-1,2-protons is in accord with previous[9] observations).

Having succeeded with the model studies, the next step was to prepare a carbohydrate-derived phosphonate reagent. The glucose-derived phosphonate **2a** was chosen in view of the reported efficient five-step preparation of thiol **22** from methyl α-D-glucopyranoside (**21**).[3] As shown in Scheme 3, *S*-alkylation of thiol **22** with diethyl iodomethylphosphonate followed by oxidation produced the required HWE reagent **2a** in 40% overall yield from **21**.

With HWE reagent **2a** in hand, we investigated its reaction with diisopropylidene mannofuranose **7** (Scheme 4). We were delighted to discover that the HWE/conjugate-addition sequence proceeded in high yield (86%) to produce the adduct sulfone **23** (as a mixture of diastereomers). The key halogenation-RBR was again carried out using the conditions devised by Chan et al.[6b] giving *E*-alkene **24** ($J_{vinyl} = 15.9$ Hz) as the only isolable product. Alkene hydrogenation and concomitant debenzylation, followed by acetylation for characterization purposes, gave the novel disaccharide **25** in 69% yield over the two reactions. The four-pot sequence shown in Scheme 4 involves 11 transformations (HWE, conjugate addition, halogenation, RBR, reduction, 3 × debenzylations, 3 × acetylations); the overall yield of 30% is noteworthy, though capable of improvement.




***Scheme 3.*** Preparation of glucose-derived phosphonate **2a**.

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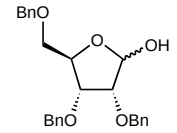
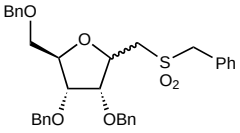
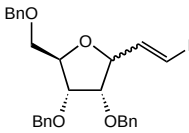
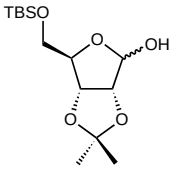
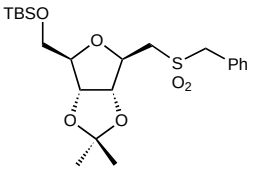
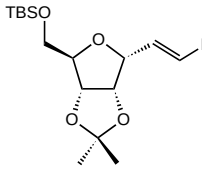
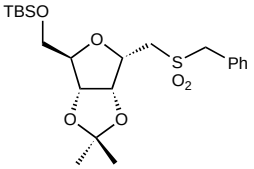
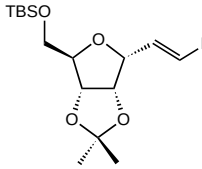
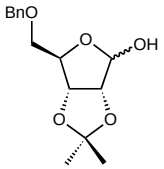
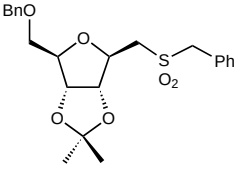
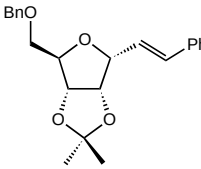
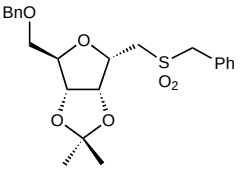
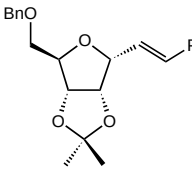
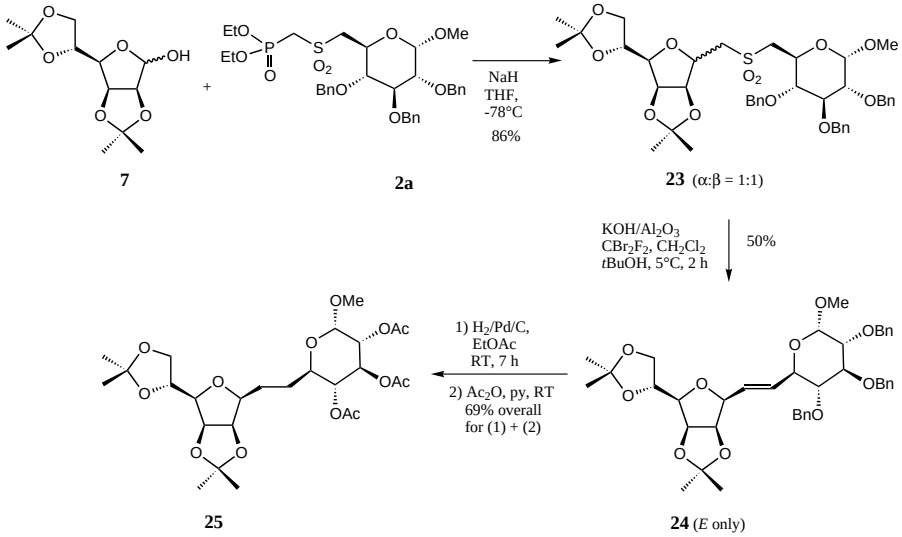
***Table 1:*** HWE/conjugate-addition/RBR sequence with phosphonate **6** and a range of protected carbohydrates[a,b]

| Monosaccharide | HWE/conjugate-addition adduct | RBR product |
|---|---|---|
| 1)  **10** |  **11** 74% (α:β = 1:1) |  **12** 83% (α:β = 1:2.4) |
| 2)  **13** |  + **14** (22%)[c] |  **16** 77% (α:β = 4:1) |
| |  **15** (32%)[c] |  **16** 81% (α:β = 6:1) |
| 3)  **17** |  + **18** (32%)[c] |  **20** 78% (α:β = 7:1) |
| |  **19** (30%)[c] |  **20** 70% (α:β = 8:1) |

[a] 1) NaH (1.1 equiv), phosphonate **6** (1.1 equiv) in THF at RT and then add lactol (1 equiv) and stir for 6–18 h; 2) Sulfone (1 equiv) in *tert*-butyl alcohol–$CH_2Cl_2$ at 0 °C then add KOH-$Al_2O_3$ (14 g mmol$^{-1}$ sulfone) and then $CBr_2F_2$ (10 equiv) and stir at 0 °C for 30 min; 3) Dilute with $CH_2Cl_2$, stir for 10 min, filter through Celite, concentrate and purify by column chromatography on silica. [b] all alkenes > 99% *E*. [c] **14**/**15** and **18**/**19** were readily separated by chromatography.




***Scheme 4.*** C-disaccharide synthesis using phosphonate **2a**; py = pyridine.

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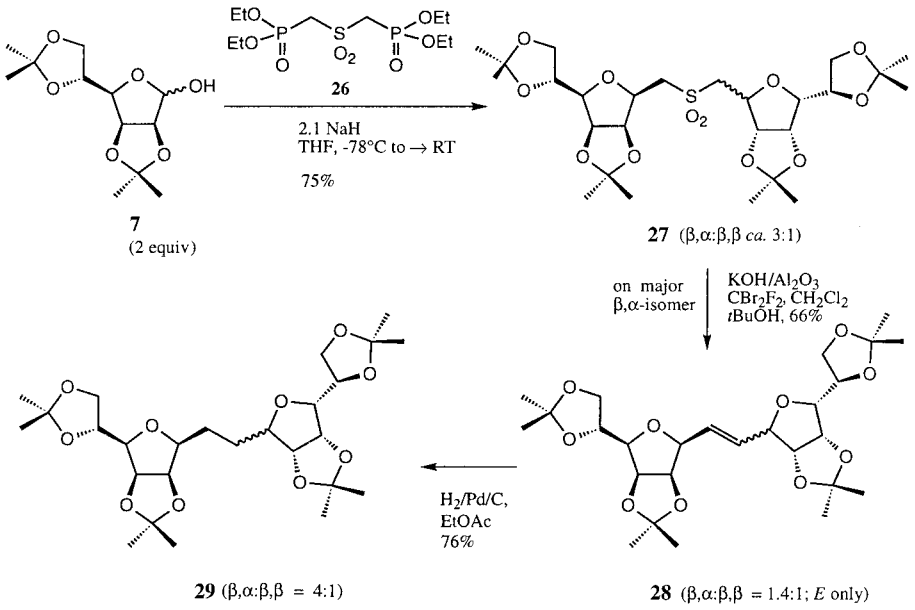
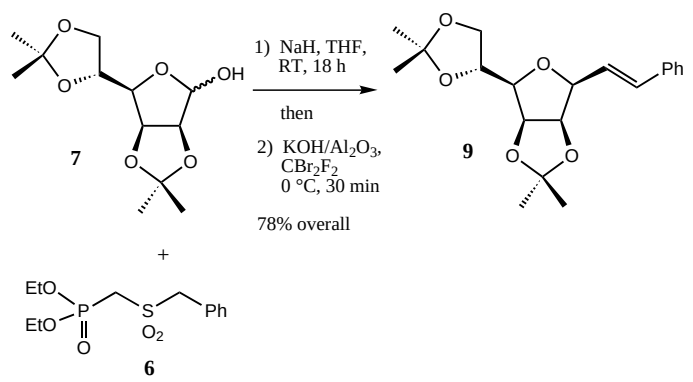



***Scheme 5.*** Two-directional C-disaccharide synthesis using bisphosphonate **26**.

We have also shown that a two-directional variant of this methodology can be used to prepare symmetrical C-disaccharides, as shown in Scheme 5. The requisite bisphosphonate **26** has been described for the synthesis of distyryl sulfones.[10] The double HWE reaction using **26** and diisopropylidene mannofuranose **7** worked extremely well in the HWE/conjugate-addition C-glycosidation sequence giving diastereomeric sulfones **27**, in a combined yield of 75 %. RBR on the major stereoisomer (β,α-**27**) using the Meyers–Chan procedure gave alkene **28** in 66 % unoptimized yield, and hydrogenation produced the novel C-linked bisfuranose disaccharide **29** in 76 % yield.

Finally, we have established that the original model study involving the Horner–Wadsworth–Emmons/conjugate addition sequence with substrates **6** and **7** followed by tandem halogenation-Ramberg–Bäcklund reaction can be carried out as a "one-pot" transformation (Scheme 6). Thus, **7** was added to the deprotonated phosphonate **6** and the mixture stirred at RT overnight. After cooling the mixture to 0 °C, the base and halogenating agent (KOH-$Al_2O_3$, $CBr_2F_2$) were added and the mixture stirred for about 30 minutes. A standard work-up (see Experimental Section) produced C-glycoside **9** in 78 % purified yield, a considerable increase on the two-step method (56 % overall yield). It should be noted that the Meyers–Chan procedure was successful in THF–$CH_2Cl_2$ and that *tert*-butanol, which is normally employed as a cosolvent,[6b] was not required.




***Scheme 6.*** One-pot variant of the C-glycoside synthesis.

In summary, we have established that a range of protected furanoses undergo a HWE/conjugate-addition/RBR sequence with benzylsulfonylphosphonate reagent **6** to produce the corresponding 2-styrenyl C-glycosides, and shown that this sequence can be performed in a "one-pot" variant in excellent yield. We have also demonstrated that monosaccharide-derived phosphonates can be employed in this methodology by utilizing the glucose-derived phosphonate **2a** to produce the mixed furanose–pyranose C-linked system **24**. Of course, by variation of the monosaccharide and the glycosyl phosphonate (**1** and **2** respectively, in Scheme 1), a range of other C-disaccharides becomes available. In addition, we have shown that a symmetrical C-linked bisfuranose system **29** is available by a double HWE sequence. Further work is in progress to optimize and apply this new methodology, initially to prepare C-linked analogues of furanose-pyranose disaccharides.[11] It should also be noted that the HWE reaction has been shown[7] to proceed efficiently on unprotected monosaccharides and studies in this area are in progress.

## *Experimental Section*

All new compounds were fully characterized spectroscopically and by HRMS or elemental analysis.

Preparation of C-glycoside **9** by a "one-pot" procedure: A solution of phosphonate **6** (139 mg, 0.45 mmol) in THF (2 mL) was added dropwise to a suspension of NaH (18 mg, 60 % dispersion in oil, 0.45 mmol) in dry THF (6 mL) under nitrogen at RT. After stirring at RT for 10 min, a solution of 2,3:5,6-diisopropylidene D-mannofuranose (**7**) (107 mg, 0.41 mmol) in THF (2 mL) was added, and the reaction stirred at RT. After 18 h, the reaction was cooled to 0 °C, KOH-$Al_2O_3$[6b] (5.8 g) added and the suspension stirred for 10 min. $CBr_2F_2$ (0.37 mL) was added with stirring at 0 °C and the flask sealed, the stirring continued at this temperature for 30 min. The suspension was then warmed to RT and $CH_2Cl_2$ (10 mL) added. After stirring for 15 min, the reaction mixture was filtered through Celite, washing with $CH_2Cl_2$, and then the combined organic washings were concentrated in vacuo. Chromatography on silica (petroleum ether:EtOAc, 3:1) gave alkene **9** (111 mg, 78 %) as a colorless semi-solid, $R_f$ (petroleum ether:EtOAc, 3:1) 0.49, $[\alpha]_D = +91$ (*c.* 1.2, $CHCl_3$), Found: 347.1858. $C_{20}H_{26}O_5$ requires $[MH]^+$ 347.1858 (0 ppm error). Consistent $^1$H NMR, $^{13}$C NMR, IR spectroscopy, and MS data were also obtained.

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**Keywords:** C–C coupling · disaccharides · glycosides · synthetic methods · tandem processes

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