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A protecting group-free approach to *C*-glycosides using the Ramberg–Bäcklund reaction

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Abstract—The one-pot conversion of unprotected monosaccharides directly into benzylsulfonylmethylene *C*-glycosides via a Horner–Wadsworth–Emmons/ring closure process is reported. Similar reactions giving sulfone-linked disaccharides are also discussed. One-pot transformations of unprotected monosaccharides to give styrenyl *C*-glycosides, by a tandem Horner–Wadsworth–Emmons/ring closure–halogenation/Ramberg–Bäcklund sequence, is then described.

Recent discoveries in glycomics have emphasised the fundamental importance of carbohydrates in a wide range of biological processes and have stimulated a renaissance in studies concerning the chemistry and biochemistry of carbohydrates.[1] The development of new synthetic procedures for the preparation of monosaccharides, *O*-glycosides, polysaccharides, glycosylated lipids, glycoproteins, etc., have been of major importance in this area.[2] However, in the search for carbohydrate-based biological probes, enzyme inhibitors and drugs, the hydrolytic lability of *O*-linked carbohydrates can present a major problem. An attractive solution to this problem is to prepare the *C*-glycoside analogue of the bioactive compound, the replacement of the acetal functionality by an ether conferring the required stability.[2,3] There is persuasive evidence that the conformational differences between the *O*- and *C*-linked analogues is minimal,[4] and *C*-glycoside analogues have been reported, which possess similar,[5] or even greater,[6] biological activity than the parent system. Consequently, many procedures have been developed to access *C*-glycosides, *C*-linked disaccharides, etc.[3–8] The drawback to many of these existing methods is their low efficiency, particularly due to the length of the synthetic routes and the extensive use of protection/deprotection sequences.

We originally developed a new route to *exo*-glycals, *C*-glycosides, *C*-linked disaccharides and *C*-glycosyl amino acids,[8b–e] based on the Ramberg–Bäcklund reaction[9] of *S*-glycosyl dioxides. In order to streamline this process, we recently designed a simplified route to *C*-glycosides (and *C*-disaccharides), which employs two consecutive tandem sequences as illustrated in Scheme 1.[8a] Thus, treatment of protected furanose **1** with sulfonylphosphonate reagent **2** produced *C*-glycoside sulfone adduct **3** by a tandem Horner–Wadsworth–Emmons/ring closure sequence. Then, sulfone **3** was subjected to a tandem halogenation/Ramberg–Bäcklund sequence producing styryl *C*-glycoside **4** in 88% yield as a single isomer. These two sequences could be telescoped into a two-step, one-pot reaction, which gave *C*-glycoside **4** in 78% overall yield.[8a]

The next objective, which is the focus of this letter, was to extend the above Horner–Wadsworth–Emmons (HWE)/Ramberg–Bäcklund strategy to prepare *C*-glycosides without the requirement for hydroxyl protecting groups. Such an approach would produce unprotected *C*-glycosides if these were the target compounds, or partially protected products if these were required for further elaboration. A search of the literature revealed that only a handful of examples have been reported in which unprotected monosaccharides undergo reaction with stabilised Wittig or HWE reagents;[10] encouragingly, however, it had been established that phenylsulfonylmethylenephosphonate reagents can be successfully employed in such reactions.[10a,d] We therefore started out by investigating the reaction between the

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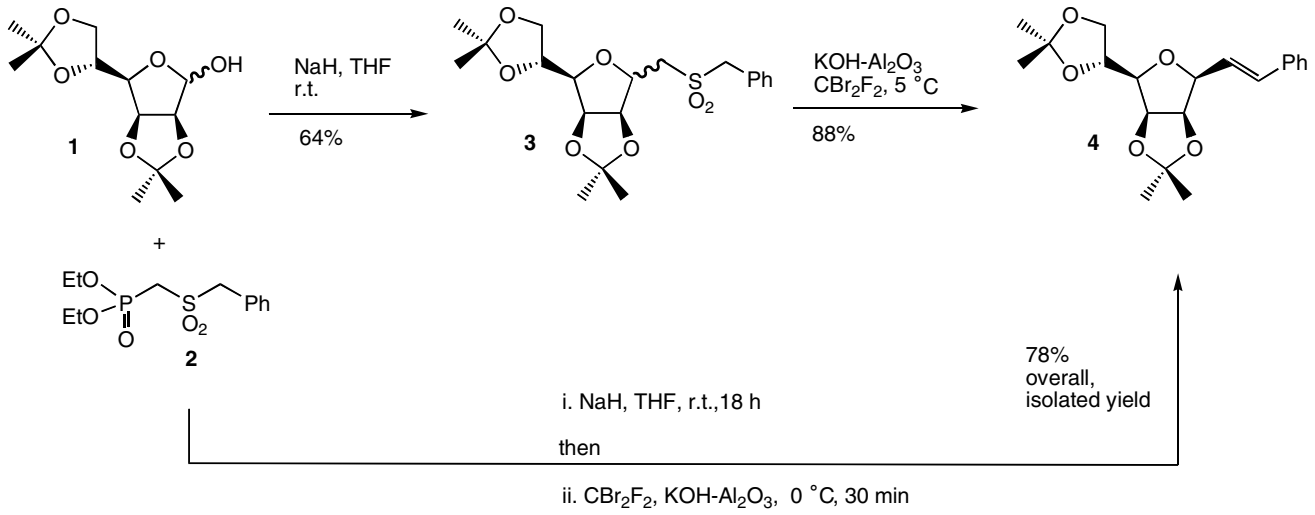


Scheme 1.

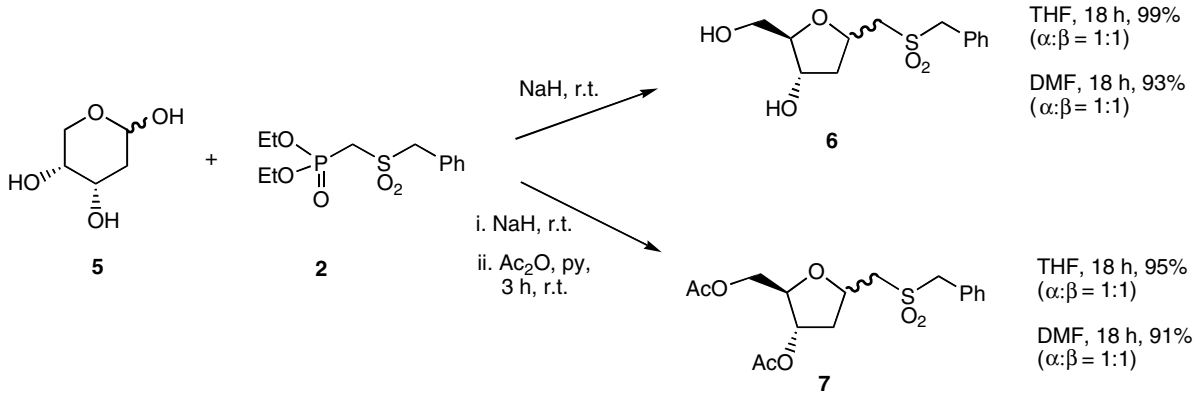
benzylsulfonyl HWE reagent **2**[8a,11] and 2-deoxy-D-ribose **5** (Scheme 2).

We were delighted to find that the HWE/ring closure process proceeded in excellent yields using sodium hydride in THF, giving adduct **6** in 99% yield as a 1:1 diastereoisomeric mixture, which was fully characterised ('anomeric' δ_C 73.8, 73.5 ppm).[12,13] We also demonstrated that the product mixture can be acetylated in situ to produce diacetate **7** in a comparable yield. In addition, we found that similar results were obtained using DMF as solvent.

These results encouraged us to investigate a range of monosaccharides in the reaction with benzylsulfonylphosphonate reagent **2**. The results are summarised in Table 1.

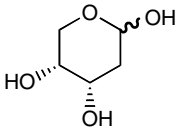
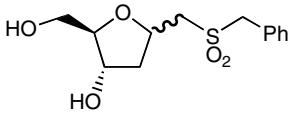
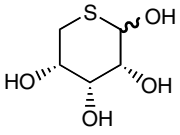
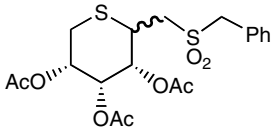
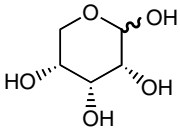
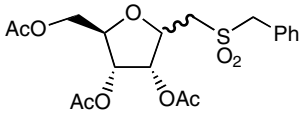
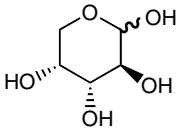
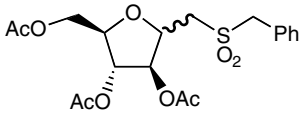
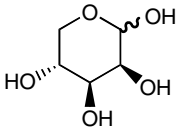
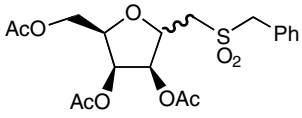
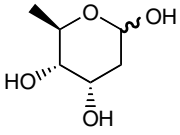
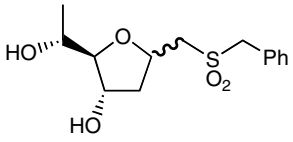
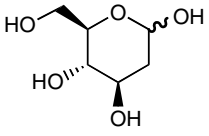
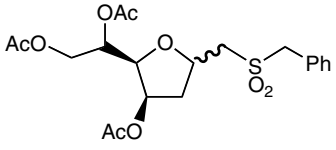
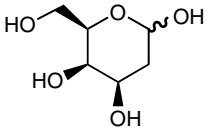
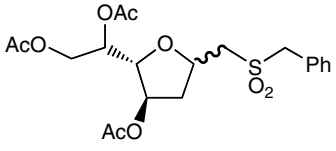
As can be seen, the methodology was successful with a range of unprotected monosaccharides including both pentoses (entries i–v) and hexoses (entries vi–viii). After the success with 2-deoxyribose (entry i), 5-thioanalogue **8** was successfully homologated (entry ii), as was D-ribose itself (entry iii). In a similar manner, D-arabinose **12** and D-lyxose **14** gave the corresponding sulfonyl *C*-glycosides **13** and **15**, respectively, in excellent yields (entries iv and v). Success was also achieved with D-digitoxose **16**, 2-deoxy-D-glucose **18** and 2-deoxy-D-galactose **20** (entries vi–vii). As expected,[10d] the reaction with D-glucose proceeded extremely slowly and heating the reaction resulted in the degradation of benzylsulfonylphosphonate reagent **2**.

In addition to the examples shown in Table 1, we have demonstrated that the more complex carbohydrate-derived phosphonate reagents **22**[8a] and **24**[14] undergo reaction with 2-deoxy-D-ribose **5** to produce the partially protected 'sulfonyl disaccharides' **23** and **25**. Although unoptimised, these results indicate that complex disaccharide precursors can be prepared from unprotected monosaccharide substrates using this methodology (Scheme 3).



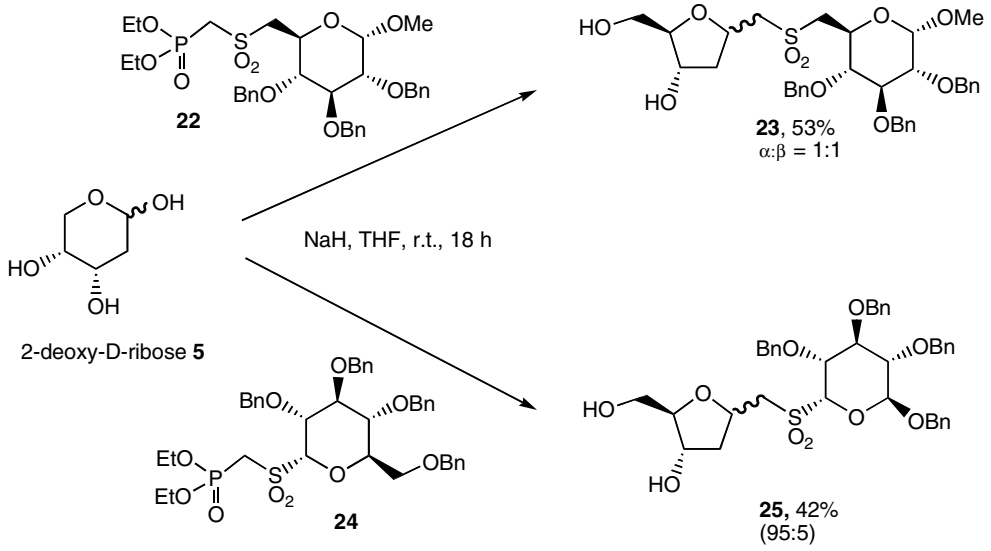
Scheme 2.

Table 1. HWE/ring closure reactions using benzylsulfonylphosphate reagent **2**

Entry	Sugar	Solvent	*T* (time/h)	Product	Yield (%) (α:β)
i[13]	 2-deoxy-D-ribose **5**	THF	rt (18)	 **6**	99 (1:1)
ii[a]	 5-thio-D-ribose **8**	DMF	rt (16)	 **9**	51 (1:1)
iii[a]	 D-ribose **10**	DMF	rt (16)	 **11**	51 (35:65)
iv[a]	 D-arabinose **12**	THF	rt (16)	 **13**	91 (1:1)
v[a]	 D-lyxose **14**	DMF	rt (16)	 **15**	87 (1:1)
vi	 D-digitoxose **16**	THF	rt (16)	 **17**	89 (1:1)
vii	 2-deoxy-D-glucose **18**	DMF	rt (24)	 **19**	74 (1:1)
viii[a]	 2-deoxy-D-galactose **20**	DMF	rt (24)	 **21**	43 (1:1)

[a] In these reactions the product was acetylated in situ to aid isolation.

Having established that a range of unprotected and partially protected monosaccharides undergo the HWE/cyclisation sequence with methylenesulfonylphosphonates, we went on to carry out preliminary studies to examine the feasibility of a one-pot HWE/cyclisation/Ramberg–Bäcklund sequence on unprotected monosaccharides (Scheme 4). In these reactions, the HWE/cyclisation sequence was carried out as before and then,



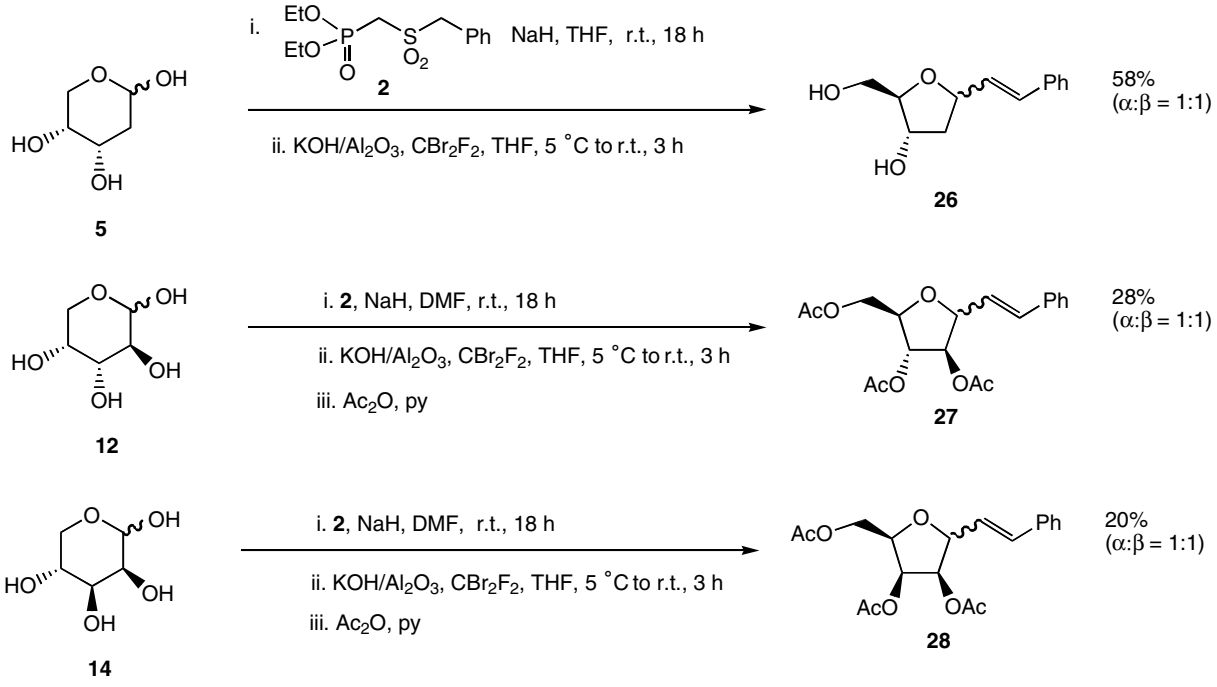
Scheme 3.

in the same reaction vessel, the tandem halogenation/Ramberg–Bäcklund procedure developed by Chan was effected by the addition of dibromodifluoromethane and supported KOH.[15]

Initial studies concentrated on the reaction of 2-deoxy-D-ribose **5**. Several variations in solvent and reaction temperature were explored but the best involved the use of THF as solvent for both processes, with the HWE sequence being carried out at rt, and the tandem halogenation/Ramberg–Bäcklund process at 5 °C to rt. Under these conditions the styrenyl *C*-glycoside **26** was obtained as an α:β mixture (1:1) in 58% yield after chromatography (full characterisation details are provided).[13]

We went on to briefly establish that this sequence was not limited to a single monosaccharide. Thus (Scheme 4), D-arabinose **12** and D-lyxose **14** were both converted into the corresponding styrenyl *C*-glycosides **27** and **28**, respectively, by a one-pot HWE/cyclisation–tandem halogenation/Ramberg–Bäcklund process followed by acetylation (to aid characterisation). These processes were not optimised but served to establish the potential generality of the procedure.

We are currently optimising the procedures described herein, both in terms of yield and stereoselectivity, and applying the methodology to prepare more complex target molecules with potential bioactivity.



Scheme 4.

Acknowledgements

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11. Prepared by *S*-alkylation of benzylthiol with diethyl iodomethylphosphate followed by oxidation using Oxone™. This compound has been previously reported: Sindt, M.; Schneider, S. B.; Mieloszynski, J. L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *174*, 163–176.
12. All new compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry.
13. Representative experimental procedures:
(a) Preparation of sulfonyl *C*-glycoside **6**: A solution of phosphonate **2** (139 mg, 0.45 mmol) in dry THF (5 ml) was added dropwise to a suspension of NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol) in dry THF (5 ml) under N_2 at rt. After stirring at rt for 10 min, 2-deoxy-D-ribose **5** (55 mg, 0.41 mmol) was added in one portion and the reaction stirred at rt overnight (18 h). The reaction mixture was diluted with brine (10 ml) and saturated aq NH_4Cl (10 ml) and extracted with EtOAc (4×20 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under vacuum. Purification of the crude product by flash chromatography (EtOAc) gave **6** (115.7 mg, 99%) as an inseparable mixture of diastereomers (α:β = 1:1 by ^{1}H NMR spectroscopy); colourless oil, R_f (EtOAc) 0.12; ν_{max} (liquid film) 3600–3200 (br), 3064, 3034, 2925, 1694, 1654, 1604, 1494, 1455, 1404, 1302, 1257, 1202, 1118, 1074 cm^{-1}; MS (CI) *m/z*: 304 (MNH_4^+); HRMS: found 304.1221, $C_{13}H_{22}NO_5S$ requires 304.1219 (−0.9 ppm error), which displayed consistent ^{1}H and ^{13}C NMR data.
(b) Preparation of styrenyl *C*-glycoside **26**: A solution of phosphonate **2** (139 mg, 0.45 mmol) in dry THF (5 ml) was added dropwise to a suspension of NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol) in dry THF (5 ml) under N_2 at rt. After stirring at rt for 10 min, 2-deoxy-D-ribose **5** (55 mg, 0.41 mmol) was added in one portion and the reaction stirred at rt. After 18 h, the reaction mixture was cooled to 0 °C, KOH/Al_2O_3[15] (5.8 g) added and the suspension stirred for 10 min. CBr_2F_2 (0.37 ml) was added with stirring at 0 °C, the flask sealed and the stirring continued at this temperature for 30 min. The reaction mixture was then warmed to rt for 3 h and then CH_2Cl_2 (10 ml) was added. After stirring for 15 min, the reaction mixture was filtered through a pad of Celite®, washing with CH_2Cl_2. The combined organic washings were concentrated under vacuum. Purification of the crude product by flash chromatography (EtOAc) gave **26** (52.7 mg, 58%) as a mixture of diastereomers (α:β = 1:1 by ^{1}H NMR spectroscopy); colourless oil, R_f (EtOAc) 0.45; ν_{max} (liquid film) 3439 (br), 3367 (br), 3081, 3024, 2946, 2923, 2899, 2866, 1596, 1494, 1447, 1381, 1347, 1294, 1229, 1123, 1092, 1053, 1001, 971, 881, 836 cm^{-1}. Careful chromatography allowed a partial separation of the two

diastereomeric products: less polar isomer: $[\alpha]_D$ +18.2 (*c* 0.01, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.40–7.20 (m, 5H, Ph), 6.62 (dd, *J* 16.0, 0.8 Hz, 1H, =C–*H*), 6.15 (dd, *J* 16.0, 6.0 Hz, 1H, =C—*H*), 4.40 (m, 1H, OC*H*—C=), 4.18 (m, 1H, C*H*–OH), 3.89–3.79 (m, 2H, CH_2–OH), 3.68 (t, *J* 12.0 Hz, 1H, C*H*–O), 2.26 (br s, 1H, –O*H*), 2.07 (m, 1H, C–CH_2–C), 2.00 (br s, 1H, –O*H*), 1.75 (ddd, *J* 14.3, 11.0, 2.4 Hz, 1H, C–CH_2–C); δ_C (100.6 MHz, $CDCl_3$) 136.6, 130.9, 128.9, 128.5, 127.7, 126.4, 71.5, 67.2, 66.9, 65.9, 37.5; more polar isomer: $[\alpha]_D$ +7.9 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.40–7.20 (m, 5H, Ph), 6.63 (d, *J* 16.0 Hz, 1H, =C—*H*), 6.20 (dd, *J* 16.0, 6.0 Hz, 1H, =C—*H*), 4.14 (dd, *J* 12.5, 2.0 Hz, 1H, C*H*–O), 3.99 (dd, *J* 12.0, 6.0 Hz, 1H, OC—*H*—C=), 3.82 (m, 2H, C*H*–O and CH_2–OH), 3.63 (m, 1H, C*H*–OH), 2.22 (br s, 2H, 2 × –O*H*), 1.99 (ddd, *J* 12.0, 6.0, 2.0 Hz, 1H, C–CH_2–C), 1.70 (m, 1H, C–CH_2–C); δ_C (100.6 MHz, $CDCl_3$) 136.4, 130.9, 128.6, 128.5, 127.8, 126.5, 76.6, 70.3, 68.7, 67.9, 35.8.

14. Prepared from 2,3,4,6-tetrabenzyl thioglucose using Schmidt's procedure: Zhu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1081–1085; Zhu, X.; Stolz, F.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 7367–7370.
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