Pergamon

Tetrahedron Letters 39 (1998) 8179–8182

TETRAHEDRON LETTERS

# A Ramberg-Bäcklund Approach to Exo-Glycals

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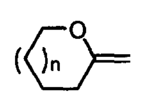
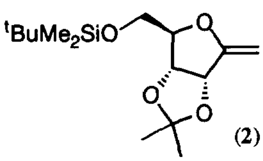
Received 29 July 1998; accepted 28 August 1998

***Abstract:*** A new route to exo-glycals is described which starts from *S*-glycoside dioxides and utilises Meyers' variant of the Ramberg-Bäcklund rearrangement. The methodology is successful with glucose, galactose, mannose, xylose, fucose and ribose derivatives, and has been used to prepare di-, tri- and tetra-substituted alkenes.

1-Exomethylene sugars **1** (*e.g.* **2**[1] and **3**[2]) are valuable synthetic intermediates[1-5] which can also be used as glycosidase inhibitors.[6] They have been further elaborated by a range of procedures[1-5] and have been employed to prepare novel *C*-glycosides,[1-5] *C*-disaccharides[2,3] and ketoglycosides,[5] and used as key intermediates in natural product syntheses.[1] A number of procedures have been published[1-6] for the preparation of compounds **1** but the method of choice would appear to be methylenation of the corresponding lactones using dicyclopentadienyl(dimethyl)titanium (or the Tebbe reagent).[4,5b,7]



(**1**) n = 0, 1



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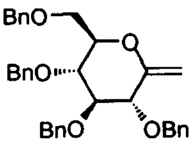
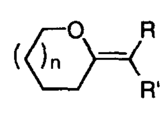


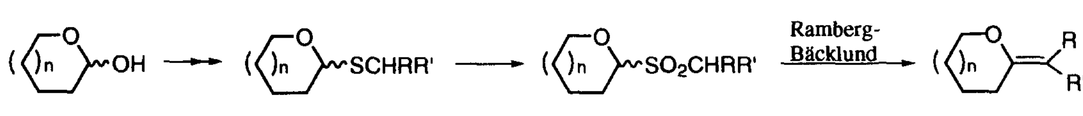
(**3**)



(**4**) n = 0, 1

The corresponding substituted alkenes **4** are also of considerable interest[8] but no general method exists for their preparation. Wittig-based routes have been employed to prepare dichloro-,[9] difluoro-,[10] dithio-[11a] and trimethylsilyl-[11b] alkenes, and recently the conditions have been described (toluene, 140°C, sealed vessel) for the reaction of sugar lactones with carbomethoxymethylenetriphenylphosphorane.[12] Other routes are much less direct.[8] We were interested in devising a more general route to compounds of type **4** which would provide access to disubstituted (R = R' = H), trisubstituted (R ≠ H, R' = H), and tetrasubstituted (R = R' ≠ H) systems. Our plan was to utilise sulfones **7** in the Meyers' variant[13,14] of the Ramberg-Bäcklund rearrangement[15] as shown in Scheme 1. An advantage of this sequence is that there are many published procedures for the conversion of carbohydrates **5** into suitably protected *S*-glycosides **6**.[16a,b]

**Scheme 1** (n = 0, 1)



(**5**) (**6**) (**7**) (**4**)

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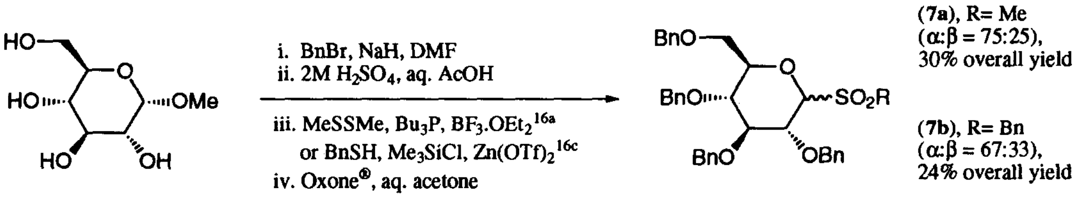
*PII:* S0040-4039(98)01822-X

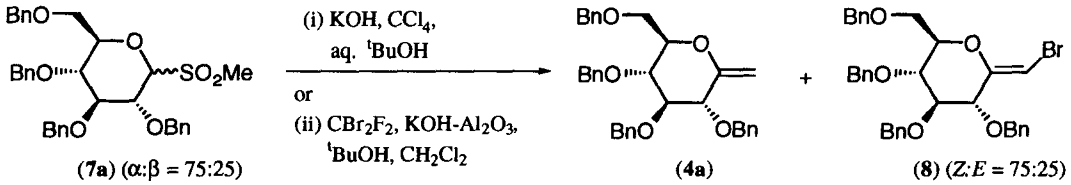
The first objective, the preparation of suitable precursors for the Ramberg-Bäcklund study, was readily achieved (Scheme 2).[17] This is illustrated for the methylsulfonyl **7a** and benzylsulfonyl **7b** derivatives of D-glucose, but similar procedures were used for other sugars and other substituents. Standard literature procedures were employed to prepare the majority of the sulfides,[16a,b] although Susaki's zinc triflate-mediated glycosidation procedure[16c] was modified to prepare some of the thioglycosides (see Scheme 2).

**Scheme 2**



Initial Ramberg-Bäcklund studies were carried out on methylsulfone **7a** (α:β = 75:25) and the results are shown in Scheme 3. We were delighted to observe that the standard Meyers' conditions[13] gave the exo-methylene compound **4a** in 72% yield. Chan *et al.* have recently described new conditions ($CBr_2F_2$, KOH-$Al_2O_3$)[14] for effecting the Ramberg-Bäcklund rearrangement of sulfones, and these produced methylene compound **4a** in 57% yield. In this case, alkene **4a** was accompanied by vinyl bromide **8** (32%, *Z:E ca.* 75:25), a potentially interesting substrate for Pd(0) catalysed cross coupling reactions. The amount of vinyl bromide was decreased by carrying out the reaction at 5°C, and at -10°C alkene **4a** was the only product, but in very low yield (even though all of the starting material was consumed). Methylene compound **4a** was fully characterised and gave NMR data fully consistent with published values.[7]

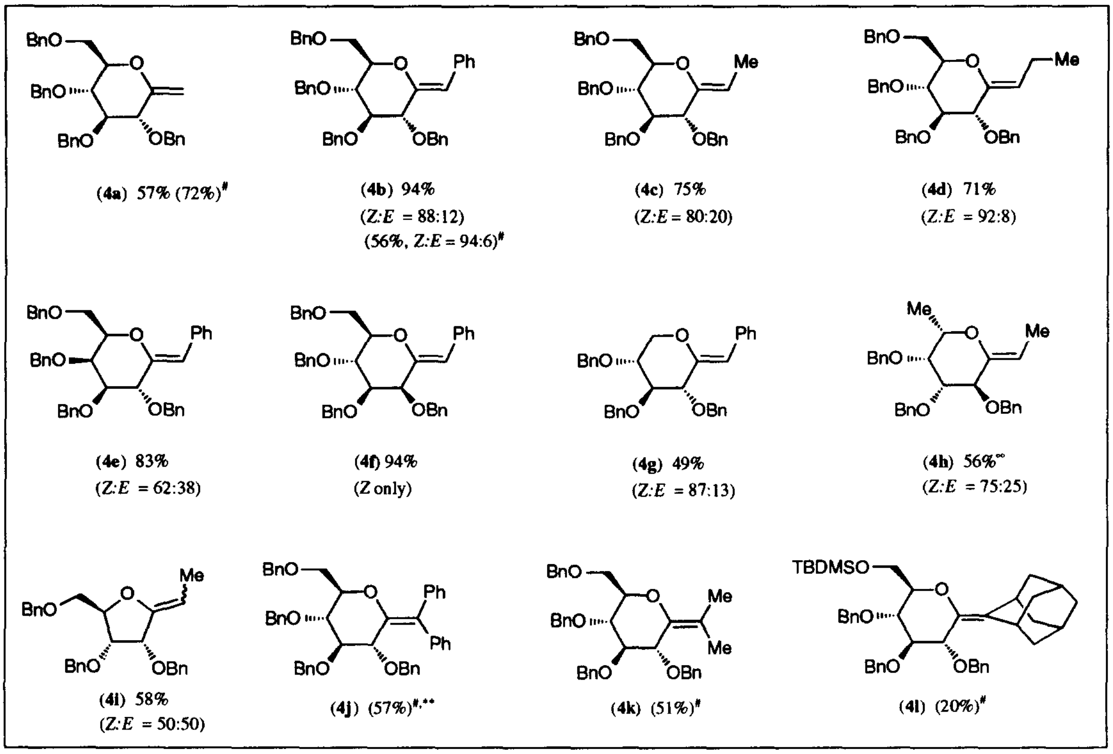
**Scheme 3**



| | (4a) | (8) |
|---|---|---|
| (i), 60°C | 72% | - |
| (ii), rt | 57% | 32% |
| (ii), 5°C to rt | 54% | 15% |
| (ii), -10°C | 10% | - |

We next went on explore the viability of this methodology for the preparation of trisubstituted D-glucose derived alkenes **4b**,[2] **4c** and **4d** (Figure). In view of its mildness, and the facile work-up procedure, the Chan method was used in most examples. As can be seen, phenyl, methyl and ethyl substituted alkenes were available in good to excellent yields with the *Z*-alkene predominating (stereochemical confirmation for several examples was provided by NOE studies). Other sugars were investigated next and, although these processes are unoptimised, galactose, mannose, xylose, fucose and ribose derived alkenes **4e** - **4i** were equally accessible. We have also established that tetrasubstituted alkenes (*e.g.* **4j** - **4l**) are available by this methodology, although in these cases the required transformation was only observed using the classical Meyers' conditions.[13] Further work is needed to optimise these yields, but the availability of tetrasubstituted alkenes, including the highly constrained adamantene derivative **4l**, is noteworthy.

**Figure Exo-glycals prepared *via* the Ramberg-Bäcklund approach**[*] (reactions carried out using $CF_2Br_2$[14] unless otherwise indicated[#])



(**4a**) 57% (72%)[#]

(**4b**) 94% (*Z*:*E* = 88:12) (56%, *Z*:*E* = 94:6)[#]

(**4c**) 75% (*Z*:*E* = 80:20)

(**4d**) 71% (*Z*:*E* = 92:8)

(**4e**) 83% (*Z*:*E* = 62:38)

(**4f**) 94% (*Z* only)

(**4g**) 49% (*Z*:*E* = 87:13)

(**4h**) 56%[∞] (*Z*:*E* = 75:25)

(**4i**) 58% (*Z*:*E* = 50:50)

(**4j**) (57%)[#,**]

(**4k**) (51%)[#]

(**4l**) (20%)[#]

[*] All reactions were carried out on mixtures of α– and β–sulfones with the exception of **4f** and **4h** (α–only).

[#] Carried out using standard Meyers' conditions at 60°C.[13]

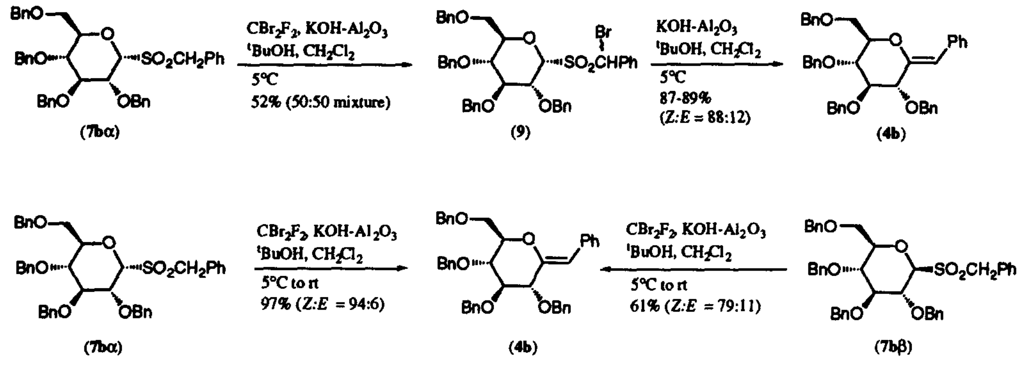
[∞] In this example, yields were based on NMR analysis of the reaction mixture: *ca.* 20% of the corresponding vinyl bromides and *ca.* 24% unreacted starting material were also present.

[**] Yield based on recovered starting material.

The most gratifying aspect of this Ramberg-Bäcklund transformation is that it is compatible with 2-alkoxy substituents: the ease with which anomeric carbanions eliminate C-2 alkoxides to give glycals has bedevilled *C*-glycoside synthesis until recently.[18] The production of vinyl bromide by-products during some of the Ramberg-Bäcklund rearrangements (Scheme 1) suggests that α–sulfonyl bromination is occurring at the non-anomeric site. This has been confirmed (Scheme 4a) by carrying out the bromination of **7bα** with a reduced quantity of base (*ca.* 0.5 g/mmol **7b** vs. *ca.* 7 g/mmol **7b**) for a shorter time (2 h vs 20 h). This produced the monobrominated adduct **9** as a separable 50:50 diastereomeric mixture in 52% yield based on recovered starting material (accompanied by **4b**, 31% based on recovered starting material). The structure of bromide (*S*)-**9** was confirmed by X-ray crystallographic analysis.[19] Treatment of the individual bromides **9** with base under the conditions employed for the one pot process, gave the expected alkene **4b** in high yield, with the same *E*:*Z* ratio being obtained from each diastereomeric bromide. No epimerisation of **7bα** to **7bβ** or *vice versa,* was observed in these studies. Subsequent deprotonation presumably occurs at the anomeric site and, under the reaction conditions employed, episulfone formation must be faster than 1,2-elimination.

A brief investigation of the stereoselectivity of the process, in terms of the relationship between the anomeric stereochemistry of the starting material and the *Z*:*E* ratio of the products, has also been carried out (Scheme 4b). The α-anomer **7bα**, which reacts at a faster rate, gives a much higher *Z*:*E* ratio of **4b** than does **7bβ**. Further research is needed to rationalise this result and to extend the study to other carbohydrate precursors.

Scheme 4



In summary, a range of glucose, galactose, mannose, xylose, fucose and ribose derived alkenes are readily available from *S*-glycoside dioxides *via* the Meyers' variant of the Ramberg-Bäcklund rearrangement. We are currently optimising this methodology and exploring its synthetic potential.[20]

## Acknowledgements

We thank the Government of Papua New Guinea for an HEP Fellowship (F. K. G.) and the University of York for a studentship (D. E. P.). We are also grateful to Dr. G.-J. Boons and Mr. R. Geurtsen (University of Birmingham) for a gift of the adamantyl sulfide used in the preparation of **4l**.

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