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Synthetic Applications of Ramberg-Bäcklund Derived Exo-Glycals

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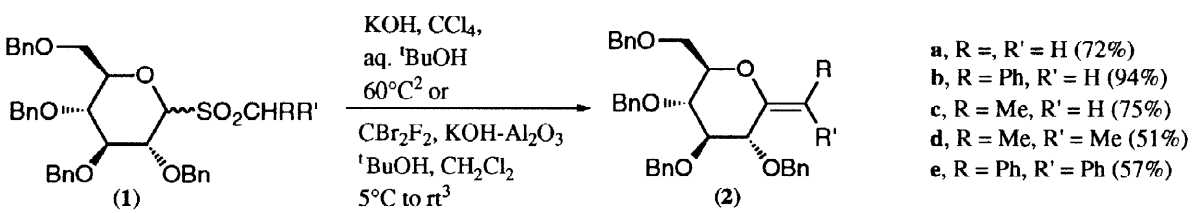
Abstract: Synthetic applications of the title glycals, prepared from *S*-glycoside dioxides using the Meyers' variant of the Ramberg-Bäcklund rearrangement are described. These include a formal total synthesis of a novel β–glycosidase inhibitor, and an efficient route to spirocyclic glucose derivatives. In addition, silyl methodology has been developed which allows unprotected exo-glycals to be synthesised.

In the preceding paper[1] we described a new procedure for preparing glucose-derived exo-glycals from *S*-glycoside dioxides using the Meyers' variant[2,3] of the Ramberg-Bäcklund rearrangement[4] (Scheme 1). This chemistry can be employed to prepare the parent methylene system (**2a**, R = R' = H), but strength of the methodology is that tri- and tetrasubstituted alkenes **2b-e** are also available. In addition, galactose, mannose, xylose, fucose and ribose derived alkenes are readily prepared. Herein we report synthetic applications of some of these alkenes and other applications of this new methodology.

Scheme 1



1-Methylene glucose derivative **2a** has been extensively elaborated by other groups (Scheme 2). Thus, hydroboration-oxidation produces exclusively the β–hydroxymethyl derivative **3**:[5] recently the intermediate organoborane has been utilised in Suzuki coupling reactions giving *C*-glycosides **4**.[6] Dipolar cycloaddition using carbomethoxynitrile oxide produced isoxazoline **5** in a stereoselective manner,[5] whereas dimerisation using boron trifluoride etherate gave the novel *C*-disaccharide **6**.[7] Radical addition of thiolacetic acid gave adduct **7**[8] and epoxidation with dimethyldioxirane (DMDO) produced diastereomeric epoxides **8**[8,9] which can undergo alcoholysis to ketopyranose disaccharides **9**.[9] As a minor addition to this list of chemical transformations, we have shown that dihydroxylation[10] of alkene **2a** occurs smoothly and diastereoselectively to produce tetrabenzylgluco-2-heptulopyranose **10** in 84% yield as a crystalline solid {m.p. 111°C, $[\alpha]_D$ +14 (c 0.15, $CHCl_3$); lit.[11] m.p. 112.5-113.5°C, lit.[11] $[\alpha]_D$ +14.7 (c 0.97, $CHCl_3$)} with other data consistent with literature values.[12]

The major advantage of this flexible Ramberg-Bäcklund approach to exomethylene compounds, however, is that substituted alkenes **2b-e** are readily available. As shown in Scheme 3, we have utilised the *Z*-phenyl derivative **2b** in a formal synthesis of the *C*-glycoside **13**, a novel β–glycosidase inhibitor recently described by Schmidt and Dietrich.[13] Thus, hydroboration using borane-THF followed by oxidation gave a separable 25:75 mixture of α– and β–alcohols **11** and **12** in 65% overall yield. The structure of β–alcohol **12** was confirmed

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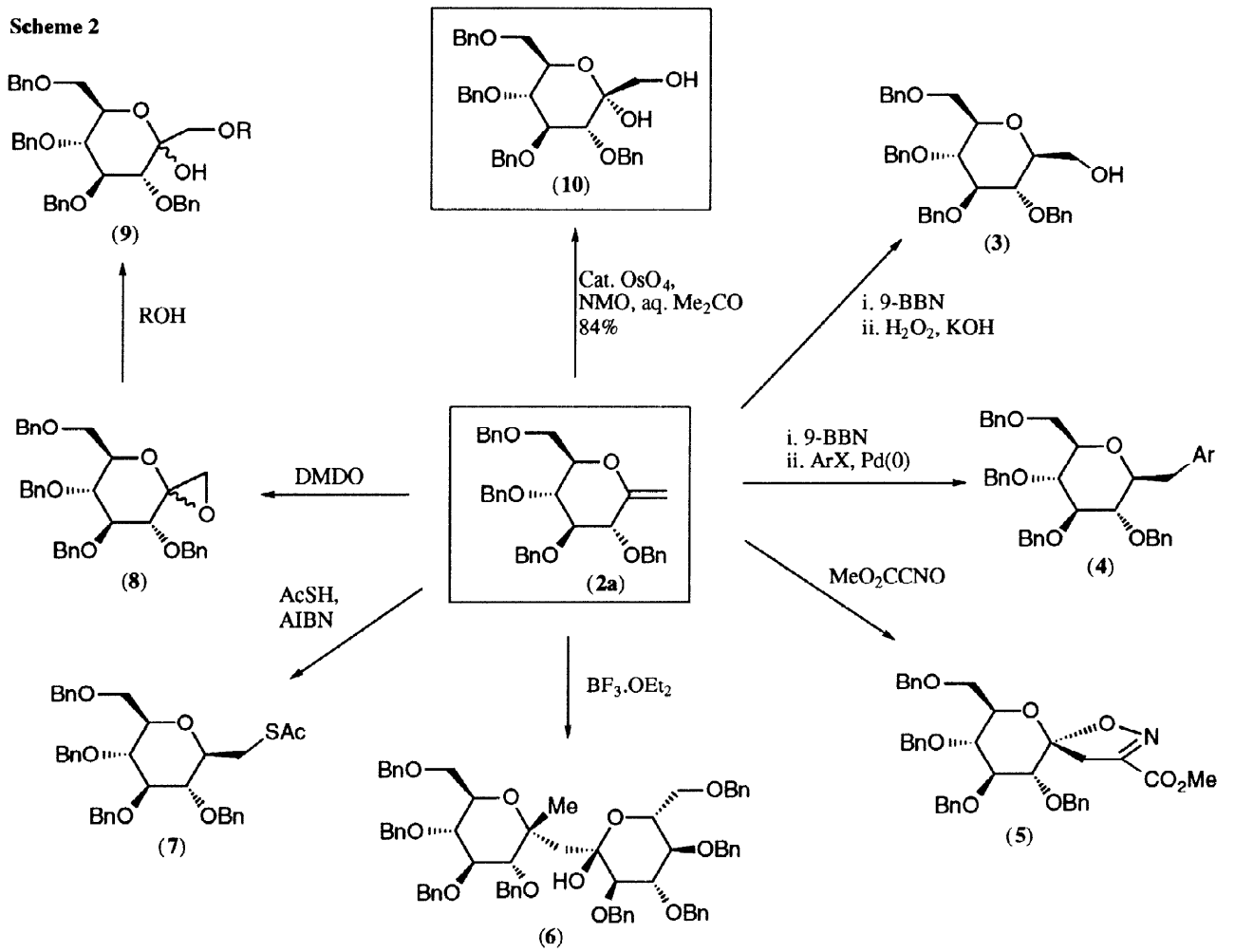
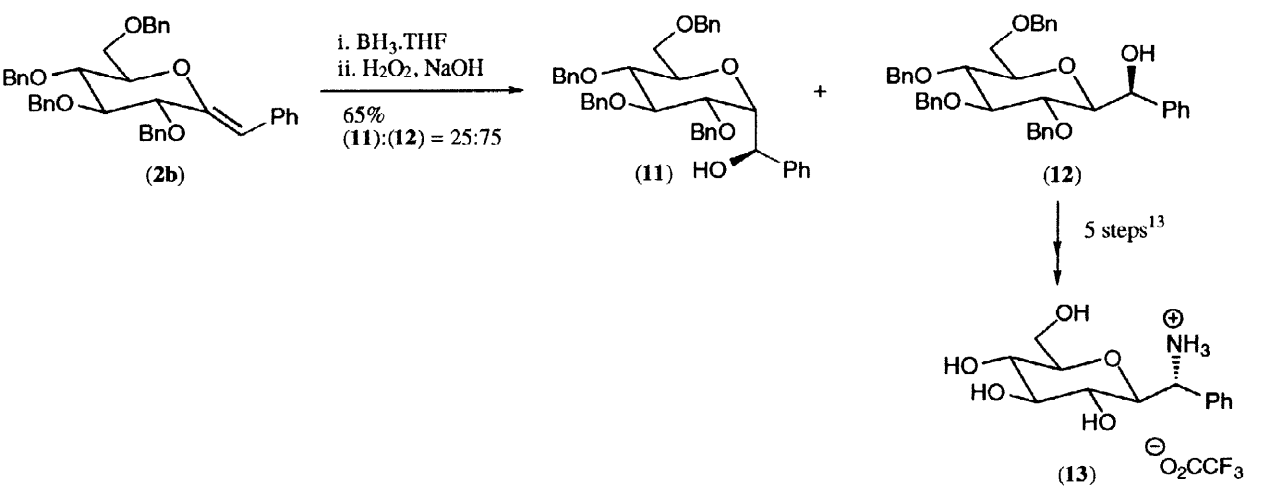
Scheme 2



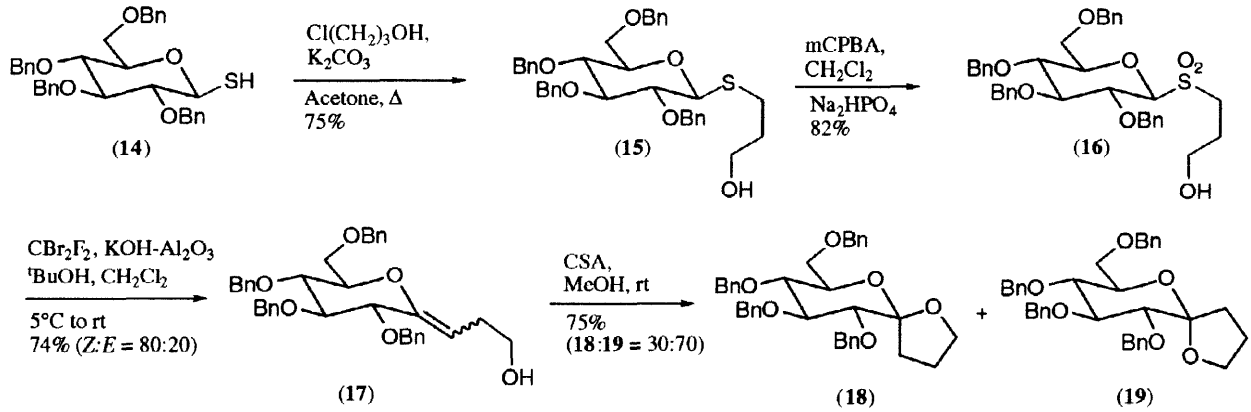
by comparison of optical rotation {[α]$_D$ +8.5 (c 1.5, $CHCl_3$), [α]$_D$ (authentic) +7.5 (c 1.0, $CHCl_3$)} and ^{1}H-NMR data with those from authentic material.[13] Schmidt and Dietrich converted alcohol **12** into enzyme inhibitor **13** in five high yielding steps.[13] The advantage of this new procedure is the brevity of the synthetic route shown in Scheme 3: in the published route,[13] eight steps were required to prepare alcohol **12** from D-glucal (12% overall yield).[13]

Scheme 3



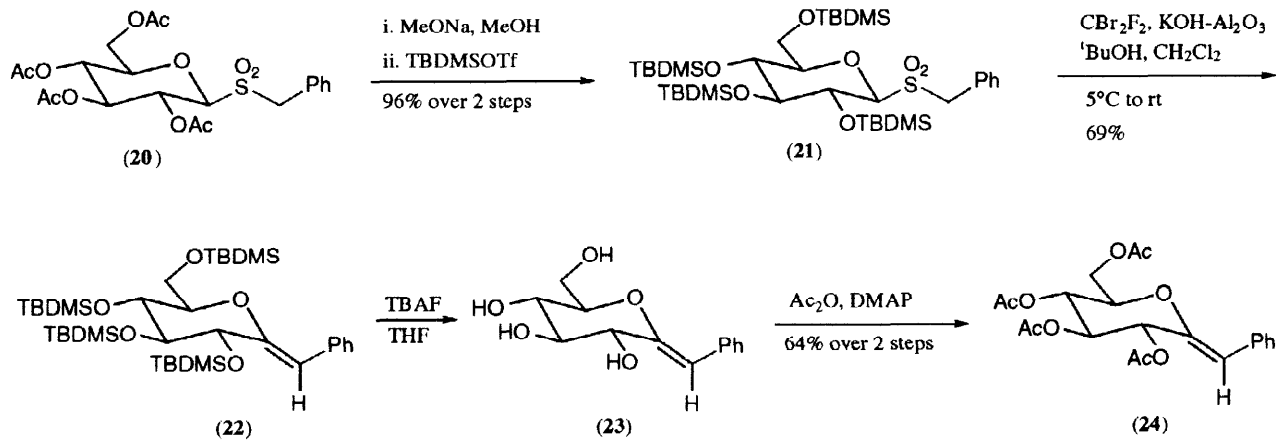
We next turned our attention to the use of exo-glycals for the preparation of the spirocyclic sugars **18** and **19**. These compounds, which are simplified analogues of natural products such as papulacandin D,[14] have recently been prepared by a photolytic route.[15] In our new synthesis (Scheme 4), the benzylated thioglucose derivative **14**[16] was alkylated giving sulfide **15** which was oxidised to sulfone **16**, both steps proceeding in good yield. We were delighted to find that the unprotected alcohol **16** underwent Ramberg-Bäcklund rearrangement smoothly using Chan's CBr_2F_2 conditions[3] giving exo-glycal **17** in 74% yield (Z:E = 80:20).[17] Cyclisation was effected by treatment of enol ether **17** with camphorsulfonic acid (CSA) in methanol to produce a separable mixture of spiroacetals **18** and **19** (30:70) in 75% combined yield {**18**, m.p. 69-71°C; lit.[15] m.p. 70-71°C. **19**, δ_C ($CDCl_3$): 107.3 (C-1); lit.[15] δ_C ($CDCl_3$): 107.3}.

Scheme 4



Finally, we explored the compatibility of other protecting goups with the Ramberg-Bäcklund conditions (Scheme 5). Exo-glycals have proved to be valuable glycosidase inhibitors.[18] For our methodology to be of use in this area, however, it was important to be able to remove the hydroxyl protecting groups without reducing or hydrolysing the enol ether moiety. Thus, the readily available[19] sulfone **20** was deacetylated and then silylated with *t*-butyldimethylsilyl (TBDMS) triflate in almost quantitative yield over the two steps. Ramberg-Bäcklund rearrangement of **21** proceeded smoothly to give alkene **22** in 69% yield, exclusively as the *Z*-isomer (confirmed by NOE studies). Efficient desilylation was accomplished using tetrabutylammonium fluoride (TBAF), and the tetraol **23** was acetylated for characterisation purposes producing **24**. Compound **24** {$[\alpha]_D$ +110 (c 1.0, $CHCl_3$)} was fully characterised and the NMR data confirmed the presence of the exo-methine moiety [δ_H ($CDCl_3$) 5.76 (s); δ_C ($CDCl_3$) 111.4].

Scheme 5



We are currently optimising the Ramberg-Bäcklund methodology for exo-glycal synthesis, and exploring its applications for the synthesis of more complex *C*-glycosides and *C*-disaccharides.

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References and Notes

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17. Representative Ramberg-Bäcklund rearrangement: Preparation of exo-glycal **17**. Dibromodifluoromethane (0.5 ml, 5.3 mmol) was added dropwise over a minute to a vigorously stirred mixture of sulfone **16** (270 mg, 0.42 mmol) and alumina-supported potassium hydroxide (2.60 g)[3] in *t*-butyl alcohol (6 ml) and dichloromethane (3 ml) kept at 5°C under N_2. The mixture was then stirred at rt for 3.5 h after which it was diluted with dichloromethane and the supported base removed by suction filtration through a pad of Celite. The reaction vessel and the filter cake were rinsed thoroughly with dichloromethane and the combined filtrates concentrated. The crude product was purified by silica gel chromatography (EtOAc-petrol, 4:1 → 1:1) to afford exo-glycal **17** (178 mg, 74%) as a colourless oil (80:20, *Z:E*); R_f 0.1 (EtOAc-petrol, 1:4); HRMS (FAB): found, 603.27187 $(M+Na)^+$. $C_{37}H_{40}O_6Na$ requires 603.27226 (0.6 ppm error), which was fully characterised by IR and NMR spectroscopies.
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19. Prepared from pentaacetoxyglucose in *ca.* 60% overall yield by thiol displacement (BnSH, $SnCl_4$) and then oxidation (Oxone®).