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The synthesis of polyoxygenated, enantiopure cyclopentene derivatives using the Ramberg–Bäcklund rearrangement

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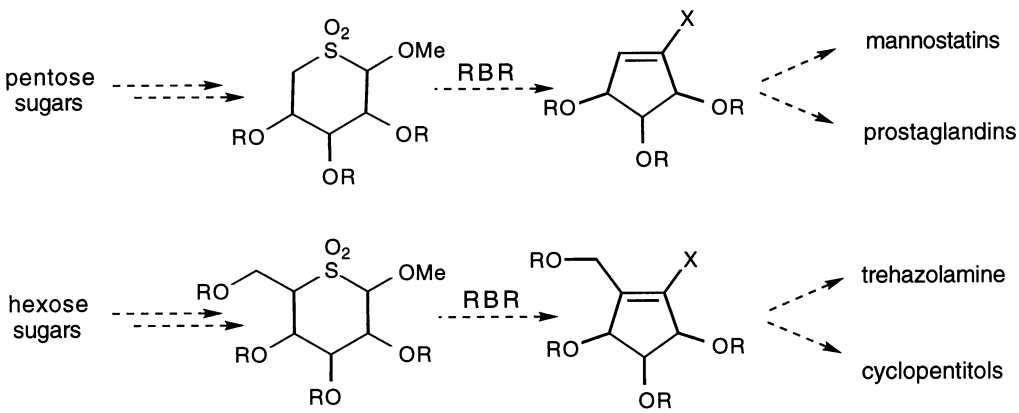
Abstract—A novel approach to polyoxygenated enantiopure cyclopentenes, α-chlorocyclopentenones and cyclopentenones is described which utilizes the Ramberg–Bäcklund rearrangement of thiosugar-derived sulfones. A formal synthesis of the natural aminocyclopentitol, trehazolamine is also reported.

A wide range of compounds containing polyoxygenated cyclopentenes or their derivatives exist in nature.[1] These include prostaglandins,[2] mannostatins,[3] trehazolamine[4] and cyclopentitols.[5] In an ongoing study to investigate synthetic applications of the Ramberg–Bäcklund Rearrangement (RBR),[6] we now report the use of thiosugar-derived sulfones as precursors to enantiopure cyclopentenes (Scheme 1). Cerè et al. recently demonstrated the use of mannose-derived sulfones in the synthesis of conduritols,[7] but to date there have been no reported syntheses of cyclopentenes via the RBR of oxidized thiosugars.

We first investigated the use of pentose sugars and prepared benzyl-protected methyl 5-thio-D-xylopyranoside **1** and methyl 5-thio-D-ribopyranoside **2** following the methods of Whistler[8a] and Hughes.[8b] Oxidation of **1** and **2** by *m*-chloroperbenzoic acid gave the novel sulfones **3** and **4** in a reasonable overall yield (Scheme 2).[9]

The Ramberg–Bäcklund Rearrangement of **3** under Meyers' conditions ($KOH/CCl_4/^tBuOH$),[10] gave a 5:1 mixture of enol ethers **5** and **6** (Table 1, entry i). The major product, **5** results from double chlorination followed by episulfone formation and loss of sulfur dioxide. These enol ethers are easily separated by chromatography and have a reasonable stability on silica. Similarly (entry ii), RBR of ribose-derived sulfone **4** gave enol ethers **7** and **8** (ca. 3:1) in 69% overall yield.[11]

Treatment of enol ethers **5**–**8** with aqueous acid resulted in the formation of enones **9**–**12** in good yields



Scheme 1. (X = H or OMe).

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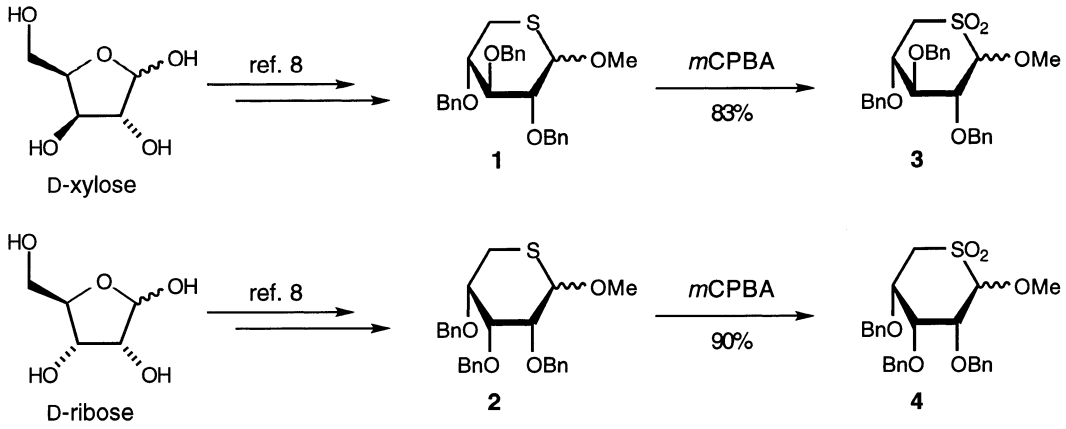
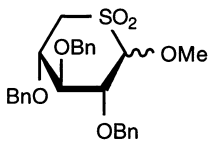
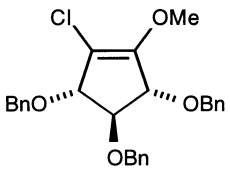
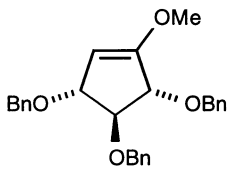
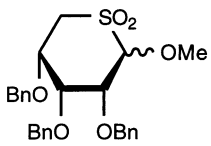
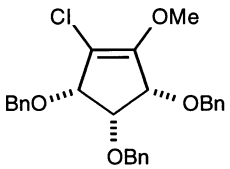
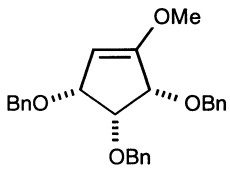
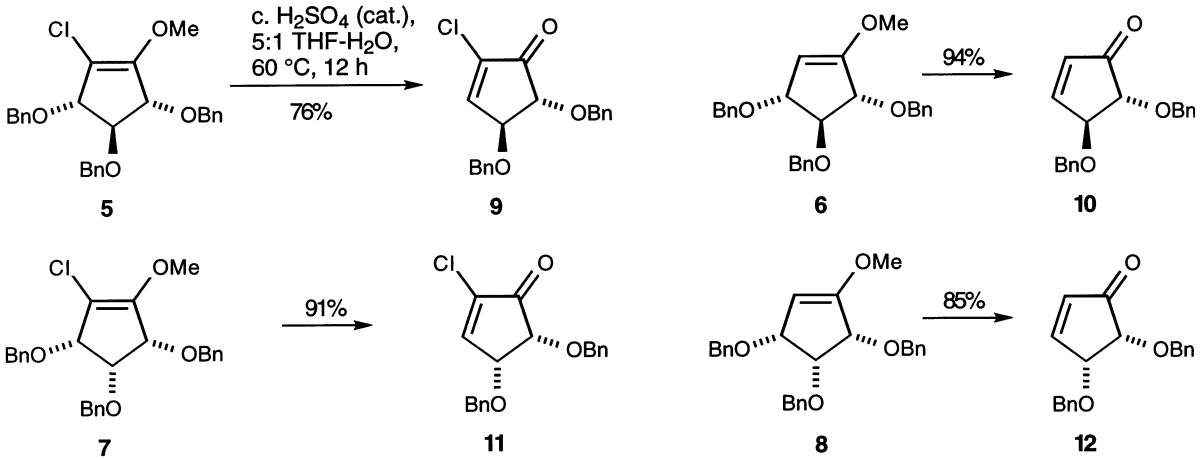


Scheme 2.

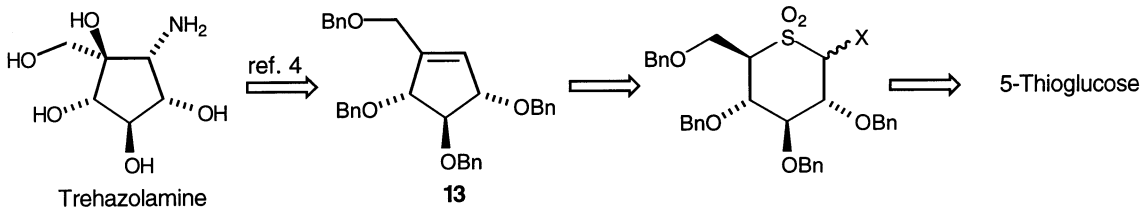
Table 1. Ramberg–Bäcklund Rearrangement of sulfones **3** and **4**[a]

Entry	Sulfone	Products[b]	
(i)	 **3**	 **5** (50%)	 **6** (11%)
(ii)	 **4**	 **7** (52%)	 **8** (17%)

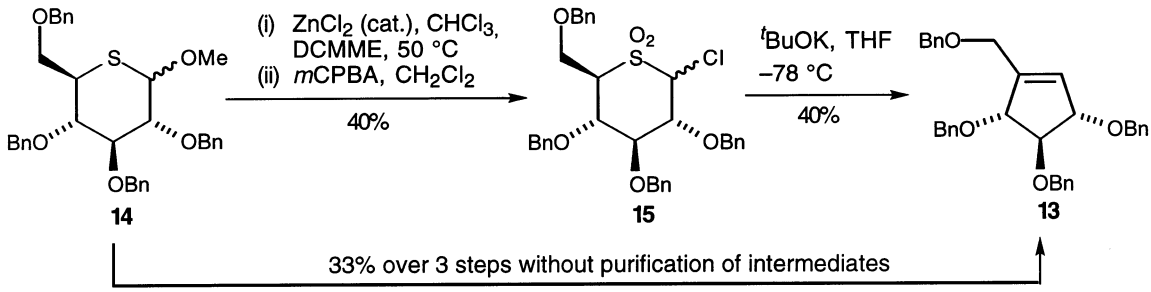
[a] 3:2 CCl_4-^{t}BuOH, KOH, 60°C. [b] Yields are of isolated enol ethers after column chromatography.



Scheme 3.



Scheme 4.



Scheme 5.

(Scheme 3). In the case of enones **10** and **12**, optical rotation values are in good agreement with the literature {**10**: $[\alpha]_D$ +63.9 (*c*. 0.84, $CHCl_3$): Lit.[12] (enant.): $[\alpha]_D$ −61.7 (*c*. 1.5, $CHCl_3$). **12**: $[\alpha]_D$ +21.0 (*c*. 0.2, $CHCl_3$): Lit.[12] (enant.): $[\alpha]_D$ −22.1 (*c*. 0.5, $CHCl_3$)}.

As a natural extension to the work with pentose sugars, we next investigated the RBR of a thioglucose-derived sulfone. Compound **13** has previously been synthesized by Chiara and co-workers,[4] and is an advanced intermediate in the synthesis of trehazolamine, the aglycone of the trehalase inhibitor, trehazolin. We therefore explored the RBR route to **13** illustrated retrosynthetically in Scheme 4.

Benzylated methyl 5-thio-D-glucopyranoside **14** was prepared from diacetone D-glucose following the method of Yuasa et al.[13] Treatment of **14** with $ZnCl_2$/dichloromethyl methyl ether (DCMME)[14] gave the corresponding anomeric chloride which was immediately oxidized to chlorosulfone **15** in 40% overall yield (Scheme 5). Treatment of **15** with ^{t}BuOK in THF at −78°C to effect the RBR gave cyclopentene **13** in 40% overall yield after chromatography. The chlorination/oxidation/RBR sequence could also be carried out without purification of the chlorosulfone **15**: in this case, the overall yield for the 3-step sequence was 33%. The optical rotation of **13** was in good agreement with the literature value {$[\alpha]_D$ +38.5 (*c*. 1.95, $CHCl_3$). Lit.[4] $[\alpha]_D$ +37.5 (*c*. 1.7, $CHCl_3$)}.

In conclusion, we have demonstrated that enantiopure, polyoxygenated cyclopentenes can be easily synthesized by the Ramberg–Bäcklund rearrangement of sulfones prepared from readily-available thiosugars. Enones **9**–**12** are suitable precursors for the synthesis of prostaglandin-type molecules, and α-chloroenones **9** and **11** have potential application in Pd-catalyzed coupling reactions. Cyclopentenes derived from thioglucose should prove useful for the preparation of analogues of cyclopentitols, and in addition, we have completed a formal synthesis of the aglycone trehazolamine in good yield from thioglucose. Further research is currently underway to extend this methodology and utilize the cyclopentene/cyclopentenone products for the synthesis of more complex natural products.

Acknowledgements

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