Facile annulation of six-membered ether rings on to carbohydrate template based on ring closing metathesis. Synthesis of enantiopure bicyclic ethers

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Annulation of cyclic ethers on to furanosugars has been achieved through ring closing metathesis using Grubbs catalyst to afford highly functionalised enantiopure bicyclic ethers 4a and 4b. The bicyclic ether 4a has been transformed to the enantiopure monomeric ether 6 through cleavage of the sugar ring.

Cyclic ethers having six- to nine-membered rings occur frequently in nature as structural units in a wide range of natural products. Representative examples include monomeric ether dactyline, the bicyclic ether elatone and polycyclic ether brevotoxins. In view of continual increase in the number of substances bearing cyclic ethers in nature, development of a general route for the synthesis of cyclic ethers appears to be of utmost importance. We envisaged that annulation of cyclic ethers on to carbohydrate ring through ring closing metathesis (RCM) would provide an easy access to enantiopure bicyclic ethers which could also serve as precursors to monomeric ethers through facile cleavage of sugar ring. In recent years RCM of dienes has emerged as a powerful technique for the construction of ring system of various sizes. Incorporation of rigid acyclic conformational control elements or cyclic conformational constraints has been found to facilitate RCM reactions. While annulation via RCM on to pyranosugars has been investigated in detail, to the best of our knowledge there is no report of RCM based annulation on to furanosugars which impose a lesser degree of conformational constraint than the pyranosugars. We herein report facile annulation of six-membered cyclic ethers on to a furanosugar using RCM reaction leading to the synthesis of enantiopure bicyclic ethers.

1,2,5,6-Di-O-isopropylidene-α-D-glucofuranose 1 was chosen as the furanosugar. Coupling of the furanosne 1 through its sodium salt with allyl bromide afforded the O-allylated furanosne 2a in 78% yield. Selective cleavage of the 5:6-acetonide moiety in 2a with 75% aqueous acetic acid followed by diehydroxylation of the resulting diols afforded the diene 3a [1H NMR: δ 1.32 (s, 3H), 1.51 (s, 3H), 3.84 (d, J = 3 Hz, 1H), 3.97-4.17 (m, 3H), 4.57-4.68 (m, 2H), 5.16-5.40 (m, 3H), 5.8-6.0 (m, 3H); 13C NMR: δ 21.8 (Me), 26.2 (Me), 70.5 (OCH2), 78.1 (OCH), 83.8 (OCH), 105.1 (OCH), 111.3, 132.9 (CH), 140.2. Thus, annulation of cyclic ethers on to appropriate carbohydrate derivative via ring closing metathesis provides a convenient route for entry into the family of polycyclic ethers.

The annulated sugars thus obtained can be employed to provide the enantiopure monomeric ethers (Scheme II). For example, acid treatment of the furanopyran 4a afforded the lactol 5. Oxidation of the diol 5 with NaOCl followed by LiAlH4 reduction afforded the highly functionalised dihydroxypyrone 6, [α]D25 = -130.6° [1H NMR: δ
Reagents and Conditions: (i) NaH, THF-HMPA, CH$_2$=CHCH$_2$Br for 2a and CH$_3$=C(Me)CH$_2$Br for 2b; (ii) I$_2$, Ph$_3$P, imidazole, toluene, reflux; (iii) Cl$_2$Ru(PCy$_3$)$_2$=CHPh.

Scheme I

Reagents and Conditions: (i) 1N HCl, 1,4-dioxane, reflux, 1hr; (ii) a—NaI$_2$, MeOH; b—LAH, Et$_2$O.

Scheme II

3.56-3.60 (m, 1H), 3.79-3.95 (m, 3H), 4.13-4.36 (m, 2H), 5.94-6.05 (m, 2H); $^1$C NMR: $\delta$ 62.9 (OCH$_2$), 63.0 (OCH), 66.4 (OCH$_2$), 78.4 (OCH), 126.7 (CH), 130.6 (CH)] in 20% overall yield in three steps.

In conclusion, we have demonstrated that annulation on to furanosugar through RCM proceeds smoothly to produce bicyclic ethers. Cleavage of the sugar ring of the bicyclic ethers provides a convenient route for entry into enantiopure functionalised dihydropyran.

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References

4 Fore review of ring closing metathesis see: