# A Novel Approach Towards *cis*- and *trans*-Fused Pyranopyrans Based on Ring-Closing Metathesis Reaction of Carbohydrate Derivatives

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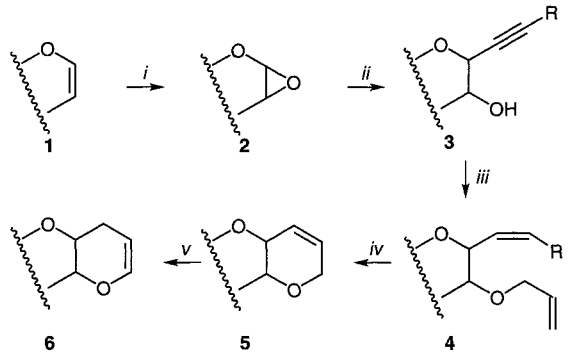
**Abstract:** A novel synthesis of both *cis*- and *trans*-fused pyranopyran systems, based on ring-closing metathesis of glycal derived dienes, is described. Isomerisation of the resulting allylic double bond provides a new cyclic enol ether, thus opening the way to an iterative synthesis of *cis*-(*trans*-)fused cyclic polyethers.

It is well recognised that *trans*-fused polytetrahydropyrans are essential structural elements of several marine toxins, *e.g.* the brevetoxins[1] and ciguatoxins.[2] On the other hand, the occurrence in nature of *cis*-fused cyclic ethers is restricted to a few examples, *i.e.* the dactomelynes[3] and several subunits of maitotoxin.[4] The interesting biological properties and the highly complex nature of these biotoxins have led to the development of iterative procedures[5] for the construction of *trans*-fused polyoxacycle frameworks. The latter is nicely illustrated by the total synthesis of brevetoxin B.[6]

Recently, we disclosed a stereoselective route of synthesis (see Scheme 1) of both α- and β-*C*-alkynylglycosides **3**[7] from α-1,2-anhydrosugars **2**, which in turn are readily available by epoxidation of glycals **1** with 3,3-dimethyldioxirane.[8]



**Operations:** *i* epoxidation. *ii* ring-opening. *iii* a) reduction, b) allylation. *iv* RCM reaction. *v* isomerisation

**Scheme 1**

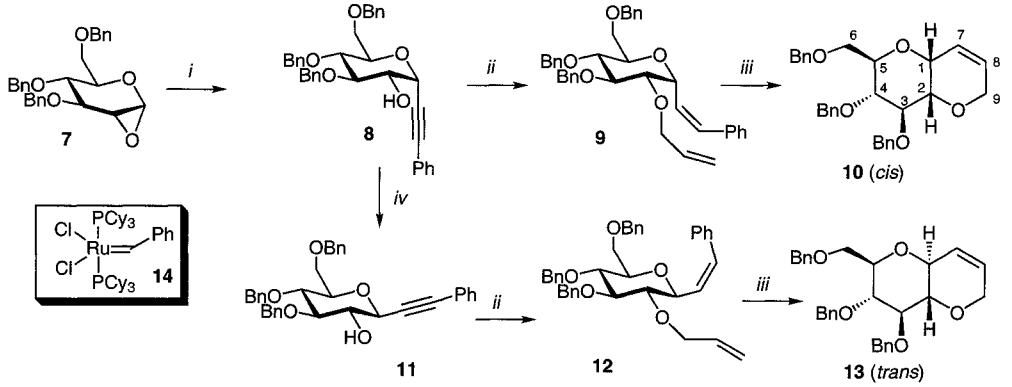
It occurred to us that a sequential transformation of the alkynyl and neighbouring hydroxyl group in **3** into an alkenyl group and allyl ether would afford diene **4**. Ring-closing metathesis[9] (RCM) reaction of **4** followed by isomerisation of the allylic ether would give access to the *trans*- or *cis*-fused cyclic ethers **6**, which in principle are amenable to construct similarly fused oligocyclic ethers by an iterative procedure.

In order to substantiate the viability of the above formulated concept, we first explored the feasibility of transforming the known[8] α-1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose (**7**) into the *cis*-fused derivative **10** by the sequence of events depicted in Scheme 2.

Thus, stereoselective ring-opening of the 1,2-anhydro function in **7** with lithium phenyl acetylide, prepared *in situ* by the reaction of *n*-butyllithium with phenyl acetylene, in the presence of zinc chloride proceeded smoothly to give the homogeneous α-*C*-glucoside **8**. Partial reduction of the acetylenic function in **8** employing Lindlar's catalyst,[10] followed by allylation of the free hydroxyl group with allyl bromide and sodium hydride in DMF afforded diene **9** in 70% yield over the three steps. Reaction of **9** with Ru-catalyst **14**[11] (5 mol%) in toluene at 50 °C showed a clean conversion of the diene into the expected *cis*-fused bicyclic system **10**.[12]

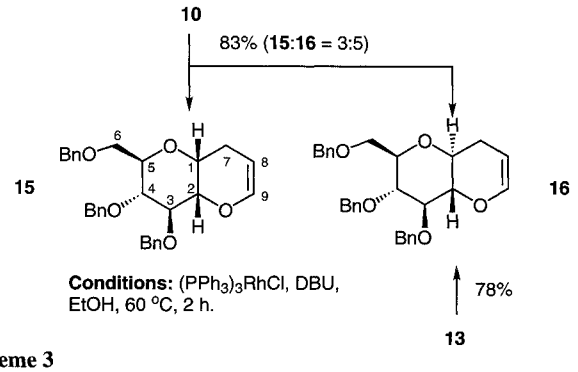
The effective transformation of **8** into **10** was an incentive to prepare the isomeric *trans*-fused bicyclic ether **13**. To this end, the β-*C*-glucoside **11**, prepared from **8** in a three-step sequence,[7] entailing complexation of the triple bond with dicobaltoctacarbonyl, acid-catalysed epimerisation and then decomplexation with iodine, was subjected to the same procedure mentioned earlier for the transformation of **8** into **10**. Thus, partial reduction of the acetylene group in **11** and subsequent allylation of the free 2-OH gave diene **12** in an overall yield of 70% based on **8**. RCM reaction of **12** employing catalyst **14** (5 mol%) in toluene at 50 °C led to the isolation of the *trans*-fused bicyclic derivative **13** in 60% yield.[12]

At this stage, attention was focused on the isomerisation (Scheme 3) of the allylic ether function in both **10** and **13** into the required isomeric vinyl ethers. Fortunately, exclusive formation of the *trans*-fused glycal **16** took place by heating (60 °C) a solution of **13** for 2 h in ethanol



**Reagents and conditions:** *i* phenylacetylene, *n*-BuLi, $ZnCl_2$, THF, 78%. *ii* a) $H_2$, Lindlar, quinoline, EtOAc, b) NaH, allyl bromide, DMF, 90% **9**, 92% **12**. *iii* **14** (5 mol%), toluene, 50 °C, 82% **10**, 60% **13**. *iv* a) $Co_2(CO)_8$, $CH_2Cl_2$, b) 0.1 equiv.TfOH, $CH_2Cl_2$, c) $I_2$, THF, 76%.

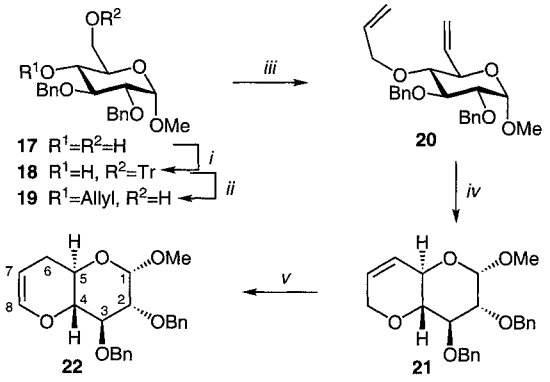
**Scheme 2**




**Scheme 3**

containing Wilkinson's catalyst and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).[13] On the other hand, subjection of **10** to the same isomerisation conditions resulted, as gauged by TLC analysis and NMR spectroscopy, in the formation of the *cis*-fused bicyclic enol ether **15** as well as the *trans*-fused product **16** in a ratio of 3:5. The predominant formation of **16** from **10** indicates that the reaction is under thermodynamic control.

The results obtained so far show that the RCM reaction of carbohydrate-derived dienes is a promising approach towards the construction of valuable pyranopyran systems. The latter is demonstrated further in the successful conversion of methyl 2,3-di-*O*-benzyl-α-D-glucopyranose **17**[14] into the *trans*-fused bicyclic glycal **22** by the seven-step process shown in Scheme 4.




**Reagents and conditions:** *i* TrCl, pyridine. *ii* a) allyl bromide, NaH, DMF, b) pTsOH, $CH_2Cl_2$/MeOH (1/1), 70%. *iii* a) DMSO, $(COCl)_2$, TEA, $CH_2Cl_2$, -78 °C to rt, b) methyltriphenylphosphonium bromide, *n*-BuLi, THF, -40 °C to rt, 60%. *iv* **14** (3 mol%), toluene, rt, 93%. *v* $(PPh_3)_3RhCl$, DBU, EtOH, 50 °C, 60%.

**Scheme 4**

Selective tritylation of the primary hydroxyl group in **17** and subsequent allylation of 4-OH in **18** gave, after detritylation, compound **19** in an overall yield of 70%. Swern-oxidation of **19** followed by Wittig olefination with methyltriphenylphosphonium bromide in the presence of *n*-butyllithium led to the isolation of the diene derivative **20** in 60% yield. RCM reaction of **20** with ruthenium complex **14** in toluene proceeded smoothly at room temperature to give **21** in 93% yield. Isomerisation of the double bond in **21** *via* the aforementioned procedure afforded **22** in 60% yield as a single isomer.[12]

In conclusion, the results presented in this paper show that carbohydrates are versatile starting compounds for the assembly of highly functionalised *cis*- and *trans*-fused allylic and vinylic bicyclic ethers. The scope and limitation of our approach, which nicely complements previously reported[15] routes to analogous cyclic enol ethers by ring-closing metathesis of enol ethers, will be reported in due course.

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(12) All new compounds were fully characterised by spectroscopic techniques ($^1$H-NMR, $^{13}$C-NMR, MS). Spectroscopic data for relevant examples: **10**: $^1$H-NMR (300 MHz, $CDCl_3$): 7.45-7.19 (m, 15H), 5.96-5.80 (2x ddd, 2H, H-7, H-8), 4.98-4.88 (m, 3H), 4.84-4.59 (m, 4H, H-1, PhC<u>H</u>), 4.20-4.09 (m, 3H, H-2, 2x H-9), 3.94 (app. t, 1H, H-3), 3.74-3.63 (m, 4H, H-4, H-5, 2x H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$): 138.63, 138.15, 137.95, 129.63 (C-7/C-8), 128.34, 127.86, 127.64, 125.89 (C-7/C-8), 77.91, 77.60, 74.76, 74.31 (C-2), 73.95 (C-3), 73.46 (C-4/C-5), 72.69 (C-4/C-5), 69.10 (C-6), 67.43 (C-1), 60.46 (C-9).
**16**: $^1$H-NMR (300 MHz, $CDCl_3$): 7.40-7.11 (m, 15H), 6.36 (ddd, 1H, H-9), 5.00-4.75 (m, 3H), 4.68 (ddd, 1H, H-8), 4.62-4.48 (m, 3H), 3.75-3.44 (m, 7H), 2.40-2.30 and 2.19-2.09 (2x m, 2H, H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$): 142.83 (C-9), 138.70, 138.10, 137.95, 128.33, 127.88, 127.65, 127.51, 98.33 (C-8), 84.19, 79.08, 78.68, 75.17, 74.93, 73.46, 72.19, 68.98 (C-6), 26.74 (C-7). **22**: $^1$H-NMR (300 MHz, $CDCl_3$): 7.42-7.21 (m, 10H), 6.38-6.34 (m, 1H, H-8), 4.87 (AB, 2H), 4.73 (AB, 2H), 4.69-4.65 (m, 1H, H-7), 4.58 (d, 1H, H-1), 3.97 (app. t, 1H, H-3), 3.85 (ddd, 1H, H-5), 3.55 (dd, 1H, H-2), 3.50 (app. t, 1H, H-4), 3.39 (s, 3H), 2.25-2.15 and 2.11-2.00 (2x m, 2H, H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$): 143.12 (C8), 138.75, 138.07, 128.25, 128.11, 127,93, 127.75, 127.70, 127.34, 98.55 and 98.11 (C-1 and C-7), 78.98, 78.97, 78.94, 75.19, 73.47, 63.81, 55.17, 26.46 (C-6).

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