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A Novel and Flexible Synthesis of Pyranose Spiroacetal Derivatives

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Abstract: A three-step approach to chiral pyranose [5,4], [5,5], [5,6] and [5,7] unsaturated spiroacetal derivatives from perbenzylated glucopyranolactone **1** is presented. The strategy involves Grignard addition of vinyl or allyl magnesium bromide to **1** to give **2** and **12**, respectively, K-10 mediated glucosidation of different terminal alkenols with **2** and **12** followed by ring-closing metathesis.

Key words: unsaturated spiroacetals, glucosidation, ring-closing metathesis.

It is well recognised that the semi-rigid dioxa-spiroacetal function is a characteristic element of the unique molecular architecture of several biologically important natural products. Most naturally occurring chiral spiroacetals fall into a 1,7-dioxaspiro[5,5]undecane, 1,6-dioxaspiro[4,5]decane or 1,6-dioxaspiro-[4,4]nonane structural category.[1] For example, the symmetrically disposed 1,7-dioxaspiro[5,5]undecane motif constitutes the major component of the sex-pheromone of the olive fruit fly *Dacus oleae*.[2] The same spiroacetal motif is also an essential part of the vastly more complex antiparasitic agents (*i.e.* avermectins[3] and milbemycin[4]) or polyether antibiotics of the monensin[5] and okadaic acid[6] type. The most common route to spiroacetals involves acid catalysed acetalisation of a dihydroxyketone progenity under thermodynamic control resulting, by virtue of the anomeric stereoselection process,[7] in the predominant formation of a bicyclic acetal having an axial orientation of the alcoholic substituents. However, this well-explored approach is not fully compatible with acid-labile protective groups in complex molecules.

We here report a highly stereoselective route to unsaturated spiroacetals by ring-closing metathesis (RCM) reaction of a terminal alkene-*O*-alkene arrangement at the anomeric centre of sugars.

A crucial step in our approach is the installment of the two terminal alkene functions at the anomeric centre. It turned out that the latter could be readily achieved (see Scheme 1) in three steps from perbenzylated D-glucono-1,5-lactone (**1**). Thus, addition of vinyl Grignard reagent to **1** gave exclusively α-epimer **2**, the ^{1}H-NMR data of which were in excellent agreement with those of the same epimer prepared earlier from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.[8] Condensation[9] of **2** with allylalcohol under the influence of Montmorillonite K-10 and molecular sieves (4Å) proceeded with retention of configuration at C-1 to give the homogeneous allyl-1,2-dideoxy-α-D-*gluco*-oct-1-eno-3-ulopyranoside derivative **3** in an overall yield of 68%. RCM reaction of **3** in the presence of Grubbs[10] ruthenium catalyst **4** (6 mol%) gave, after stirring for 16 h at 60 °C followed by flash chromatography, the homogeneous[11] perbenzylated 1,6-dioxa-(5R)-spiro[4,5]dec-3-ene derivative **5** in an excellent yield. The stereochemistry at the spirocenter in **5** was firmly established (see

0040-4039/98/$ - see front matter
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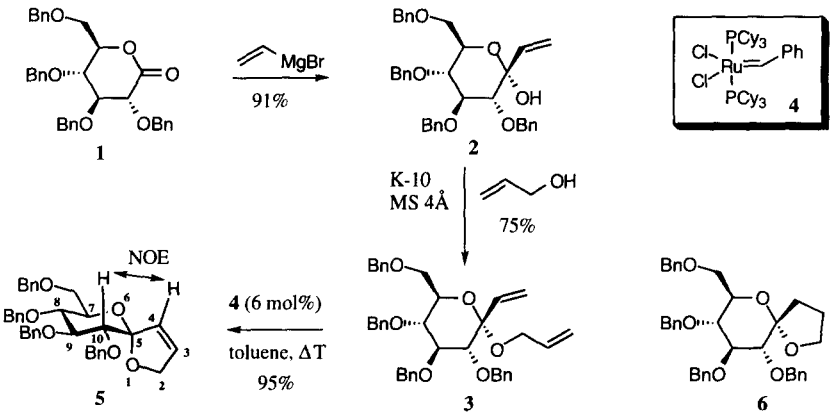
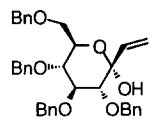
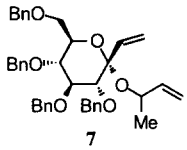
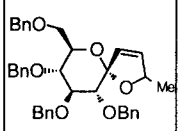
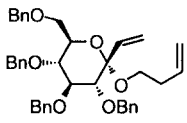
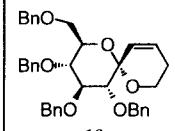
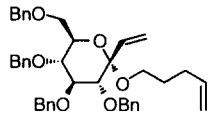
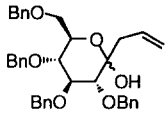
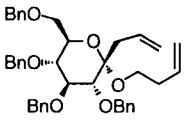
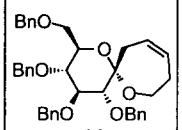
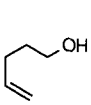
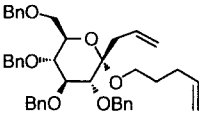
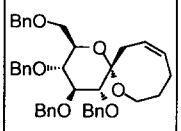
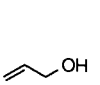
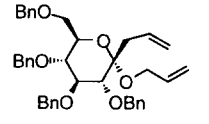
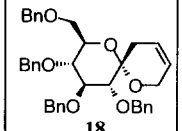
Scheme 1) by NOE difference experiments. In addition, the structure of **5** was also corroborated independently by its nearly quantitative transformation into the known[12] saturated spiroacetal **6** *via* catalytic hydrogenation in the presence of platinum oxide.

Scheme 1



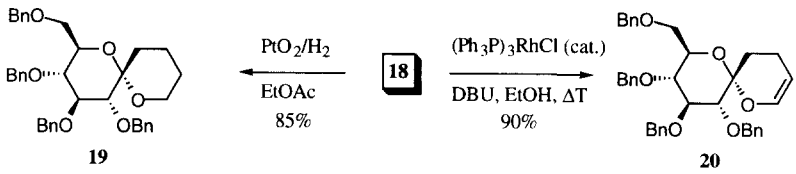
The exploitation of this approach is demonstrated further (see Table 1) in the synthesis of several categories of spiroacetals. It can be seen (entry 1 in Table 1) that RCM reaction of anomerically pure **7**, obtained by K-10 mediated glucosidation of (±)-1-methyl-2-propen-1-ol with **2**, afforded the spiroacetal derivative **8** as a mixture of diastereoisomers (ratio 4:1). Furthermore, RCM reaction (entry 2) of **9**, resulting from stereoselective glucosidation of 3-buten-1-ol with **2**, gave the known[13] chiral 1,7-dioxa-(6R)-spiro[5,5]undec-4-ene derivative **10** in an excellent yield. On the other hand, similar treatment (see entry 3) of diene **11**, derived from **2** and 4-penten-1-ol, did not lead to the expected 1,8-dioxa-(7R)-spiro[5,6]dodec-5-ene derivative, but gave instead, as based on NMR spectroscopy and mass spectrometry, a dimeric product. In addition, the unwanted dimerisation could not be prevented by lowering the concentration[14] of the substrate (*i.e.* 0.01 M) combined with a higher amount (15 mol% instead of 6 mol%) of catalyst **4**. It has been reported[15] that the site of ring closure, instead of the ring size, is of prime importance for productive RCM reaction. Consequently, diene **13** would be a more suitable substrate than position isomer **11** in undergoing a RCM. The requisite precursor **12** of **13** was obtained as a mixture of anomers (α/β = 4/1) by addition of allylmagnesium bromide to lactone **1**. Fortunately, K-10-MS 4Å mediated condensation of **12** with 3-buten-1-ol resulted in the exclusive formation of the α-isomer **13**. The ensuing RCM reaction of **13** proceeded smoothly to give (entry 4) the 1,8-dioxa-(7R)-spiro[5,6]dodec-4-ene derivative **14** in an excellent yield.[11] The use of **12** as starting material is illustrated further in the successful preparation of the two spiroacetal derivatives **16** and **18** (see entries 5 and 6). Thus, RCM reaction of chiral pure **15**, resulting from the stereoselective K-10 glucosidation of 4-penten-1-ol with **12**, gave the perbenzylated 1,9-dioxa-8(R)-spiro[5,7]tridec-5-ene derivative **16** in an overall yield of 72%.[11] Similarly, RCM of **17** led to the chiral spiroacetal **18** which could be readily transformed into the known[13] saturated spiroacetal **19** *via* catalytic hydrogenation in the presence of platinum oxide (see Scheme 2). Moreover, isomerisation of the allyl ether function in **18** into the isomeric vinyl ether derivative **20** proceeded in a near quantitative yield by heating (60 °C) a solution of **18** for 1 h in ethanol containing Wilkinson's catalyst and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU).[11]

Table 1. Synthesis of chiral pyranose spiroacetals

Entry	Donor	Acceptor	K-10 product[a]	Yield (%)	RCM product[b]	Yield (%)
1	 **2**		 **7**	60	 **8**	55
2	**2**		 **9**	71	 **10**	88
3	**2**		 **11**	72	Dimer	55
4	 **12** (α/β = 4/1)		 **13**	69	 **14**	95
5	**12**		 **15**	80	 **16**	90
6	**12**		 **17**	69	 **18**	82

a) 1.2 mass equiv. K-10, 6 equiv. acceptor, MS 4Å, CH_2Cl_2, RT, b) **4** (6 mol%), toluene, 60 °C, N_2 atmosphere, 16 h.

Scheme 2



19 **20**

The mild and stereoselective three-step approach described in this paper presents a novel and versatile route to different categories of unsaturated spiroacetals. Furthermore, elaboration of the double bond in these spiroacetals may give access to intermediates suitable for the construction of bicyclic systems with a different pattern of substitution. For example, the methodology followed for the preparation of the spiroacetal **20** may be readily adopted for the fabrication of the spiroacetal segment of monensin.[16] The scope and implementation of our methodology to the synthesis of functionalised spiroacetals will be published in due course.

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11) All new compounds were fully characterised by spectroscopic techniques (^{1}H-NMR, ^{13}C-NMR, MS). Selected spectroscopic data of compound: **14**: $[\alpha]_D$ +47.7 ($CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.32-7.19 (m, 20H), 5.69 (m, 1H), 5.52 (m, 1H), 4.92-4.52 (m, 8H), 4.07 (bt, 1H), 3.90-3.39 (m, 5H), 3.63 (bt, 1H), 3.33 (d, 1H), 2.75 (m, 2H), 2.42-2.19 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.7, 129.7, 128.7-127.6, 124.7, 101.4, 84.7, 83.6, 78.7, 75.6, 74.9, 73.3, 71.5, 68.7, 61.8, 36.3, 31.3. MS (FAB): 629 $[M+Na]^+$. **16**: $[\alpha]_D$ +15.8 ($CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.41-7.30 (m, 20H), 5.89 (m, 2H), 5.09-4.68 (m, 8H), 4.19 (bt, 1H), 4.05 (d, 1H), 3.84-3.59 (m, 5H), 3.57 (d, 1H), 2.79 (dd, 1H), 2.45-2.04 (m, 5H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.6, 138.1, 137.9, 137.8, 131.2, 128.2-127.3, 126.3, 102.0, 84.7, 83.5, 78.4, 74.8, 75.4, 73.1, 72.0, 68.4, 59.2, 35.0, 30.7, 23.7. MS (FAB): 643 $[M+Na]^+$. **20**: $[\alpha]_D$ +8.4 ($CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7-26-7.16 (m, 20H), 6.25 (d, 1H), 4.92-4.50 (m, 9H), 4.16 (bt, 1H), 4.21-4.11 (m, 1H), 3.79-3.62 (m, 3H), 3.40 (d, 1H), 2.05-1.49 (m, 4H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 139.6, 138.6, 138.2, 137.7, 128.4-127.5, 102.3, 97.6, 83.0, 82.6, 78.3, 75.6, 75.5, 74.8, 73.1, 71.8, 68.4, 26.8, 16.0. MS (FAB): 615 $[M+Na]^+$.
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