An iodoetherification–dehydroiodination strategy for the synthesis of complex spiroketals from dihydroxyalkene precursors†

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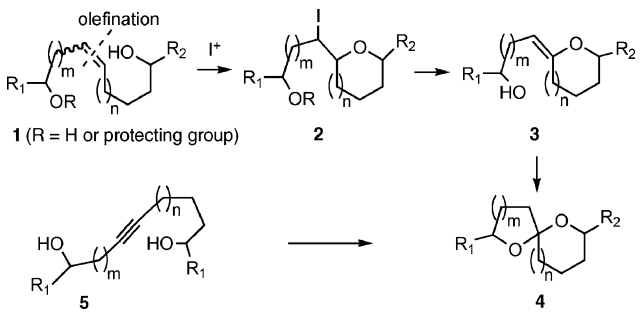
Dihydroxyalkenes or their monoprotected alcohol derivatives are transformed to 5,5- and 5,6-spiroketals through a sequence involving an initial iodocyclization, followed by a silver triflate mediated spiroketalization step on the derived hydroxy-iodoether.

Introduction

Spiroketal subunits comprise the structures of several groups of biologically interesting natural products.[1] Their conformational and geometric characteristics also make them attractive as scaffolds in diversity-oriented synthesis.[2] Accordingly, spiroketal synthesis has attracted considerable attention. Classically, spiroketals have been synthesized through acid-catalyzed cyclization of ketodiol precursors.[1a,b] Several elegant methodologies have been devised to address structural complexity.[3] Methods that employ straightforward segment coupling reactions and mild conditions for spiroketalization are particularly appealing. In this vein, we envisaged an approach in which a dihydroxyalkene or a partially protected derivative **1** is transformed to a spiroketal **4** (Scheme 1). Iodoetherification of **1** could lead to iodinated cyclic ethers like **2**.[4] Dehydroiodination of **2** provides a highly reactive enol ether **3**, which would undergo spiroketalization under mildly acidic conditions. In essence, the alkene moiety in **1** is regioselectively functionalized to an acetal, and acts as an alkyne synthon. The strategy may be therefore complementary to the metal-promoted spiroketalization of dihydroxyalkynes (*e.g.* **5**).[5] Importantly, since precursors like **1** are obtainable *via* straightforward olefination reactions, this methodology allows for a highly convergent synthesis of complex spiroketals. We have reported a preliminary application of this strategy to the ABCD bis-spiroketal system of azaspiracid **1**.[6] Herein, we describe a more detailed investigation into the scope of this method.



Scheme 1 Synthetic strategy.

Results and discussion

Except for **29**, the dihydroxyalkene derivatives were prepared *via* an olefin cross-metathesis (CM) using an excess of one of the olefin partners (Table 1).[7] The metathesis reactions were performed on various highly oxygenated alkene partners and afforded yields of the CM product ranging from 65–85%.[8] For yield optimization, easier purification of the CM product or the requirement for a partially protected dihydroxyalkene, it was sometimes more practical to perform the CM with protection of the alcohol groups in one or both of the reaction partners. The diene precursor **29** was assembled through the Wittig olefination of known aldehyde **11**[9] and phosphonium salt **18**.

Spiroketal precursors **19**, **21**, **23** and **24** were designed to get a preliminary evaluation of the feasibility with respect to different ring sizes (Table 2). Based on previous investigations[10] on the relative rates of iodoetherification of hydroxyalkenes, we argued that dihydroxyalkenes like **19** and **21** or **23** should favor the 5-*exo*-trig and the 6-*exo*-trig pathways, respectively, over other modes of cyclization. Therefore, it should be possible to use substrates **19**, and **21** or **23** in which the eventual alcohols of the spiroketal are unprotected, as precursors to 5,5- and 5,6-spiroketal frameworks, respectively. Thus, treatment of **19**, **21** and **23** with IDCP (iodonium dicollidine perchlorate) in dichloromethane provided a mixture of cyclization products in 85, 85 and 70% yield respectively. However, the NMR data for these structures did not allow for distinction between the possible regioisomeric cyclization products. These structures were tentatively assigned as **31**, **32** and **33** based on the aforementioned regioselectivity considerations. Exposure of the individual product mixtures to silver triflate in dichloromethane in the presence of collidine led to 5,5-spiroketal **43a**,**b** in 70% yield, and the 5,6 frameworks **44a**,**b** and **45a**,**b** in 74 and 55% yield respectively. The mixture **43a**,**b** was chromatographically inseparable and this made stereochemical assignment of the spiroketal configuration in individual components impossible. However, mixtures **44a**,**b** and **45a**,**b** were separable, and their stereochemistry was assigned by 2D COSY and NOESY NMR (see ESI†). It should be noted that while the gross structures of spiroketals **43a**,**b**, **44a**,**b** and **45a**,**b** support the structures assigned to **31**, **32** and **33** respectively, the possibility that the corresponding regioisomer resulting from the 5-*endo*-trig pathway could also lead to the identical spiroketal products, makes structures **31**, **32** and **33** ambiguous. In the event, the isolation of

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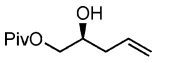
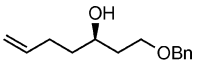
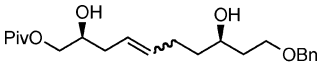
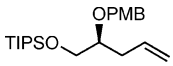
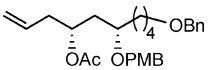
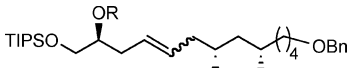
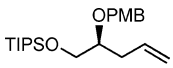
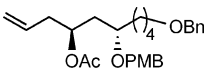
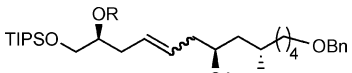
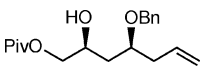
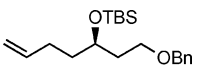
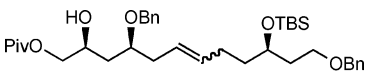
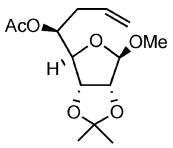
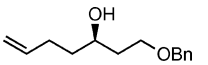
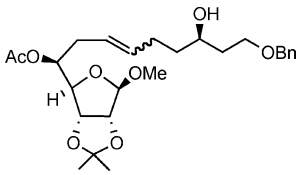
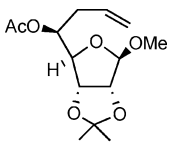
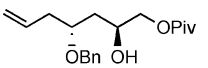
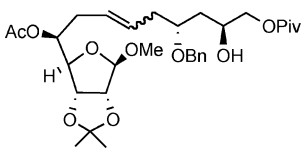
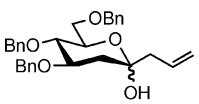
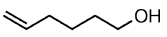
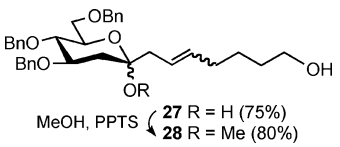
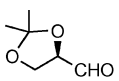
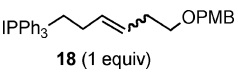
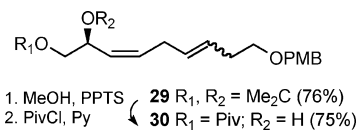
† Electronic supplementary information (ESI) available: Experimental procedures, physical data and NMR spectra for selected new compounds. See DOI: 10.1039/b719247a

Table 1 Synthesis of dihydroxyalkene derivatives and **23**

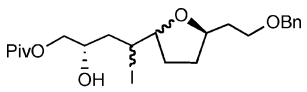
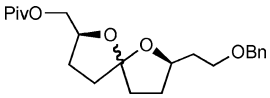
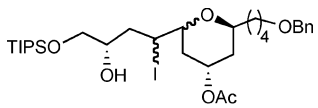
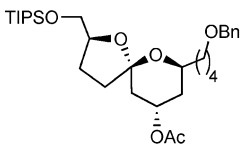
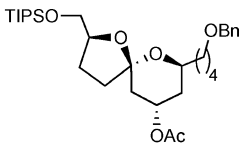
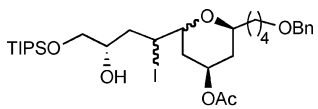
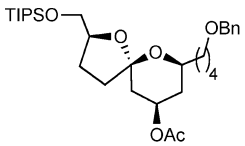
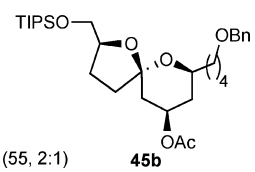
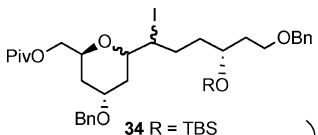
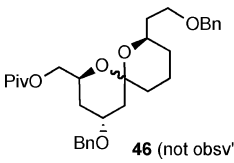
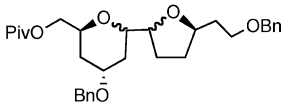
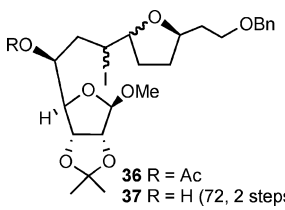
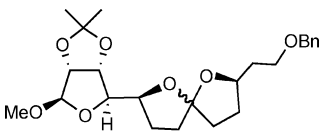
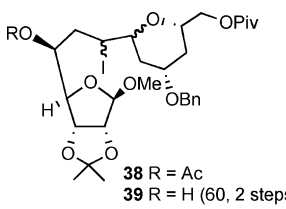
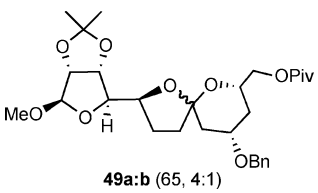
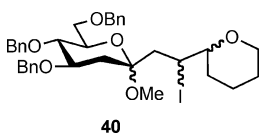
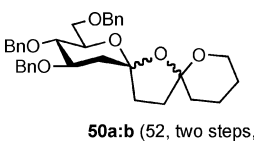
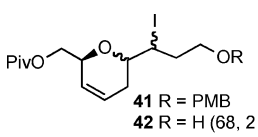
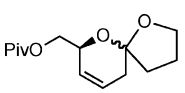
Olefination precursor[a]	Olefination precursor[a]	Dihydroxyalkene derivatives (yield)
 **6** (1 equiv)	 **12** (3 equiv)	 **19** (88%)
 **7** (3 equiv)	 **13** (1 equiv)	 DDQ → **20** R = PMB (65%), **21** R = H (81%)
 **7** (3 equiv)	 **14** (1 equiv)	 DDQ → **22** R= PMB (56%), **23** R = H (67%)
 **8** (1 equiv)	 **15** (3 equiv)	 **24** (67%)
 **9**(3 equiv)	 **12** (1 equiv)	 **25** (67%)
 **9** (3 equiv)	 **16** (1 equiv)	 **26** (50%)
 **10** (1 equiv)	 **17** (4 equiv)	 MeOH, PPTS → **27** R = H (75%), **28** R = Me (80%)
 **11** (3 equiv)	 **18** (1 equiv)	 1. MeOH, PPTS 2. PivCl, Py → **29** R_1, R_2 = Me_2C (76%), **30** R_1 = Piv; R_2 = H (75%)

[a] Except for **29**, the dihydroxyalkene derivatives were prepared by CM with 10 mol% Grubbs 2nd generation catalyst in CH_2Cl_2 using an excess of one of the olefin partners. For optimal yields, CM's were in certain cases performed on protected alcohol derivatives and the CM product deprotected to give the precursor for the iodoetherification step. The homodimer derived from the alkene that was used in excess was obtained as a side product. Compound **29** was prepared through a Wittig olefination.

a single spiroketal framework starting from dihydroxyalkenes **19** and **21** in reasonable yields suggests that for 5,5- and 5,6-spiroketal systems, selective protection of the alcohols that constitute the eventual acetal residue may not be necessary.

The extension of the strategy to 6,6-spiroketals was next examined using the hydroxyalkene **24** as a test substrate. In this case, the expectation that 5-*exo*-trig would be favored over 6-*exo*-trig or 6-*endo*-trig pathways meant that protection of one of the two alcohols of the eventual spiroketal would be necessary. Accordingly, **24** was treated with IDCP under the standard conditions, and the product **34** was desilylated to provide **35**, the precursor for the spiroketalization step. However, treatment of **35** under the standard conditions led to adjacently linked THF-THP **47**, and not the desired spiroketal **46**. This result suggested that the iodoetherification step yielded **34** as expected, but the subsequent AgOTf-mediated reaction favored THF rather than

Table 2 Synthesis of iodoethers and spiroketals

Alkene	Iodoether (yield)[a]	Spiroketal (yield of mixture, epimer ratio)[b]
19	 **31** (85)	 **43a:b** (70, 1:1)
21	 **32** (85)	 **44a** **44a:b** (74, 3:1)  **44b**
23	 **33** (70)	 **45a** **45a:b** (55, 2:1)  **45b**
24	 **34** R = TBS **35** R = H (68, 2 steps) CSA, MeOH	 **46** (not obsv'd)  **47** (85)
25	 **36** R = Ac **37** R = H (72, 2 steps) K_2CO_3 MeOH	 **48a: b** (76, 1:1)
26	 **38** R = Ac **39** R = H (60, 2 steps) K_2CO_3 MeOH	 **49a:b** (65, 4:1)
28	 **40**	 **50a:b** (52, two steps, 6:1)
30	 **41** R = PMB **42** R = H (68, 2 steps) DDQ. CH_2Cl_2	 **51a:b** (70, 1.2:1)

[a] Iodocyclization reactions were performed by treatment of the dihydroxyalkenes or their mono-protected derivatives with IDCP in anhydrous CH_2Cl_2. [b] Except for **50**, spiroketals were obtained by exposure of the hydroxy-iodide precursor to a mixture of AgOTf and collidine in anhydrous CH_2Cl_2. For **50**, the iodo-acetal **40** was treated with AgOTf in wet THF.

spiroketal formation. This result suggests that application of this strategy to 6,6-spiroketals might in general be problematic, and consequently we focused on evaluating the synthetic scope for 5,5- and 5,6-frameworks.

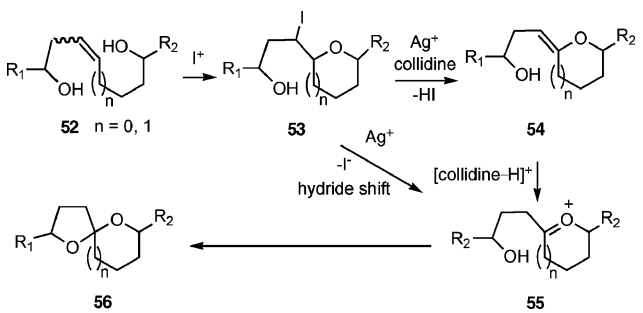
The results for carbohydrate-derived substrates **25** and **26** illustrate the compatibility in more highly functionalized settings. The mono-acetates **25** and **26** (as opposed to their deacetylated diol derivatives) were initially screened because these were the direct products from the CM reaction. Thus, iodoetherification of **25** and **26**, followed by acetate hydrolysis of the resulting acetoxy-iodoethers, provided the spiroketalization precursors **37** and **39**. Treatment of the latter with AgOTf in the presence of collidine provided the 5,5- and 5,6-spiroketals **48a**,**b** and **49a**,**b** in 76 and 65% yield respectively. When the deacetylated diol derivatives of **25** and **26** were subjected to a two-step iodoetherification–spiroketalization sequence, **48a**,**b** and **49a**,**b** were produced in similar overall yield and epimer ratio to the material obtained from the three-step iodoetherification–deacetylation–spiroketalization sequence on **25** and **26**.

In order to determine whether the stereochemistry in the iodoether impacts on the stereoselectivity of the AgOTf-mediated spiroketalization reaction, the latter was performed on individual diastereomers of THP-iodide **33** and THF-iodide **37**. In both cases the ratio of spiroketals produced from the individual iodoether diastereomers was very similar to that obtained from the corresponding mixture (that is, *ca.* 2 : 1 for **45a**:**45b** and 1 : 1 for **48a**:**48b** respectively). These results suggested that the stereochemistry of the iodoether precursor is not directly transferred to the spiroketal product.

The conversion of hydroxy-acetal-alkene substrate **27** to the bis-spiroketal **50** was next investigated. However, iodoetherification of **27** produced a complex mixture, in part due to unwanted 5-*endo*-trig cyclization involving the OH group of the lactol. The methyl acetal **28** was therefore subjected to the iodocyclization procedure and the crude product exposed to AgOTf in wet THF (without added collidine). This sequence afforded a mixture of bis-spiroketals **50a**,**b** in 52% overall yield from **28**.

The transformation of **30** to **51a**,**b** illustrates that the chemoselective elaboration of diene substrates may be possible. Thus, IDCP cyclization on **30** followed by removal of the PMB protecting group provided the hydroxy-iodo-dihydropyran **42**, which led to the spiroketal mixture **51a**,**b**.

The observation that the stereoselectivity of the spiroketalization step is not affected by the stereochemistry of the iodoether precursor is consistent with a mechanism involving the cyclic oxocarbenium ion **55**. However, the pathway leading to **55** is more conjectural (Scheme 2). Intermediate **55** could arise from protonation of an initially formed exocyclic enol ether **54**, or *via* iodide activation in **53** and cation formation, followed by hydride transfer. That enol ether **54** (or its endocyclic isomer) was not observed in the crude reaction mixture, even though spiroketalization occurs in the presence of excess collidine, supports the direct formation of **55** from **53**. However, the possibility that **54** is formed then rapidly converted to product under the reaction conditions cannot be excluded.



Scheme 2 Mechanistic analysis.

Conclusion

In conclusion, the transformation of dihydroxyalkenes or their partially protected derivatives to highly substituted 5,5- and 5,6-spiroketal frameworks has been explored. The compatibility of this strategy with a wide variety of functional groups and the availability of the dihydroxyalkene precursors through straightforward olefination procedures, of which the olefin metathesis is a prominent example, makes this an attractive methodology for the convergent assembly of complex targets. More extensive mechanistic and synthetic investigations are underway and will be reported in due course.

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