Synthesis of *C*-furanosides from a D-glucal-derived cyclopropane through a ring-expansion/ring-contraction sequence†‡

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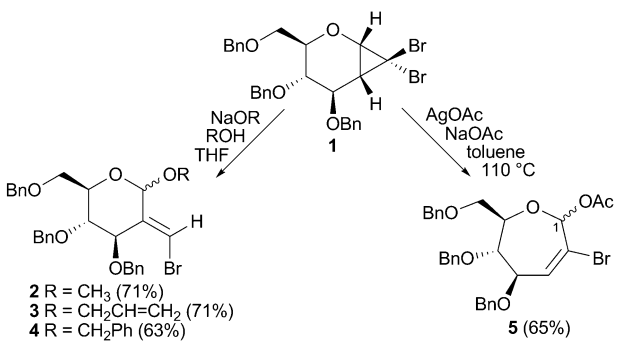
***gem*-Dibromocyclopropane 1, prepared from tri-*O*-benzyl-D-glucal, undergoes thermal and silver-promoted ring expansion in the presence of alcohols to give substituted oxepines. With further heating, ring contraction to highly substituted tetrahydrofurans follows. These represent *C*-furanosides, potentially useful as precursors to *C*-nucleosides and other carbohydrate mimics.**

Carbohydrates are valuable chiral pool reagents[1] due to their degree of functionalisation and defined stereochemistries. Cyclopropanation of carbohydrate scaffolds[2] enables the preparation of a diverse range of modified sugars, such as *C*-branched glycosides[3,4] and septanoside precursors.[4–7] Carbohydrate mimics such as these are sought after for, *inter alia*, their inhibition of carbohydrate-processing enzymes.[8] Halogenated cyclopropanes are widely used in synthesis on account of their controllable chemistry.[9] Jayaraman and co-workers have demonstrated the utility of 2-oxyglycal-derived *gem*-dihalocyclopropanes in generating a range of septanosides, including di- and tri-saccharides.[6] We have recently shown that *gem*-dibromocyclopropane **1**, derived from D-glucal, provides 2-branched pyranosides **2–4** upon treatment with basic oxygen nucleophiles (Scheme 1).[4] Alternatively, silver-promoted ring expansion in the presence of nucleophilic acetate efficiently delivers oxepine **5** in a reasonable yield and as a 3.5 : 1 mixture of *C*1-stereoisomers.[4]

The pursuit of a range of seven-membered cyclic products related to **5** led us to explore the silver-promoted reactions of cyclopropane **1** with allyl alcohol and methanol. As with the formation of acetate **5**,[4] a temperature of approximately 100 °C was necessary for efficient cyclopropane ring opening. This is in striking contrast to ring expansions of the lower homologues, bicyclo[3.1.0] systems, which typically proceed at ambient temperature in the presence of silver salts.[10] Synthesis of the allyloxy compound **6** was carried out in refluxing allyl alcohol (bp 98 °C), with silver acetate added to promote bromide abstraction and ring opening (Scheme 2). As shown in Table 1, the desired oxepine **6** was isolated as a mixture of C1-epimers,§ along with a small amount of the acetate product **5** (entry 1). To circumvent the formation of **5**, use of a non-nucleophilic counterion seemed prudent. However, the yield of the expected product **6** obtained with silver nitrate (entry 2) was no better than with silver acetate, despite the lack of a competing nucleophilic silver counter-ion. It was postulated that the nitric acid by-product is detrimental to the acetal functionality within **6**, and this was borne out by the subsequent experiment in which the reaction was refluxed for an extended time (entry 3). After 3 days, none of the expected oxepine **6** was isolated; instead, three compounds bearing highly functionalised tetrahydrofuran rings were obtained in a combined yield of 51%. One was assigned the structure **7**, which contains a brominated enol ether side-chain. The remaining two compounds appeared to be diastereomers represented by structure **8**. These assignments were made on the basis of the obtained 1D and 2D NMR data,¶‖ and were supported by mass spectrometry.

Use of silver trifluoroacetate as the promoter gave a mixture of oxepine **6**, tetrahydrofurans **7** and **8** after 3 days reaction in allyl alcohol (entry 4). Finally, an attempt to ring expand cyclopropane **1** in the absence of silver salts produced, after 2 days of refluxing in allyl alcohol, the tetrahydrofuran products **7** and **8** in a combined yield of 57% (entry 5).

In contrast to the reactivity with allyl alcohol, silver-mediated reactions in methanol were sluggish and low yielding. For instance, the silver acetate reaction resulted in 15% yield of oxepines **9** alongside 61% recovered starting material **1** after 5 days (entry 6).[4] This is because the requirement for high temperature (*ca.* 100 °C) to promote the cyclopropane ring expansion in this system is not met by methanol (bp 65 °C). Thereafter, subjection of cyclopropane **1** to thermal ring expansion in methanol was performed in a sealed tube under microwave conditions[14] (130 °C, *ca.* 8 bar) for 1 hour. The enol ether **10** and acetal **11** (the latter as a mixture of two stereoisomers) were isolated in a combined yield of 74%, and no oxepine was observed (entry 7). When the microwave reactions in methanol were halted prematurely (*e.g.* after only 10 minutes), the crude reaction mixtures contained oxepines **9** as well as traces of *C*-furanosides **10** and **11** (entry 8).



Scheme 1 Divergent reactions of D-glucal-derived cyclopropane **1**.[4]

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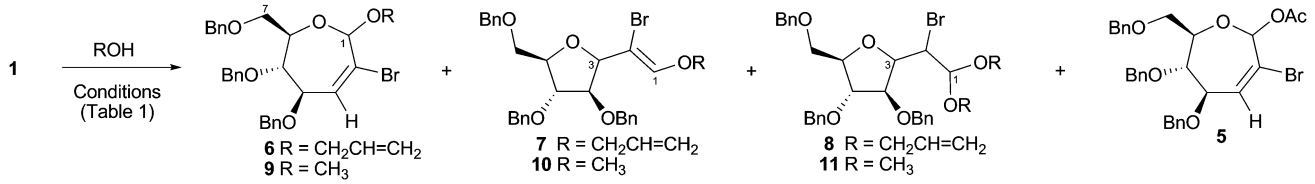


Scheme 2 Formation of oxepines and/or substituted tetrahydrofurans from cyclopropane **1**.

Table 1 Silver-mediated and thermal reactions of cyclopropane **1** in allyl alcohol or methanol

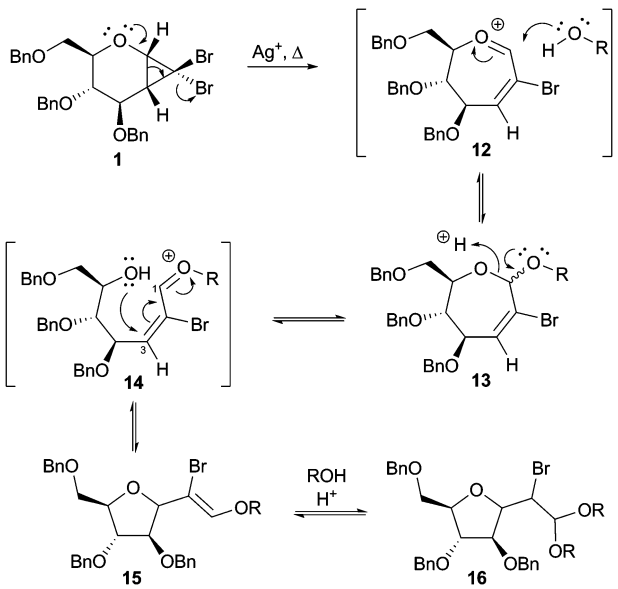
					Yield[a]				
Entry	ROH	Additive	Temperature	Time	**6** or **9**[b]	**7** or **10**	**8** or **11**[b]	**5**	**1**
1	CH_2=$CHCH_2OH$	AgOAc	98 °C	27 h	51%, 1.1 : 1	0%	0%	4%	13%
2	CH_2=$CHCH_2OH$	$AgNO_3$	98 °C	29 h	50%, 1 : 1.8	0%	0%	0%	16%
3	CH_2=$CHCH_2OH$	$AgNO_3$	98 °C	3 d	0%	15%	36%, 1 : 2.5	0%	0%
4	CH_2=$CHCH_2OH$	$AgOCOCF_3$	98 °C	3 d	22%, 1 : 1.8	22%	8%, *ca.* 1 : 10[c]	0%	5%
5	CH_2=$CHCH_2OH$	None	98 °C	2 d	0%	12%	45%, 1 : 1.6	0%	0%
6	CH_3OH	AgOAc	65 °C	5 d	15%, 1 : 2.8	0%	0%	0%	61%
7	CH_3OH	None	130 °C (MW)	1 h	0%	13%	61%, 1 : 3	0%	4%
8	CH_3OH	AgOAc	100 °C (MW)	10 min	4%, 3 : 1	Trace	Trace	0%	*ca.* 70%

[a] Yields quoted are isolated yields, with the exception of compounds **1**, **10** and **11** in entry 8, in which the quantity of compound **1** was estimated from the ^{1}H NMR spectrum of the crude reaction mixture, and **10** and **11** were detected by TLC. [b] Ratios quoted are calculated from the yields of the separated stereoisomers, and are shown as the isomer with higher TLC mobility followed by the more polar isomer. For **6** and **9**, the isomers have been assigned such that the ratios give β-anomer : α-anomer. [c] This ratio is of the isolated but unseparated isomers of **8**.

It appears that the *C*-furanosyl products are formed *via* the oxepines upon heating of the cyclopropane ring expansion reaction for prolonged times. In confirmation, heating a solution of the major isomer of oxepine **6** in allyl alcohol at reflux in the presence of silver nitrate gave, after one day, the tetrahydrofurans **7** and **8**, with only a trace of the oxepine **6** remaining in the crude reaction mixture (according to ^{1}H NMR spectroscopy). Similarly, reaction of oxepine **6** (as a mixture of epimers) with allyl alcohol in the absence of silver salts led to formation of the acetal isomers **8**.

A likely mechanism for the formation of the *C*-furanoside products from cyclopropane **1** is shown in Scheme 3. Cyclopropyl ring opening is thermally allowed and is promoted by silver(I) salts; attack on the intermediate **12** by an alcohol provides, after deprotonation, the oxepine isomers **13**. Acid-promoted ring opening of the oxepine acetal and attack by the ring oxygen at C3 of the highly activated, conjugated alkene in intermediate **14** would lead to the bromoenol ether **15**. The observation of only a single isomer of the isolated enol ethers **7** and **10** is consistent with electron delocalisation in oxonium intermediate **14** and preferred attack of the hydroxyl group from one face of the alkene. The bromoenol ether of **15** is highly reactive towards electrophilic addition, and is converted into the acetal **16**. The mechanistic processes encompassing transformation of oxepine **13** into **15** and **16** are catalysed by acid and are related to those proposed by Skattebøl in a less substituted system.[15] It is noteworthy that the reactions in which these tetrahydrofuran products dominate are those in which a stoichoimetric amount of hydrogen bromide or nitric acid is released upon cyclopropane opening and formation of the oxepines (*viz.* Table 1, entries 3, 5, 7).

The products obtained are highly functionalised, enantiomerically pure tetrahydrofurans.[16] They are closely related to intermediates used previously in the formation of ulosonic acids[17] and *C*-nucleosides.[18,19]



Scheme 3 Proposed mechanism of formation of tetrahydrofuran products from cyclopropane **1**.

In conclusion, D-glucal-derived cyclopropane **1** undergoes silver-mediated or thermal ring expansion in alcohol solvents to provide complex oxepines. Further reaction leads to ring contraction and the formation of a series of highly substituted tetrahydrofuran derivatives (**7** and **8**, **10** and **11**); these represent new *C*-glycosides with potential for elaboration to *C*-nucleosides and glycosidase inhibitors.

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Notes and references

§ In the crude mixtures obtained from all the silver-mediated reactions of **1** in allyl alcohol, the ratio of allyloxy-substituted oxepines **6** was *ca.* 1 : 1.4, as judged by ^{1}H NMR integration. The major allyloxy-substituted oxepine epimer has been assigned as the 1*S*-isomer (the α-anomer, using carbohydrate nomenclature) on the basis of a nOe enhancement of the H-7 signal upon irradiation of H-1. Similar ratios were observed in reactions with methanol, and the ^{1}H and ^{13}C NMR shifts of the methoxy compounds correlated very closely with the allyloxy derivatives, leading to assignment of the major component of **9** as the α-anomer. However, the isolated ratios varied between experiments. For instance, in Table 1, entry 1, the isomer that was isolated in a greater quantity was actually the minor isomer. This indicates that erosion of the true yield of the major isomer occurred during column chromatography in our efforts to obtain pure material.

¶ The enol ether moiety of **7** was evident in the NMR spectra by virtue of the alkene proton signal at δ 6.69, which was directly connected (HSQC) to a carbon at δ 146. This position demonstrated a long-range coupling (HMBC) with an allyloxy group, indicating the two groups might comprise an enol ether moiety. It also showed HMBC correlations with an unprotonated carbon resonating at δ 101.6, which was assigned as the adjacent olefinic carbon at C-2, and an oxymethine at δ 82.4 (C-3). No HMBC correlation was observed between positions 3 and 6; however, the signals were fully consistent with the tetrahydrofuran ring structure of **7**. Assignment of the enol ether stereochemistry came from treatment of the bromoenol ether **7** with *n*-butyllithium, to effect bromine-for-lithium exchange, and a subsequent water quench. While the product was not isolated, the singlet corresponding to H-1 in the ^{1}H NMR spectrum was now observed at δ 6.53 as a doublet with a coupling constant of 12.5 Hz, indicative of an enol ether with an *E*-configuration.[11] Tentative assignment of the stereochemistry of enol ether **7** as 3*R* (β-*pseudo*-anomer) has been made on the basis of the ^{1}H NMR shift of H-3 (δ 4.37) in comparison with related compounds.[12] The structural and stereochemical determination of the methyl variant **10** was made similarly.

‖ The two partially separable isomers of **8** were obtained in a 1 : 2.5 ratio. Both contained an acetal signal in their ^{13}C NMR spectra, at δ 101.9 and δ 100.2, respectively, which were directly connected (HSQC) to protons at δ 4.80 and δ 4.44, respectively. The acetal position in the major isomer showed HMBC cross-peaks to two allyl groups and a methine (δ_H *ca.* 4.28, δ_C 52.3). The chemical shifts and correlation pattern indicated that this latter centre could be a bromomethine functional group. This system displays an HMBC correlation with an oxymethine at C-3 that is part of the tetrahydrofuran ring. The minor isomer displayed similar spectroscopic properties and was assigned as a diastereoisomer of the same structure. It seems likely that the two observed compounds of structure **8** are epimers at C-2 (the bromomethine) because the stereochemistry at C-3 would not be expected to interchange in the formation of the acetal isomers from enol ether **7**. The same arguments are applicable to dimethyl acetal **11**. The fact that the ^{13}C chemical shifts of the C-3 position in all four compounds are so consistent (allyl isomers: δ 81.7 and 81.0, methyl isomers: δ 79.9 and 81.1) lends credence to these assignments. Furthermore, the magnitudes of these chemical shifts compare favourably with similar compounds that were assigned the β-*pseudo*-anomeric configuration, while being significantly downfield of those assigned the opposite configuration.[13]

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