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Heterocyclic Synthesis by C–C Bond Formation. Tetrahydrofuran and Tetrahydropyran Synthesis via Oxonium Ion-mediated Cyclisation Reactions

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Abstract: Dimethyl(methylthio)sulfonium tetrafluoroborate triggers ionisation and cyclisation of hemithioacetals **3** to give tetrahydrofurans **8-11** in good yields and stereoselectivities. The homologous sulfone analogues **17** give tetrahydropyrans on treatment with ethylaluminium dichloride.
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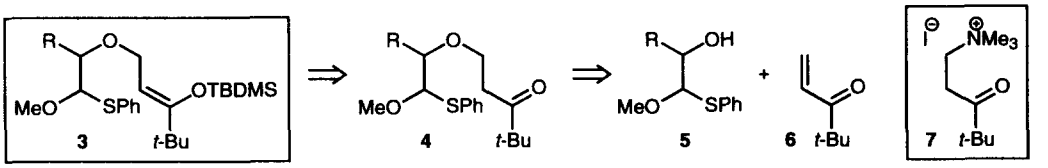
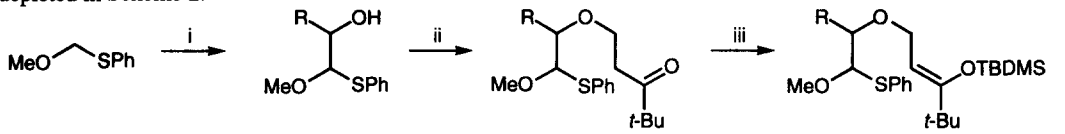
We have been looking at stereoselective *C*-glycosidation reactions involving the cyclisation of thioglycoside derivatives possessing nucleophilic functionality appended by a covalent tether.[1] In particular, we investigated the anomeric cation-mediated cyclisation of substrates **1**, and found that whilst reaction of both diastereomeric thioglycosides gave exclusively cis-fused bicyclic products **2**, the extent of asymmetric induction to the stereocentre in the newly-formed 5-membered ring depended on the stereochemical relationship between the anomeric leaving group and the pendant enol ether-containing moiety. We became interested in a variant of this process in which the oxonium ion triggering cyclisation was part of an *acyclic* array, and in which the anticipated products were substituted tetrahydrofurans.[2] In this Letter we report the results of these studies, and describe related cyclisations which give rise to tetrahydropyran products.

Our attention initially was focused on cation-mediated cyclisation reactions of hemithioacetals **3** (Scheme 1). As in the previous work, we were keen to design substrates possessing a leaving group which could selectively be labilised in the presence of oxygen functionality. It was anticipated that **3** would readily be available from hemithioacetal **5** and enone **6** via precursor ketones **4**. Intermediates **5** would be made from methoxy(phenylsulfenyl)methane and aldehydes. Lithiation of methoxy(phenylsulfenyl)methane under standard



Scheme 1

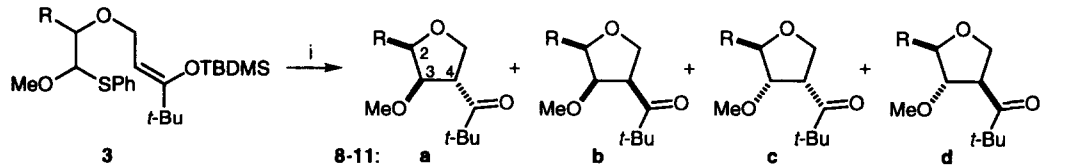
conditions[3] and quenching with aldehydes gave adducts **5** in good yields. Alkylation of **5** was best carried out under phase-transfer conditions using enone **6** generated in situ from the quaternary ammonium salt **7**, which gave adducts **4** in mostly good yields.[4] Compound **7** was easily prepared on large scales by quaternisation of the product of Mannich reaction of pinacolone with formaldehyde and dimethylamine;[5] the use of **7** in this way circumvented practical problems associated with the volatility and lachrymatory properties of **6**. As with the cyclic substrates **1**, silyl enol ether formation was effected by the addition of non-nucleophilic base to *premixed* **4** and TBDMSOTf at -78°C, thereby minimising E1cB-type elimination of **5**. In accord with our previous results,[1] cyclisation substrates **3** were formed as single geometric isomers, and were assigned *Z*-geometry on the basis of n.O.e. enhancements observed between the vinylic and *tert*-butyl protons. The syntheses of **3** are depicted in Scheme 2.



	5(R = CH_3): 85%	**4**(R = CH_3): 76%	**3**(R = CH_3): 96%
	5(R = *n*-C_6H_{13}): 74%	**4**(R = *n*-C_6H_{13}): 67%	**3**(R = *n*-C_6H_{13}): 99%
	5(R = *i*-C_3H_7): 90%	**4**(R = *i*-C_3H_7): 67%	**3**(R = *i*-C_3H_7): 95%
Scheme 2	**5**(R = *i*-C_4H_9): 89%	**4**(R = *i*-C_4H_9): 48%	**3**(R = *i*-C_4H_9): 99%

Reagents and conditions: (i) *t*-BuLi, (1.1 eq), THF, -78°C, add RCHO, then AcOH–THF (1M, 1.1 eq), -78°C→rt; (ii) **7** (4 eq), Aliquat® 336 (0.1 eq), CH_2Cl_2 (0.4M)–50% aq NaOH (1:2), rt, 3.3 h; (iii) add KHMDS (2.5 eq) to **4** + TBDMSOTf (1.5 eq), THF (0.03M), -78°C, 5 min, -78°C→rt, 40 min.

For the cyclisation reactions of **3**, we were keen to find a non-metallic thiaphile which did not require prior preparation. Dimethyl(thiomethyl)sulfonium tetrafluoroborate (DMTSF)[6] appeared to be ideal in this regard, with the added attraction that the reactions would give volatile and hydrolytically labile by-products. In the event, treatment of dichloromethane solutions of **3** containing DBU with a two-fold excess of DMTSF at low temperature caused smooth disappearance of starting material and the formation of diastereomeric mixtures of tetrahydrofurans. In all of the cyclisations, two major isomers, **a** and **b**, and two minor isomers, **c** and **d** were formed.[7] It was further observed that the less abundant of the two major isomers (**b**) could be converted into the more abundant compound (**a**) by prolonged treatment with a large excess of DBU in CH_2Cl_2 at room temperature, strongly implying that the **a** and **b** isomers were epimeric at C-4.[8] Single-crystal X-ray diffraction analysis[9] of the isopropyl-substituted product **10b** demonstrated unequivocally its all-cis nature (Figure 1), and the stereochemistry of the **a** isomers followed from their C-4 epimeric relationship. It was observed also that the *J* values for H3–H4 coupling in 3,4-trans isomers **a** were consistently lower than for the corresponding values for the 3,4-cis compounds **b**. This enabled assignment of the two minor isomers **c** and **d** as having respectively the 2,3-trans-3,4-cis and 2,3-trans-3,4-trans stereochemistries, since **c** showed significantly higher H3–H4 *J* values than **d**. The yields of tetrahydrofurans **8-11** and the diastereomer ratios (determined by ^1H nmr analysis of the crude reaction mixtures) are summarised in Scheme 3.



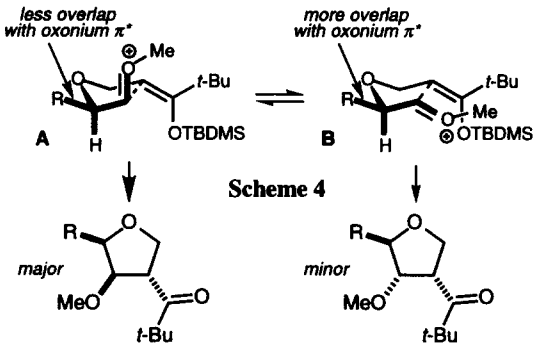
3 **8-11:**

Reagents and conditions: (i) Add DMTSF (2 eq), to **3** in CH_2Cl_2 (0.05M) + DBU (1 eq), then -40°C, 1 h, then warm to rt.

Product	R	% combined yield	% isomer a	% isomer b	% isomer c	% isomer d
8	CH_3	64	33	18	9	4
9	*n*-C_6H_{13}	72	36	22	9	5
10	*i*-C_3H_7	62	29	22	6	5
11	*i*-C_4H_9	60	27	21	7	5

Scheme 3

Inspection of the diastereomer ratios presented in Scheme 3 shows that the 2,3-cis:2,3-trans ratios range between 3.78:1 for the methyl-substituted compounds **8**, and 4.68:1 for the isopropyl-bearing analogue **10**. We rationalise this selectivity in terms of the less stabilised, and therefore more reactive conformation **A** of the intermediate oxonium ion, which does not experience the stabilising effect of electron donation from the neighbouring C–R bond enjoyed by conformation **B** (Scheme 4).



Scheme 4

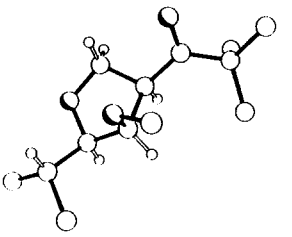


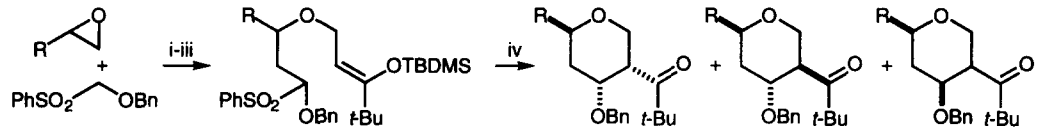
Figure 1: X-ray structure of **10b**

With the tetrahydrofurans in hand, we carried out experiments designed to demonstrate the utility of the pendant *tert*-butyl ketone group for the introduction of further oxygen functionality on the heterocycle. For example, treatment with KHMDS of a mixture of **10b** and TBDMSOTf in toluene gave the enol ether **12** as a single, *E*- geometric isomer. The exocyclic double bond in **12** was readily cleaved using in situ generated ruthenium tetroxide,[10] and the resulting ketone **13** was reduced with complete selectivity for the hydroxytetrahydrofuran **14**; this volatile alcohol was derivatised as its 3,5-dinitrobenzoate (3,5-DNB) **15**, whose X-ray crystal structure[9] demonstrated its all-cis nature (Scheme 5).

Reagents and conditions: (i) add KHMDS (2.5 eq) to **10b** + TBDMSOTf (1.5 eq), PhMe (0.03M), -78°C, 5 min, -78°C→rt, 30 min; (ii) $NaIO_4$ (4.1 eq), $RuCl_3{\cdot}H_2O$ (0.03 eq), CCl_4–MeCN–H_2O (2:2:3; 0.1M), rt, 55 min; (iii) L-Selectride® (1.7 eq), THF (0.1M), -78°C, 25 min, then HCl (0.1M); 3,5-DNBCl (1.9 eq), Et_3N (1.7 eq), DMAP (0.3 eq), CH_2Cl_2 (0.05M), rt, 7 h.

Scheme 5

Having discovered an effective and stereoselective method for tetrahydrofuran synthesis using cation-mediated cyclisation, we were eager to develop a related sequence for the synthesis of the homologous tetrahydropyran systems. In view of recent literature precedent describing the effectiveness of sulfones as leaving groups in oxonium ion-mediated cyclisations,[11] and our own studies on oxetane formation from sugar-derived anomeric sulfone precursors,[12] we looked at sulfones **17** as cyclisation substrates. By analogy with **3**, **17** were made by sequential addition of epoxides and $BF_3{\cdot}OEt_2$ to THF solutions of lithiated benzyloxy(phenylsulfonyl)methane **16**, followed by alkylation with in situ-generated **6**, and silyl etherification as before. Treatment of **17** with ethylaluminium dichloride in toluene at low temperature gave mixtures of tetrahydropyrans **18** and **19** in good yields. In both cases a substantially major product **a** was obtained, together with two minor products **b** and **c**, with **b** predominating over **c**. Compound **19a** was assigned [2*R**,4*S**,5*R**] stereochemistry by single-crystal X-ray diffraction analysis (Figure 2),[9] and the [2*R**,4*S**,5*S**] configuration of **19b** was inferred from its partial epimerisation to **19a** on exposure to DBU in dichloromethane. On the basis of these assignments, the most minor isomers **c** must possess 2,4-cis relationships, although we have not been able unequivocally to assign the relative stereochemistry at C-5. The syntheses and cyclisation reactions of **17** are summarised in Scheme 6.



Reagents and conditions: (i) **16** + *n*-BuLi (1.3 eq), THF, -78°C, add epoxide (1.5 eq) and $BF_3{\cdot}OEt_2$ (2 eq), -78°C, 30 min, then AcOH–THF (1M, 2.5 eq), -78°C→rt; (ii) **7** (4 eq), Aliquat® 336 (0.1 eq), CH_2Cl_2 (0.3M)–50% aq NaOH (1:2), rt, 15 h; (iii) add KHMDS (1.5 eq) to ketone + TBDMSOTf (1.5 eq), THF (0.05M), -78°C, 35 min, AcOH–THF (1M, 3 eq), -78°C→rt; (iv) $EtAlCl_2$ (1.3 eq), PhMe (0.05M), -78°C, 10 min, then aq $NaHCO_3$, -78°C→rt, 30 min.

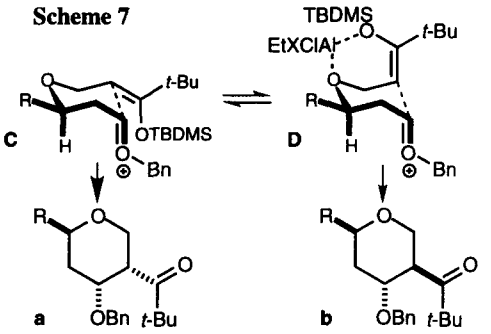
R in 17-19	% yield of 17*	product	% combined yield	% isomer a	% isomer b	% isomer c
CH_3	38	**18**	71	51	16	4
$TBDPSOCH_2$	42	**19**	72	55	12	5

*combined yield for 3 steps from **16** + epoxide

Scheme 6

We rationalise the predominant formation of isomers **a** in terms of the sterically favoured reactive conformation **C** (Scheme 7), in which the equatorial disposition of the bulky *tert*-butyl-containing side-chain minimises 1,3-diaxial interactions in the incipient six-membered ring. That **b** are the second most favoured products perhaps points towards the chelating interaction shown for conformation **D**; we have suggested this previously in order to explain an observed stereochemical dichotomy in oxetane-forming reactions.[12]

Scheme 7



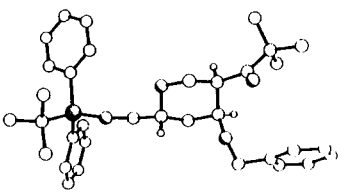


Figure 2: X-ray structure of **19a**

ACKNOWLEDGEMENTS

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4. The major impurities in these reactions were the products of addition to a second equivalent of enone of the enolate presumed to form initially. Yields for **4** (R = CH_3, *i*-C_3H_7 and *i*-C_4H_9) are after a single starting material recovery–recycle sequence.
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7. Both diastereomers of **3** (R = *n*-C_6H_{13}) gave identical diastereomer ratios in the cyclisation reaction.
8. An elimination–addition mechanism for the epimerisation was excluded by the lack of incorporation of CD_3O into **9a** observed when the reaction was carried out in the presence of CD_3OH.
9. We thank Professor David J. Williams and Dr Andrew J. P. White for the X-ray structure determinations.
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