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Stereoselective Free-Radical Cyclization on a Sugar Template
The Sulphonyl Radical as a Synthetic Tool for Functionalized Glycosides

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Abstract : The addition of a sulphonyl radical to the external double bond of an allyl glycal generates a pro-chiral carbon radical which adds to the glycal double bond with a high diastereoselectivity. Through three consecutive radical steps, the configurations of three new asymmetric centers are controlled.

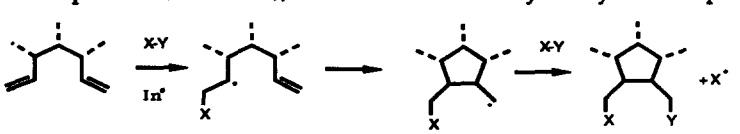
In the last years, there has been growing interest in the use of free-radical methods for the carbon-carbon bond formation in sugar derivatives.[1] The cyclizations of unsaturated radicals have much to recommend them for the formation of cyclic compounds. The conditions required are mild, they are highly regio and stereoselective, and asymmetric centers can be retained immediately next to the sites of bond formation.

It appeared that this methodology is well suited for the annulation of carbohydrate derivatives and an ever increasing number of examples illustrates their ability for the preparation of cyclopentane rings *via* radical cyclization of unsaturated halo, seleno or thiocarbonyl sugar by the tributyl tin hydride method.[2,3]

The two principal strategies are distinguished on scheme 1, whether the radical center belongs to the carbohydrate ring (path B)[3e-i] or to the side chain (path A).[3a-d]

Scheme 1

Despite the efficiency of free-radical addition reactions to cyclize and functionalize polyunsaturated compounds (Scheme 2), the addition of tributyltin hydride to propargyl glycals

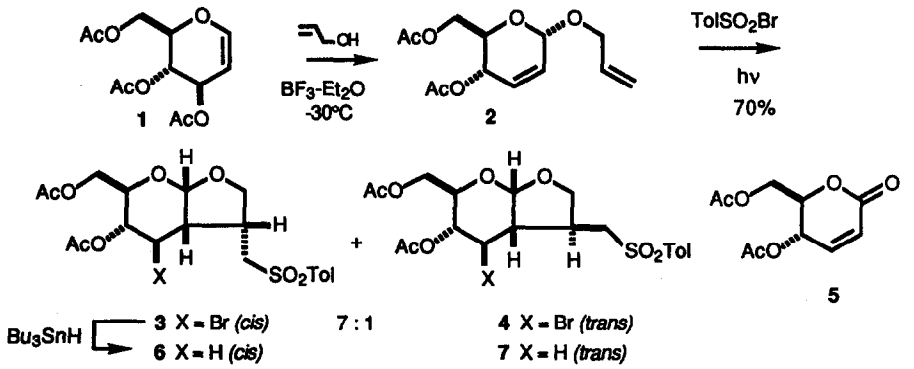


Scheme 2

is, to our knowledge, the only example in the literature where such a strategy has been applied to glycosides.[3a,3d]

We have studied the free-radical addition of sulphonyl halides to 1,6-dienes,[4] these reactions exhibit both high regio-and stereoselectivities. This led us to study the addition of tosyl bromide to O-allyl glycals.

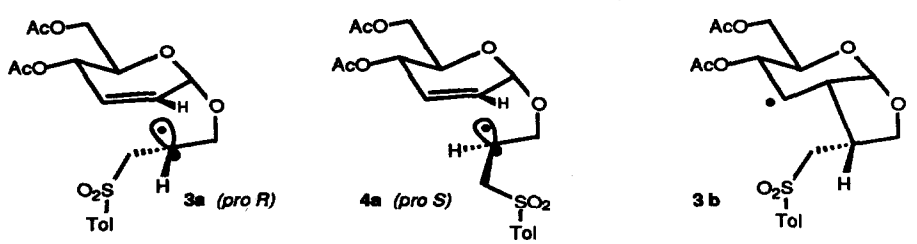
The underlying methodology is summarized in scheme 3. Its originality with regard to the afore mentioned examples, lies in the increase in functionality going from the substrate to the products, due to the formation of the radical **3a (4a)** avoiding tin hydride.



Scheme 3

It involves the ready tranformation[5] of commercially available tri O-acetyl-D-glucal **1** to the exclusively α-allyl derivative **2** and the photoinitiated addition of $TolSO_2Br$ which leads in 70% yield to the two epimers **3** and **4** isolated in a 7:1 ratio.[6] The lactone **5** is obtained as a minor by-product; we suppose it originates from the hydrolysis of **2** and a subsequent oxidation step[7]. We are currently investigating how to eliminate this undesirable side reaction.

Both cyclized products derive from the exclusive addition of tosyl radical to the terminal carbon of the allylic double bond. The stereoselective cyclization step allows to control the configuration of the three created asymmetric centers. The constraints of the rings impose an exclusive 1,2 *cis* stereochemistry and though determine the configuration at C2. The configuration at C3 is controlled by the preferred bromine atom transfer on the less hindered face of the radical **3b**.[8] The third asymmetric center, C7, is R in the major isomer **3** and S in **4**. The diastereoselectivity of the addition of the pro-chiral radical **3a - 4a** to the glycal double bond is higher (7:1) than the previous examples of carbon radical cyclizations.[3]



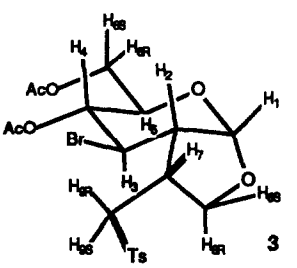
The structures were assigned on the basis of 400 MHz ^1H NMR spectra. The application of COSY experiments established ^1H-^1H correlations and allowed the analysis of the chemical shifts and the splitting patterns (Table). Furthermore the stereochemistry was confirmed by NOE experiments on both products.

The *cis-trans* ratio obtained in the cyclisation step has been determined by NMR analysis of the crude reaction mixture.[9a] Reduction of the crude reaction products by Bu_3SnH-AIBN in C_6H_{12} followed by DBU work-up[10] afforded a mixture of reduced compounds **6** and **7** in a ≈ 7 : 1 ratio. NMR analysis of isolated **6** and **7** brought an additional stereochemical proof.[9b]

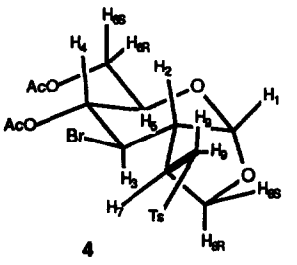
Table : 400MHz ^1H NMR of **3** and **4** : principal patterns and coupling constants

	protons	2	7	9S - 9R	3	8R - 8S	5	6R - 6S	4	1
3	δ ppm	2.73	3.07	3.20 - 3.75	3.87	3.89 - 4.36	3.95	4.01 - 4.30	5.17	5.33
	multiplicity	ddd	m	dd - dd	t	t - dd	ddd	dd - dd	t	d
		2-3=9.9		9R-9S=13.8	3-4=	8R-8S=9.8	5-4=10.3	6R-6S=12.5		
	JHz	2-7=5.7		9S-7 =11.8	3-2=	8S-7 =7.1		6S-5 =4.4		
		2-1=4.1		9R-7= 2.7	10.3	8R- 7=9.8		6R-5 =2.3		
4	δ ppm	2.57	2.83	3.13 - 3.23	3.86	3.81 - 4.30	3.95	4.04 - 4.30	5.13	5.29
	multiplicity	ddd	m	ABpart	t	dd-m	ddd	dd-m	t	d
		2-3=9.8		of ABX	3-4=	8R-8S=10.0	5-4=9.5	6R-6S=12.4		
	JHz	2-7=2.3		9A-9B=14.0	3-2=	8S-7 =3.9		6R-5 =2.4		
		2-1=4.5			9.9					

NOE enhancements
irradiating H7
H1 (11%)
H8S (7%)
H9R (5%)
H2 (12%)



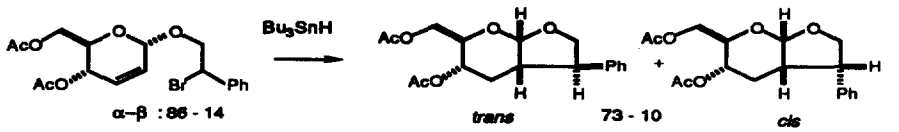
3



4

NOE enhancements
irradiating H7
H3 (10%)
H8R (6%)
HArom (2%)
irradiating H2
H4 (6%)
H1 (7%)
H9 (1%)

This stereoselectivity agrees with the stereochemical feature of other radical ring closure leading to bicylo [4.3.0] systems[11] and is consistent with the chair-like transition state model proposed by Beckwith[12], generally preferred to the boat-like one[13]. We noticed an apparent contradiction with the stereochemical outcome of the cyclization of a similar pro-chiral radical[3d] (Scheme 4).



Scheme 4

This apparent discrepancy could be explained by the fact that our reaction is a kinetically controlled irreversible process, whereas the cyclization of more stabilized phenyl substituted radicals is known to be reversible and leads to the more stable *trans* product[14] under thermodynamic control. This would apply to the example reported by De Mesmaeker [3d].

As a conclusion, these results show that the free-radical addition of sulphonyl bromide to 1,6- dienes applied on sugar template is well suited for the preparation of potentially useful bicyclic acetals of pyranoside. We are further investigating the scope of this reaction, carbohydrates providing a number of readily accessible substrates.

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6 -A 0.016 M solution of **2** in CH_2Cl_2, was irradiated in the presence of a stoichiometric amount of TsBr at 15°C during 20h. After evaporation of the solvent the separation was achieved by LC (SiO_2,$CHCl_3$-Et_2O 6-4).

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8 -In agreement with the favored introduction of an equatorial substituent on the carbohydrate ring when the substituents on the neighbouring carbons are likewise equatorial.

9 -a) The quantitative determination of the **3** : **4** ratio was performed by 400 MHz ^1H NMR, using the areas of H7 signal in each isomer. Compound **3** has been isolated in pure form (F=65°) but difficulties appeared in isolating **4** by LC, in fact **4** was isolated in a 1 : 1 ratio with the lactone **5**. b) 400MHz ^1H NMR of **6** (F=156°C) : 2.02,s,CH_3; 2.03,m,2H,H3a - H3b; 2.05,s,CH_3; 2.36,m,H2; 2.45,s,CH_3; 2.94,m,H7; 2.98-3.17,AB part of ABX, H9a - H9b, J_{9a-9b}=13.6; 3.78,t,H8a, J_{8a-8b}=9.0, J_{8a-7}=9.0; 3.93,ddd,H5, J_{5-4}=10.0, J_{6a-5}=2.2, J_{6b-5}=4.9; 4.1,t,H8b, J_{8b-7}=8.4; 4.09,dd,H6a, J_{6a-6b}=12.2; 4.27,dd,H6b; 4.74,ddd,H4, J_{4-3ax}=11.3, J_{4-3eq}=4.51; 5.32,H1,d, J_{1-2}=3.7; 7.34-7.76,4H,Arom. Irradiation of H2 induces NOE enhancements of H4 (6%) and H7(8%) signals.

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