Fine Tuning of Chemo- and Stereo-selectivity in Cyclization Reactions of Tethered Radicals Derived from 4-*O*-Substituted-α-D-*erythro*-oct-2,6-dienopyranosides. Stereoselective Access to Carbocycles and Branched-chain Sugars

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Chemoselectivity in the radical cyclization of tethered α-D-*erythro*-oct-2,6-dienopyranosides can be accomplished by changes in the nature of the tether and/or in the oxidation state at the *termini* of the olefins, to afford stereoselectively 3-deoxy-3-C-substituted carbohydrates, off-template branched-chain sugars, or functionalized cyclopentanes.

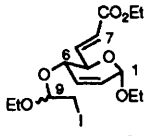
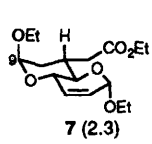
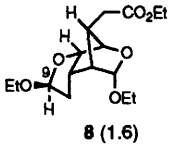
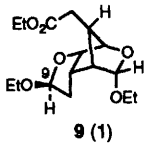
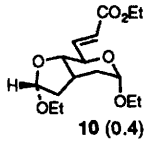
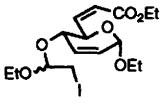
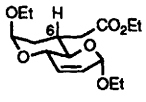
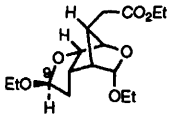
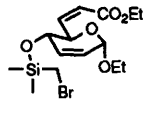
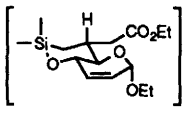
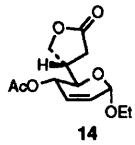
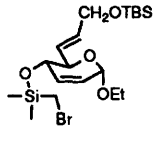
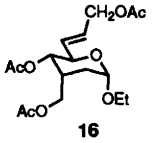
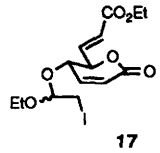
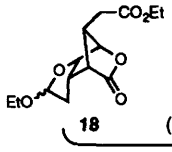
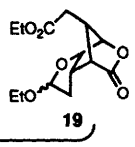
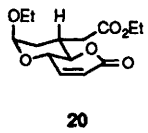
5-*Exo*- and 6-*exo*-trig radical cyclization processes are now well established procedures for the formation of carbon–carbon bonds,[1] but not much attention has been devoted to transformations in which a given radical competes for one of two possible cyclization pathways.[2,3] For example, radical **2** (Scheme 1) offers two competing *loci* for attack of the tethered radical: 6-*exo*-trig (*a*) to give **3**, and 5-*exo*-trig (*b*) to give **4**, with further 5-*exo*-trig (*c*) ring closure to give **5**. Although some examples of the individual processes have been reported,[4,5] we show in this manuscript that radicals of type **2** can be tuned to favour one or other pathway by changing (*i*) the oxidation level at the '*termini*' of the olefins, (*ii*) the nature and (*iii*) the chirality of the tether.

The substrates for this study were obtained from *E*- or *Z*-**1**.[6,7] The corresponding mixed acetal and silylmethylene ethers were uneventfully introduced.[8,9]

Subjection of compound **6**† to radical cyclization conditions (Table 1, entry i) afforded products **7–10**, in which only one of the possible C-9 stereoisomers was obtained in each case. The fact that the reaction conditions precluded equilibration of the primary products implied that each acetal stereoisomer of **6** was following a different cyclization pathway.

In confirmation of this, it was found that while (*R*)-**6** underwent preferential 6-*exo*-trig cyclization at the off-template C-6 site (entry ii), (*S*)-**6** gave only products resulting from 5-*exo*-trig ring closure at the $\Delta^{2,3}$ double bond (entry iii). These preferences may be rationalized by invoking a transition state (**A**, Fig. 1) in which (*a*) the olefin adopts a pseudo-

Table 1 Radical cyclization of 4-*O*-tethered hexa-2,6-dienopyranosides

Entry	Substrate	Reaction conditions[a]	Products (ratio)[b]	Yield[c] (%)
i	 **6**	(1)	 **7** (2.3)  **8** (1.6)  **9** (1)  **10** (0.4)	74
ii	(*R*)-**6**	(1)	**7** (3.6) **10** (1)	79
iii	(*S*)-**6**	(1)	**8** (1.7) **9** (1)	71
iv	 **11**	(1)	 **7** (1.7 : 1)  **8**	70
v	 **12**	(2)	 **13** →  **14**	49[d]
vi	 **15**	(2)	 **16**	48[d]
vii	 **17**	(1)	 **18** (2 : 1) **19**  (9 : 1) **20** 	75

[a] Reaction conditions: (1) Bu_3SnH–AIBN–C_6H_6, syringe pump addition, 15 h, ≈ 0.02 mol dm^{-3}; (2) Bu_3SnCl–$NaCNBH_3$–AIBN–$BuOH^t$, 4 h, ≈ 0.04 mol dm^{-3}. [b] By ^1H NMR (300 MHz) of the crude reaction mixture. [c] Isolated yields. [d] Overall yield from the corresponding 4-OH compounds, includes; i, $ClSi(CH_3)_2CH_2Br$, NEt_3, CH_2Cl_2; ii, cyclization [(2)]; iii, H_2O_2, KF, $KHCO_3$ in THF–MeOH reflux; iv, Ac_2O, Py.

equatorial disposition,[10] and (*b*) the ethoxy group enjoys an anomeric effect, rather than the more sterically advantageous *pseudo*-equatorial position (**B**, Fig. 1), as in the classical Beckwith, Schiesser model.[11,12]

In the case of (*S*)-**6**, the favoured transition state (**C**, Fig. 1) also enjoys an anomeric effect in the tether.

With the corresponding *Z* isomer **11**, it was not possible to separate the C-9 epimers; however cyclization gave **7** and **8** as the only products.

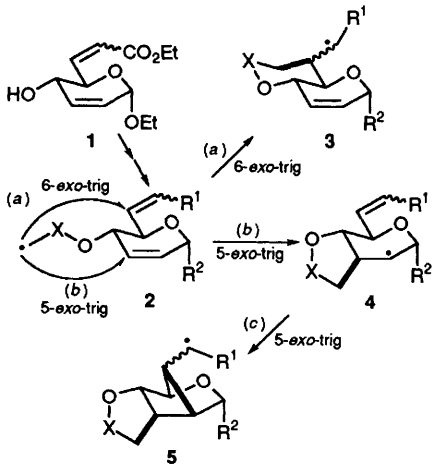
In view of these results, it was of interest to examine a substrate where the tether was achiral. As shown in entry v cyclization under the conditions of Stork and Sher[13] followed by Tamao's oxidation[14] and acetylation led to lactone **14**.‡ This result implies intermediacy of **13** in which radical ring closure has occurred chemo- and stereo-selectively at C-6.§ The complete preference for the 6-*exo-trig* pathway in **12**, might be associated with the reduced rate for the competing 5-*exo*-trig radical cyclization in α-silyl radicals.[15] That this preference could be *completely reversed* is apparent from the result with **15** in which neither double bond has a deactivating substituent. After oxidation[14] and acetylation, the 3-deoxy-3-C substituted compound **16** (*cf.* **4**, Scheme 1) was the only product obtained.

In light of the latter observation it was of interest to examine compound **17**, (Table 1, entry vii) in which both double bonds have deactivating substituents, in the hope of increasing the rate of 5-*exo*-trig ring closure[2,16] while still favouring the second cyclization [(*c*) in Scheme]. In the event, treatment of **17** with Bu_3SnH (see Table 1), gave tricyclic compounds **18** and **19** as the major products, thereby showing that 5-*exo*-trig ring closure was now the much more favoured pathway (compare entries iv and vii). The structure of the minor product **20** was correlated with **7** by means of Jones oxidation.

In summary our results show that a *Z*-unsaturated ester permits the stereoselective introduction of a branch at an off-template position of pyranosides and that this tendency is more pronounced with a silicon, rather than an acetal, tether. Differences in the activation/deactivation levels of the pendant olefins may be correlated with changes in the rates of intramolecular cyclization[2,16] in the dienic system, which results in stereoselective syntheses of branched-chain sugars or cyclopentane synthons.

We are grateful to the NSF (CHE 892003 and CHE 9311356) for financial support and the CSIC and MEC, Spain for postdoctoral scholarships to A.M.G. and J.C.L. respectively. J.C.L. is visiting Associate Professor, and is on leave from the Instituto de Química Orgánica General, (C.S.I.C.), Madrid.

Received, 17th March 1994; Com. 4/01598C



Scheme 1

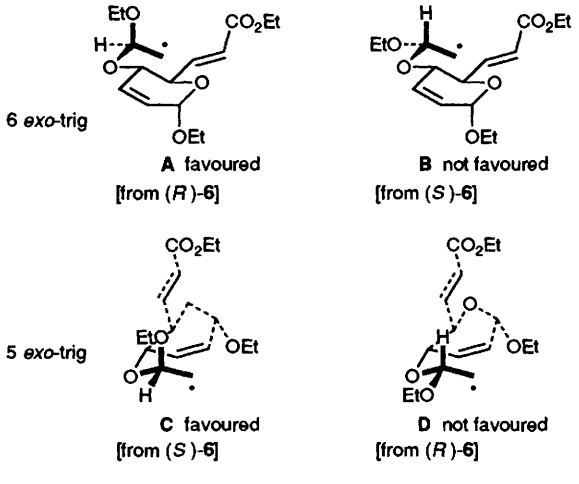


Fig. 1

Footnotes

† Compound **6** appeared as a 1 : 1 mixture of stereoisomers at C-9 that could be resolved by HPLC.

‡ Lactone **14** was unequivocally assigned by X-ray crystal analysis.

§ ^1H NMR and TLC of the crude reaction mixture after radical cyclization of **12** showed the presence of a very major compound, **13**, that could be isolated. Formation of **13**, is also explained according to the stereochemical model of Hanessian *et al.*[10]

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