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Exclusive 6-Endo Radical Cyclizations of α-Silyl Radicals Derived From Carbohydrate Allylic Silylethers

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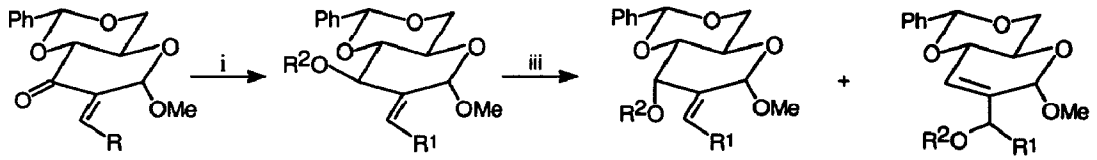
***Abstract** : The cyclization of 2-sila-3-oxa-5-hexen-1-yl radicals in conformationaly biased sugar ring systems depends on the stereochemistry of the starting allylic alcohol and proceeds exclusively via the 6-endo mode with a preference for the formation of* cis *fused-rings.*

Radical cyclization has proven to be of considerable synthetic value for the construction of complex structures.[1] In particular, carbon-centered α-silylradicals have been used in synthesis because subsequent oxidation of the silicon-carbon bond[2] allows the regio-and stereo-selective introduction of a hydroxymethyl group. Using this method chain extension of allylic alcohols is possible either at the β-olefinic carbon (*6-endo* mode),[3] or at the α-olefinic carbon (*5-exo* mode),[4, 5] with formation of new chiral centres, provided that the cyclization process (*6-endo* vs. *5-endo* mode) can be controlled. This control could be achieved by the use of conformationaly defined systems in which one of the cyclization mode will be favored by steric, stereochemical and stereoelectronic factors.[6]

In connection with our programme of multichiral arrays synthesis from sugar templates,[7] we investigated the cyclization of 2-sila-3-oxa-5-hexen-1-yl radicals derived from allylic alcohols **3** and **4**. These compounds are readily prepared from enones **1** and **2**, obtained through our recently described aldolisation-elimination sequence,[8] followed by stereospecific reduction under Luche conditions.[9] Silylation of **3** and **4** with bromomethyl dimethyl chlorosilane gave the expected bromomethylsilyl ethers **5** and **6** in good yields.



1 R = Me
2 R = Et

3 R^1 = Me, R^2 = H
4 R^1 = Et, R^2 = H
5 R^1 = Me, R^2 = $BrCH_2SiMe_2$
6 R^1 = Et, R^2 = $BrCH_2SiMe_2$

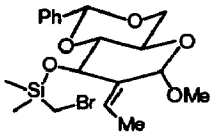
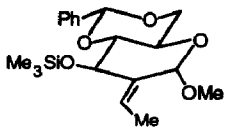
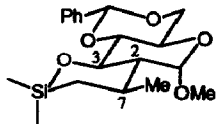
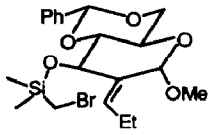
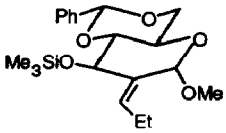
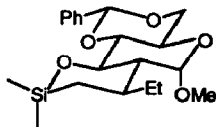
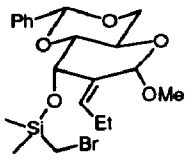
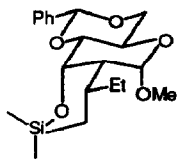
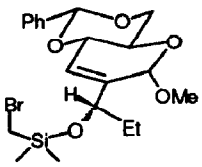
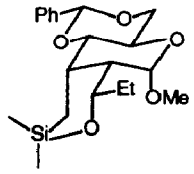
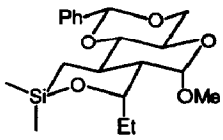
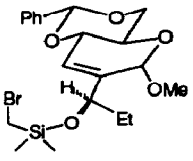
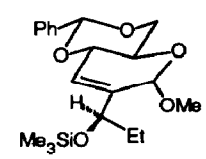
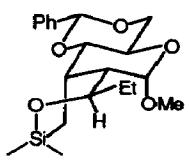
7 R^1 = Et, R^2 = $ClCH_2CO$ **8**
9 R^1 = Et, R^2 = H **10**
11 R^1 = Et, R^2 = $BrCH_2SiMe_2$ **12**

Scheme : i: $NaBH_4$, $CeCl_3$, EtOH, 73 %; ii: $BrCH_2SiMe_2Cl$, NEt_3, CH_2Cl_2, 75-90%; iii: from **4**: PPh_3, DEAD, $ClCH_2COOH$, toluene, 64%; iv: NH_3, MeOH, quant.

Radicals were generated by either the catalytic[10] or the stoichiometric tin method.[11] Surprisingly, the catalytic method gave mainly the reduction products **13** and **15**. However, the stoichiometric method allowed the formation of the cyclized product **14** (entry 1) from **5**. A low yield of **16** was obtained from **6** under the same conditions (entry 2). In both cases, a single isomer having a *trans* ring junction was obtained as seen from ^1H

nmr : $J_{1,2}$ = 3Hz and $J_{2,3}$ = 9Hz. Configuration at C-7 was established on the basis of the large $J_{2,7}$ value (10-13Hz). The configuration at C-7 was the result of attack by the radical from the top face of the double bond, whereas the *trans* ring junction arose from the capture of hydrogen by the intermediate radical at C-2 from the less hindered β face of the sugar ring system.

Table: Radical cyclisation of 2-sila-3-oxa-5-hexen-1yl

Entry	Starting Compound	Products (yield %)[a]		Coupling constants (Hz)
1				**14** : $J_{1,2}$ = 3, $J_{2,3}$ = 9, $J_{3,4}$ = 9, $J_{2,7}$ = 13
	5	**13** (30)	**14** (48)	
2				**16** : $J_{1,2}$ = 3.5, $J_{2,3}$ = 10, $J_{3,4}$ = 9, $J_{2,7}$ = 10
	6	**15** (65)	**16** (20)	
3				**17** : $J_{1,2}$ = 3.5, $J_{2,3}$ = 2, $J_{3,4}$ = 2.5, $J_{2,7}$ = 2.5
	11	**17** (92)		
4				**18** : $J_{1,2}$ = 3.5, $J_{2,3}$ = 3, $J_{3,4}$ = 5, $J_{2,7}$ = 2 **19** : $J_{1,2}$ = 3, $J_{2,3}$ = 12, $J_{3,4}$ = 10, $J_{2,7}$ =3
	12*S*	**18** (44)	**19** (15)	
5				**21** : $J_{1,2}$ = 4, $J_{2,3}$ = 5, $J_{3,4}$ = 5, $J_{2,7}$ = 3
	12*R*	**20** (20)	**21** (74)	

a) Yields refer to pure isolated compounds

If the stoichiometric method was more efficient than the catalytic method, the extent of reduction of the carbon-bromine bond was rather high and this fact could be due to stereochemical factors.[3d] In order to check this point, we prepared the corresponding axial alcohols from **3** by Mitsunobu inversion. As already mentioned

for hindered alcohols, the reaction was sluggish and strongly dependent on the acidic component.[12] Chloroacetic acid gave no reaction with **3** but gave satisfiyng results with **4**.[12b] The expected ester **7** (37%) was formed together with esters (27%) resulting from a S_N' substitution.[13] The two epimers **8*S*** and **8*R*** in a 3/1 ratio, readily separated by column chromatography, were isolated. Saponification of these esters gave alcohols **9** and **10*S*** and **10*R*** respectively which were silylated as above to provide **11**, **12*S*** and **12*R***. Cyclization of the radical derived from **11** was totally stereoselective and gave the *cis* derivative **17** in excellent yield. From a synthetic point of view, the radical cyclization of the allylic bromosilanes **12** should be of interest as a method for the stereoselective formation of a C-C bond at position 3 of a sugar. Two different behaviours were discerned (entries 4 and 5) using compounds **12**. The radical cyclization of **12*S*** gave a 75/25 mixture of **18** and **19** in 60% yield. The $J_{2,3}$ values (3 Hz in **18** and 12 Hz in **19**) confirmed the *cis* and *trans* arrangement of the rings respectively. It should be noted that the small $J_{2,7}$ values in both **18** and **19** supported the (*S*) configuration at C-7 (compare with the large $J_{2,7}$ in compound **16**). In contrast the radical cyclization of the **12*R*** derivative gave only one *cis* compound **21** ($J_{2,3}$ = 5 Hz), and a small amount of reduced compound **20**.

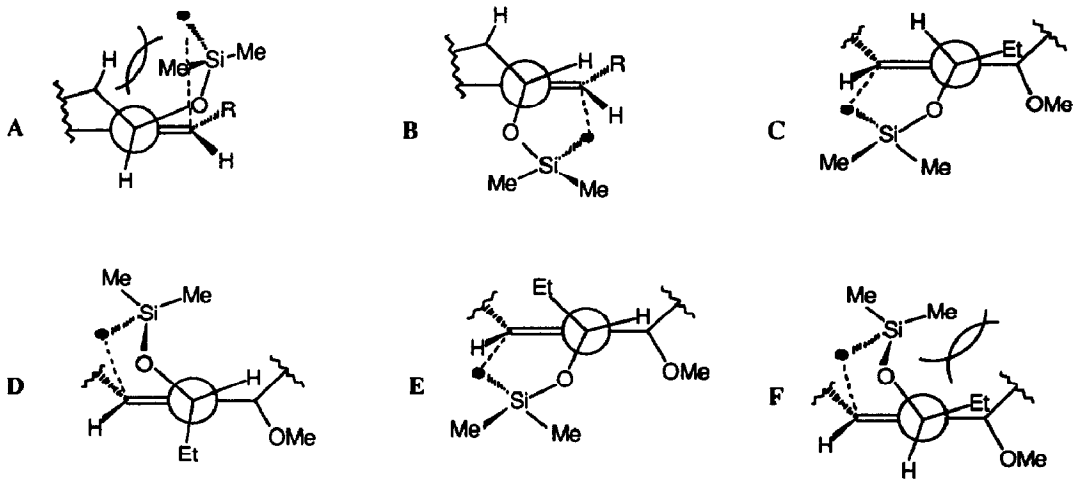


Figure: Possible transition states for radical cyclisation

In all cases, attack of the α-silyl radical on the double bond gave an intermediate radical located at C-2 which reacts with tributyltin hydride from the less hindered β-face. In order to explain the good result obtained with axially oriented α-silylradical (entry 3) versus equatorially oriented ones (entries 1, 2) possible transition states (t.s.) are considered on the Figure. The radical derived from **5** and **6** attacks the β-face of the double bond via the boat t.s. **A**, in which a destabilizing interaction may exist between H-4 and a methyl group on the silicon atom. This steric interaction may retard cyclization, thus favouring hydrogen capture by the intermediate α -silylradical, explaining the formation of reduced compounds **13** and **15**. In contrast, the radical derived from **11** likely reacts via a chair t.s. **B** without any destabilizing interactions. This interesting stereochemical effect is also operating in the cyclization of radicals derived from compounds **12**. In the case of **12*S***, the formation of **18** likely proceeds via the chair t.s. **C** in which the Et group occupies an equatorial orientation and the 1,3-allylic strain is minimal.[14] Thus, t.s. **C** could be favoured over the boat t.s. **D**, involved in the formation of **19**. In the case of **12*R*** the chair t.s. **E** leads to the *cis* compound **21** whereas the boat t.s. **F** which should led to the *trans* analogue of **21** is strongly disfavoured because of 1,3-diaxial interactions.

In conclusion, the cyclization of 2-sila-3-oxa-5-hexen-1yl radicals derived from conformationaly restricted *exo*- or *endo*-cyclic allylic alcohols proceed exclusively via the 6-*endo* mode. These results point out the *importance of stereochemistry of the starting alcohol for both exo and endocyclic allylic alcohols* which may be taken into account in synthesis. This radical cyclization, should allow the introduction of a hydromethyl chain at C-3 or stereoselective chain extension at C-2, and may find useful applications in the field of complex sugar synthesis.

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