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Reductive Rearrangement of 4-C-Substituted Hex-2-enopyranosides. Synthesis of 3-Deoxy Glycals

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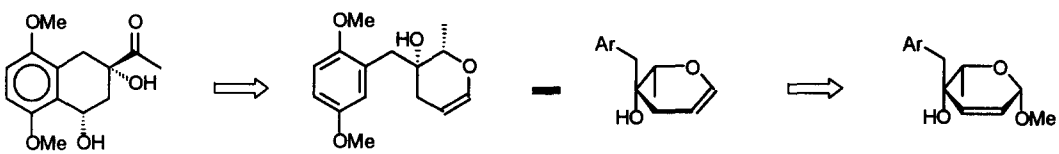
Abstract: 4-C-Substituted α-*erythro* and β-*threo* hex-2-enopyranosides *i.e.* with the 4-OH and 1-OMe groups *cis*, in contrast to their *trans* stereoisomers, are cleanly reduced by lithium aluminum hydride to the respective 3-deoxy glycals. © 1997 Published by Elsevier Science Ltd.

In connection with the ongoing project in our laboratory aimed at the synthesis of daunomycinone[1] we required dihydropyran **2** as a chiral substrate for the synthesis of an advanced intermediate, the AB-rings building block **1**[2] (Scheme 1). Retrosynthetic analysis suggests 3-deoxy glycal **2** could be obtained by the reductive rearrangement of methyl 2,3,6-trideoxy-4-C-(2,5-dimethoxybenzyl)-β-L-*threo*-hex-2-enopyranoside (**3**) (Scheme 1). However literature precedence only describes the reductive rearrangement of hex-2-enopyranosides with a secondary C4 hydroxy group.[3] In this communication we report on the results obtained with 4-C-substituted hex-2-enopyranosides, *i.e.* with a tertiary 4-OH group.



1 **2** **3**

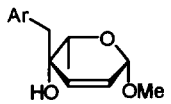
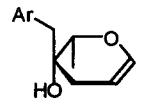
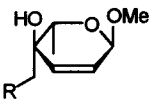
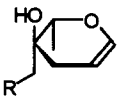
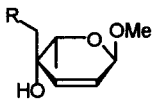
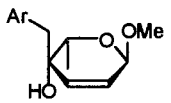
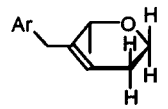
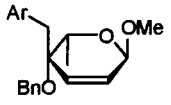
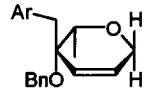
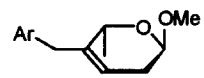
Scheme 1

Methyl hex-2-enopyranosides **3** - **10** have been obtained by the addition of the appropriate organolithium reagent to the carbonyl group of the respective 2,3-unsaturated[4] or saturated[5] 4-keto-pyranosides. In the case of saturated substrates the addition was followed by deoxygenation with concomitant introduction of the 2,3-double bond.[5] Reductive rearrangement of compounds **3** - **10** by lithium aluminum hydride (LAH) has been carried out either in ether solution at room temperature for 24 h (conditions A) or

under reflux in 1,4-dioxan for 72 h (conditions B). The resulting products were purified by flash chromatography on silica gel. All new compounds have spectrometric data (^{1}H NMR, IR) and elemental analyses or HRMS in accord with their assigned structures.[6]

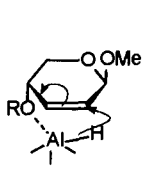
From the data collected in the Table it can be seen that the course of the reductive rearrangement depends upon the relative configuration of the substituents at C1 and C4. 4-C-Substituted hex-2-enopyranosides **3**, **4**, **5**, and **6** with the 4-OH group *cis* to the anomeric (C1) methoxyl readily afforded 3-deoxy glycals **2**, **11**, **12**, and **13**, respectively, in good yields (entries 1 - 4) under mild conditions A. These results are consistent with the one obtained previously for analogous hex-2-pyranosides without a 4-C substituent.[3a,c] However when the C1 and C4 oxygen functions are *trans* no reaction with lithium aluminum hydride under mild conditions A was

Table.

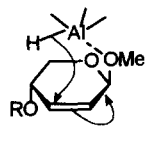
Entry	Substrate[a]	Reaction conditions[b]	Products[a] (% Yield)[c]	
1	 **3**	A[d]	 **2** (71)	**14** (trace)
2	 **4** R = C_3H_7	A	 **11** R = C_3H_7 (92)	
3	**5** R = Ph	A	**12** R = Ph (89)	
4	**6** R = Ar	A	**13** R = Ar (79)	
5	 **7** R = C_3H_7	A[d]	no reaction	
6	**8** R = Ph	A[d]	no reaction	
7	 **9**	B[e]	 **14** (22)	**2** (9)
8	 **10**	B[e]	 **15** (29)	 **16** (12)

a. Ar = 2,5-dimethoxyphenyl; b. A: LAH - ether, r.t., 24 h; B: LAH - 1,4-dioxan, reflux, 72 h. c. Yields refer to isolated products, homogenous by TLC. d. 72 h. e. No reaction under A conditions.

observed (entries 5 and 6). The more forcing conditions B, instead of producing 3-deoxy glycals, led mainly to the reduction products **14** or **15** and **16** (entries 7 and 8). Only a small amount of the 3-deoxy glycal **2** was isolated after lithium aluminum hydride reduction of the hex-2-enopyranoside **9.** These findings are at variance with the results reported by Fraser-Reid [3e] for the reduction of hex-2-enopyranosides with a free or protected secondary 4-OH group *trans* to the anomeric methoxyl. In the cases reported in his paper prolonged (72 h) reflux with LAH in 1,4-dioxan solution led to reductive rearrangement products with C1-C2 or C3-C4 double bonds. Their formation can be rationalized by the intermediacy of the LAH - pyranoside complexes as **17** and **18**, respectively, in which attack of the hydride at C2 or C3 of the allylic system can lead to the removal of the oxygen functions at C1 or C4 regardless of their relative configuration.[7] In our hands, under the conditions used by Fraser-Reid,[3e] compounds **9** and **10,** with *trans* 4-OR (R = H, Bn) and 1-OMe groups, gave small yield of such products (**2** and **16**). Apparently this mode of reduction is not effective in the case of 4-C-substituted hex--2-enopyranosides. The dramatic difference in reactivity between hex-2-enopyranosides with *cis* and *trans*



17



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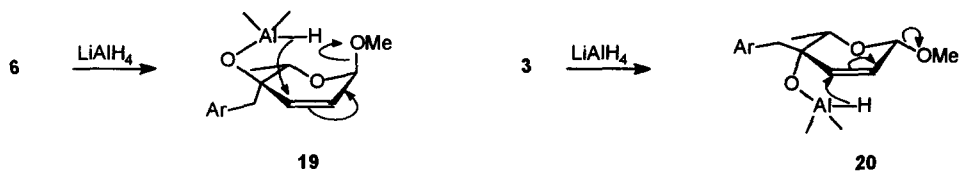
4-OH and 1-OMe substituents can be interpreted as follows. Reductive rearrangement is facile when the anomeric methoxy group of the modified hydride *e.g.* **19** can be substituted by the hydride with concomitant shift of the double bond in an intramolecular S_N2' reaction (Scheme 2). The concerted rearrangement appears to be remarkably sensitive to stereoelectronic constraints as can be inferred from the slower rate of the reaction in the case of the intermediate **20** (arising from **3**), with a pseudoequatorial methoxy group, in comparison to **19** (arising from **6**) in which this substituent occupies a pseudoaxial position, antiparallel to the incoming hydride, allowing a better overlap of its antibonding orbital σ^* with the developing π orbital of the C1-C2 double bond in the product.



19 **20**

Scheme 2

Reductive rearrangement of 4-C-substituted hex-2-enopyranosides, and presumably also of hex-2--enopyranosides with a secondary 4-OH group,[8] is a synthetically useful reaction for α-*erythro* and β-*threo* stereoisomers that is with the 4-OH and 1-OMe substituents *cis*.

ACKNOWLEDGEMENT

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3. a. Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.*, **1970**, *92*, 6661-6663; b. Radatus, B.; Yunker, M.; Fraser-Reid, B. **1971**, *93*, 3086-3087; c. Achmatowicz, O.; Szechner B. *Tetrahedron Lett.*, **1972**, 1205-1208; d. Achmatowicz, O.; Bukowski, P. *Roczniki Chem.*, **1973**, *47*, 99-114; e. Tam, S. Y.-K.; Fraser-Reid, B. *Tetrahedron Lett.*, **1973**, *49*, 4897-4900.
4. Achmatowicz, O.; Szechner, B. *Tetrahedron* **1997**, *53*, 6035-6044.
5. Achmatowicz, O.; Szechner, B. *J. Carbohydr. Chem.* submitted for publication.
6. ^{1}H NMR (200 MHz, $CDCl_3$) spectra of obtained compounds are listed below:
   2: 6.83 - 6.74 (m, 3H, aromatic); 6.28 (dt, $J_{1,2}$ = 6.0, $J_{1,3} \approx J_{1,3'}$ = 2.0 Hz, 1H, H-1); 4.62 (dt, $J_{2,3} \approx J_{2,3'}$ = 3.7 Hz, 1H, H-2); 3.84 (qd, $J_{5,6}$ = 6.4, $J_{3,5}$ = 1.5 Hz, 1H, H-5); 3.81 and 3.71 (2·s, 2·3H, 2·OCH_3); 2.89 and 2.79 (AB, J_{gem} = 13.9 Hz, C4-CH_2); 2.01 (dddd, $J_{3,3'}$ = 17.3 Hz, 1H, H-3); 1.83 (ddd, 1H, H-3'); 1.27 (d, 3H, CH_3).
   12: 7.32 - 7.23 (m, 5H, aromatic); 6.32 (dt, $J_{1,2}$ = 6.1, $J_{1,3} \approx J_{1,3'}$ = 1.9 Hz, 1H, H-1); 4.64 (ddd, $J_{2,3}$ = 3.9, $J_{2,3'}$ = 3.6 Hz, 1H, H-2); 3.90 (qd, $J_{5,6}$ = 6.6, $J_{3,5}$ = 1.2 Hz, 1H, H-5); 2.79 and 2.73 (AB, J_{gem} = 13.7 Hz, 2H, C4-CH_2); 2.09 (ddd, $J_{3,3'}$ = 17.1 Hz, 1H, H-3'); 1.80 (dm, 1H, H-3); 1.33 (d, 3H, CH_3).
   13: 6.86 - 6.70 (m, 3H, aromatic); 6.32 (dt, $J_{1,2}$ = 6.0, $J_{1,3} \approx J_{1,3'}$ = 1.9 Hz, 1H, H-1); 4.64 (ddd, $J_{2,3}$ = 4.4, $J_{2,3'}$ = 3.0 Hz, 1H, H-2); 3.93 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5); 3.83 and 3.76 (2·s, 2·3H, 2·OCH_3); 3.02 and 2.65 (AB, J_{gem} = 13.9 Hz, 2H, C4-CH_2); 2.06 -1.94 (m, 1H, H-3); 1.92 - 1.79 (m, 1H, H-3'); 1.37 (d, 3H, CH_3).
   14: 6.82 - 6.69 (m, 3H, aromatic); 5.41 (m, 1H, H-3); 4.13 (m, 1H, H-5); 3.89 (dt, $J_{1,1'}$ = 11.1, $J_{1,2} \approx J_{1,2'}$ = 4.7 Hz, 1H, H-1); 3.76 (s, 6H, 2·OCH_3); 3.61 (ddd, $J_{1',2}$ = 8.0, $J_{1',2'}$ = 4.5 Hz, 1H, H-1'); 3.31 and 3.14 (AB, J_{gem} = 15.5 Hz, 2H, C4-CH_2); 2.28 - 1.92 (m, 2H, H-2, H-2'); 1.29 (d, $J_{5,6}$ = 6.6 Hz, 3H, CH_3).
   15: 6.89 - 6.70 (m, 3H, aromatic); 6.89 - 6.70 (m, 3H, aromatic), 6.07 (ddd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 3.8, $J_{1,2'}$ = 1.7 Hz, 1H, H-2); 5.65 (dt, $J_{1,3} \approx J_{1',3}$ = 2.0 Hz, 1H, H-3); 4.69 and 4.57 (AB, J_{gem} = 12.1 Hz, 2H, OCH_2); 4.17 (ddd, 1H, H-1); 3.99 (ddd, 1H, H-1'); 3.75 and 3.67 (2·s, 2·3H, 2·OCH_3); 3.62 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5); 3.00 and 2.77 (AB, J_{gem} = 13.3 Hz, 2H, C4-CH_2); 1.41 (d, 3H, CH_3).
   16: 6.82 - 6.67 (m, 3H, aromatic); 5.27 (m, 1H, H-3); 4.62 (dd, $J_{2,3}$ = 4.4, $J_{2,3'}$ = 2.3 Hz, 1H, H-1); 4.26 (m, 1H, H-5); 3.76, 3.75 and 3.42 (3·s, 3·3H, 3·OCH_3); 3.38 - 3.15 (m, 2H, C4-CH_2); 2.49 - 2.32 (m, 1H, H-2); 2.14 - 1.98 (m, 1H, H-2'); 1.30 (d, $J_{5,6}$ = 6.8 Hz, 3H, CH_3).
7. The stereo- and regioselectivity of the reductive rearrangement have been elucidated by deuteration experiments with LAD (ref. 3e).
8. Reduction of hex-2-enopyranosides with *trans* oxygen functions at C1 and C4 gave mixtures of products. Only their ratios and not actual yields were reported (ref. 3e).

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