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ALKYLLITHIUM-PROMOTED RING FISSIONS OF HALIDES DERIVED FROM 1,4:3,6-DIANHYDROHEXITOLS

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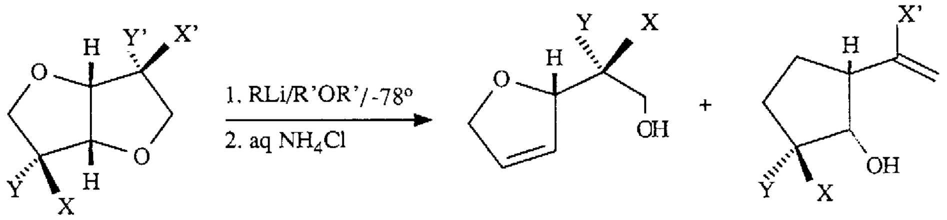
Summary: Halogen-substituted 2,6-dioxabicyclo[3.3.0]octanes, readily obtained from 1,4:3,6-dianhydro-D-mannitol may be useful sources of highly functionalized homochiral synthons. Treated with an alkyllithium the title compounds undergo dehalogenative (X = I) or non-dehalogenative ring fission (X = Cl) giving homochiral 2,5-dihydrofurans or 2-(1-halogenovinyl)tetrahydrofurans, respectively. The two elimination processes compete comparably for X = Br.

While the halogen-promoted reactions of pent-4-en-1-ols are well known and frequently used for the synthesis of functionalized tetrahydrofurans and/or dihydropyrans,[1] the reverse transformations, dehalogenative ring fissions, have received only scanty attention.[2] Nevertheless these reactions appear to deserve more study for, not only do they represent an interesting mechanistic challenge, but they also possess high synthetic value, in particular when applied to halogeno-derivatives of sugars,[2b] where they will give rise to highly functionalized homochiral products.

This communication reports some observations we have made on the ring fission of bicyclic dihalides obtained from 1,4:3,6-dianhydro-D-mannitol, **1a-e**. The three diiodides were obtained (83%) as a mixture, **1a**:**1b**:**1c** = 6.5:1:5.1 by treatment of the ditosylate of 1,4:3,6-dianhydro-D-mannitol with NaI (DMF, 100 °C, 12 h):[3] they were separated by flash chromatography (petroleum ether:Et_2O 90:10) and unequivocally assigned by ^{13}C NMR.[4,5] The dibromide was similarly prepared (LiBr, acetone, 110°C, 36 h, 85%) as a 13:1 isomer mixture from which the major isomer was obtained pure by crystallization from hexane and assigned the structure **1d**.[4] The dichloride **1e** was prepared according to a published procedure.[4,6]

Upon treatment with an equimolar amount of an alkyllithium in THF at -78°C these dihalides undergo dehalogenative and/or non-dehalogenative ring fissions, the outcome depending on the nature of the halogen and, to a lesser extent, on the alkyllithium. Thus diiodides **1a** and **1b** react by the dehalogenative course essentially exclusively giving **2a** and, respectively, **2b** along with butyl iodide. The dichloride **1e** on the other hand, reacts largely by the alternative path giving **3e**. For the dibromide **1d** the two pathways occur concurrently the product ratio **2d/3d** depending on the nature of the alkyllithium used: in THF **2d/3d** = 12 and 1.2 with BuLi and MeLi, respectively.[7,8]



X's,Y's = H unless specified otherwise

1a: X,X' = I; 1b: Y,Y' = I
1c: X,Y' = I; 1.d: X,X' = Br
1e: X,X' = Cl

R = n-Bu, Me; R'OR' = THF, Et_2O

2a: X = I
2b: Y = I
2d: X = Br
2e: X = Cl

3a: X,X' = I
3b: Y,X' = I
3d: X,X' = Br
3e: X,X' = Cl

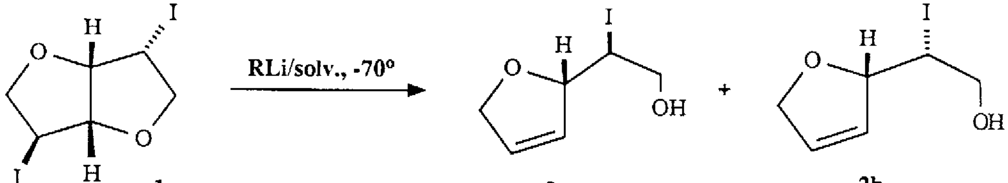
It is remarkable that no epoxides are produced in any of the above reactions,[9] although they may be readily obtained by changing the base/solvent system (MeONa/MeOH) after reaction completion.

The reactions described above are interesting on several accounts: 1. The starting materials are easily available from sugars. 2. The reaction course may be predetermined by proper choice of halogen and/or reagent/solvent system . 3. The reaction products are homochiral synthons that may be usefully elaborated toward valuable synthetic targets.

To probe the stereochemistry of the dehalogenative ring fission the exo,endo diiodide 1c provided an ideal test since loss of the endo- relative to the exo-iodine measures the incidence of syn versus anti elimination. Thus the syn/anti ratio is simply measured by the product ratio 2a/2b. The results show the stereocehmical course to be a sensitive function of the reagent/solvent system (Scheme 1).[10] The increase of syn selectivity parallels the decrease of reaction rate. Remarkably, however, the addition of TMEDA, while strongly increasing the rate, has no appreciable effect on the stereochemical pathway.

As to the mechanism, the dehalogenative ring fission is a special case of a halogen-metal exchange where the alkoxy group on C_β, though a poor nucleofuge, is rapidly expelled upon replacement of the halogen by the electropositive metal. Whether the reaction is single step

Scheme 1



1c **2a** **2b**

RLi/solv	**BuLi/THF**	**MeLi/THF**	**BuLi/Et_2O**	**MeLi/Et_2O**	**BuLi/THF***	**MeLi/Et_2O***
SYN/ANTI #	**0.8**	**1.3**	**4**	**14**	**0.8**	**15**

 # Product ratio, 2a/2b, determined by glc **(* = TMEDA, 2 eq)**

(E2-halogen)[12] or multistep, by way of an "ate" complex,[13] or it proceeds via SET,[14] the evidence above does not provide any definite clue. We are, however, actively applying various mechanistic probes which will be reported in due course. As to the path leading to **3e** or **3d**, this can be reasonably viewed as a base-catalyzed elimination where the acidic proton geminal to halogen is preferentially abstracted by the alkyllithium base while the C_β-O bond is cleaved. Whether the process may be concerted (E2) or two-step via a carbanion intermediate (E1cb) we have no evidence in favor of either.

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3. J. Kuszmann and G. Medgyes, Carbohydrate Research **1978**, 64, 135. Our overall isolated yield, 83.3%, was much higher than that reported (19.8%) by the authors, presumably because of their harsh reaction conditions (boiling DMF); these are probably responsible for the fact that the minor isomer **1b** went undetected in their hands.
4. The ^{13}C NMR spectra ($CDCl_3$) of the dihalides are: **1a**: 90.0 (C_1,C_5); 78.7 (C_3,C_7); 25.8 (C_4,C_8). **1b**: 81.5 (C_1,C_5); 76.4 (C_3,C_7); 23.4 (C_4,C_8). **1c**: 89.5 (C_1); 82.6 (C_5) 77.9 (C_7); 76.4 (C_3); 26.5 (C_8); 21.4 (C_4). **1d**: 88.4 (C_1,C_5); 76.5 (C_3,C_7); 49.9 (C_4,C_8). **1e**: 88.1 (C_1,C_3); 75.6 (C_3,C_7); 60.2 (C_4,C_8).
5. P. Sohàr, G. Medgyes, and J. Kuszmann, Org.Magn.Resonance **1978**, 11, 357. This paper reports the ^{13}C NMR spectra of compounds **1a** and **1c**. While for the latter our data match theirs within a few tenths of a ppm, those for the former differ considerably (up to 1.5 ppm). Our values have been checked on two different instruments, including a Varian XL 100, the spectrometer used by the Hungarian workers.
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7. **General procedure**. To a 0.1 M THF solution of the dihalide (1 to 3 mmol) cooled at -78°C, a 10% excess of an equivalent amount was added of BuLi or MeLi (Jansen low salt). The reaction times with MeLi were 1, 20, and 120 min for diiodides **1a** and **1b**, dibromide **1d**, and dichloride **1e** respectively. (With BuLi reaction times can be considerably shortened). The reaction mixtures were neutralized with methanolic HCl and the solvent was evaporated. The residue was purified by flash chromatography (Et_2O/petroleum ether 30/70; a 20/80 mixture was used to separate **2d** from **3d**) and distilled. The isolated yields of distilled products and their carachteristics are given below under footnote 8. Specific rotations were measured in $CHCl_3$. ^1H- and ^{13}C NMR spectra ($CDCl_3$, ppm from Me_4Si, J's in Hz) were measured at 50 and 20 MHz respectively. Analytical data (C, H, halogen) were consistent with their assigned structures.
8. **2a**: 63%; bp 106-107 °C, 0.3 mm; $[\alpha]_D^{23}$ -95.1 (c, 2.81); ^1H NMR: 5.92 (q, $\Delta\nu$ = 67 Hz, J = 6.0, 2 H, olefinic H's); 4.83 (m, 1 H, C_2H); 4.70 (q, $\Delta\nu$ = 25 Hz, J = 12.0, 2 H, C_5H_2); 4.31 (ddd, J = 6.4, 6.0, 2.6, 1 H, CHI); 3.90 (m, 2 H, $C\underline{H}_2OH$); 3.1 (br s, 1 H, OH). ^{13}C NMR: 129.0, 128.1 (d's, C_3, C_4 interchangeable); 86.7 (d, C_2); 76.8 (t, CH_2OH); 66.2 (t, C_5); 41.7 (CHBr).
   2b: 65%; bp 80°C, 0.03 mm (kugelrohr); $[\alpha]_D^{27}$ = -117.5 (C, 2.33); ^1H NMR:

6.07 (narrow m, 2 H, olefinic H's); 5.00 (m, 1 H, C_2H); 4.79 and 4.63 (low and high field H of the AB part of an ABX spin system, J's 13.3, 5.6 and 13.3, 3.7, respectively, C_5H_2); 4.10 (m, 1 H, CHI); 3.94 (d, J = 5.7, 2 H, $C\underline{H}_2OH$); 3.4 (br s, 1 H, OH). ^{13}C NMR: 129.0, 128.6 (d's, C_4, C_5, interchangeable); 89.1 (d, C_2); 76.4 (t, CH_2OH); 66.9 (t, C_5); 39.1 (CHI).

2d: 64% (from the BuLi reaction): bp 50°C, 0.01 mm (kugelrohr): $[\alpha]_D^{29}$ −109.7 (c 6.27): ^1H NMR: 5.95 (q, $\Delta\nu$ = 54 Hz, J = 7 [further splittings could not be resolved], 2 H, HC=CH); 5.17 (m, W_H 12 Hz, 1 H, C_2H): 4.71 (m, 2 H, C_5H_2); ; 4.17 (m, 1 H, CHBr): 3.92 (m, 2 H, $C\underline{H}_2OH$); 3.85 (br s, 1 H, OH). ^{13}C NMR: 129.0, 126.5 (d's, C_3 and C_4 interchangeable); 85.9 (d, C_2); 76.6 (t, CH_2OH): 64.4 (t, C_5): 58.5 (d, CHBr).

3d: 27% (from the MeLi reaction); bp 90°, 0.01 mm (kugelrohr); $[\alpha]_D^{30}$ +26.41 (c 5.26): ^1H NMR: 6.22 (dd, J's 1.8 and 1.0 Hz, 1 H, vinyl H trans to Br); 5.80 (dd, J's 1.8 and 1.3 Hz, vinyl H cis to Br); 5.02 (m, 1 H, C_2H); 4.68 (dd, J's = 10.5 and 4.4 Hz, 1 H, C_5H trans to Br); 4.60 (m, 1 H, C_4H); 4.35 (m, 1 H, C_3H); 4.25 (dd, J's = 10.5 and 1.2 Hz, 1 H, C_5H cis to Br): 2.6 (br s, 1 H, OH. ^{13}C NMR: 125.8 (s, =CBr); 118.8 (t, $=CH_2$); 84.2 (d, C_2); 77.9 (d, C_3); 75.4 (t, C_5); 50.3 (d, C_4).

3e: 78%; bp 130−131°, 20 mm; $[\alpha]_D^{26}$ +6.40 (c 6.93); ^1H NMR: 5.74 (dd J's 1.8 and 1.2, 1 H, vinyl H trans to Cl); 5.54 (dd J's 1.8 and 1.0, 1 H, vinyl H cis to Cl); 4.84 (m, 1 H, C_2H); 4.50 (dd J's = 10.2 and 4.4, C_5H trans to Cl); 4.47 (m, 1 H, C_4H); 4.33 (ddd J's = 4.4, ~1, and ~1, 1 H, C_3H); 4.09 (dd, J = 10.2, 1.2, 1 H, C_5H cis to Cl); 2.63 (d, J = 4.0, 1 H, OH). ^{13}C NMR: 135.6 (s, =CCl); 114.8 (t, $=CH_2$); 83.4 (d, C_2); 77.7 (d, C_3); 61.3 (d, C_4).

9. In the reaction of **1a** with MeLi a non negligible amount (~7%) was isolated of the rearranged halohydrin 2-(1-hydroxy-2-iodoethyl)-2,5-dihydrofuran. This product is likely to have arisen from LiI ring opening of the epoxide formed from **2a**, perhaps in the course of quenching.
10. Our results are similar to those obtained by Sugita and coworkers in their study of the BuLi-promoted dehalogenative elimination of 1-bromo-2-methoxy-1,2-diphenylethane.[11] In this acyclic system exclusive syn elimination was observed in the less polar solvents (hexane, benzene, diethyl ether) while the syn and anti steric courses were found to compete comparably in the better solvating and donor solvents such as diglyme and THF.
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