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Reductive opening of glycal derived highly functionalized 2,3-epoxy-1-iodides with zinc dust: an efficient method for the synthesis of acyclic long chain polyhydroxylated terminal alkenic alcohols☆

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Abstract—The synthesis of densely functionalized acyclic long chain terminal alkenic alcohols was achieved by reductive opening of glycal derived 2,3-epoxy-1-iodides, with commercial zinc dust alone in a short reaction time with excellent yields involving a simple reaction procedure and easy work-up. A mechanism involving an organometallic intermediate is proposed.

A great deal of interest has been devoted in recent years towards the synthesis of acyclic, long chain, polyhydroxylated, terminal alkenic alcohols owing to their various applications in diverse areas such as synthetic, medicinal and pharmaceutical chemistry.[1] Recent literature reports have also revealed that long chain polyhydroxylated (highly functionalized) terminal alkenic alcohols serve as valuable building blocks for many natural and bioactive compounds.[2] Moreover, highly functionalized terminal olefins comprise one of the most important classes of compounds for functional group transformation, giving alcohols, amines, aldehydes, carboxylic acid derivatives, ethers and epoxides as the products of catalytic reactions.[3]

The usefulness of terminal alkenic alcohols as valuable intermediates has attracted a number of synthetic strategies for their synthesis.[4,5] Reduction of 2,3-epoxy-1-halides is one among them. The reductive opening of epoxy halides is very interesting from the mechanistic as well as the synthetic viewpoint. However, many of the literature methods involve the use of expensive reagents, vigorous reaction conditions,[5a] tedious work-up procedures, long reaction times and in some cases give low yields of products. Therefore, the search for effective reagents for the preparation of densely functionalized terminal alkenic alcohols starting from 2,3-epoxy-1-iodides is still of interest.

For the last few years, our group has been actively involved in the synthesis of glycal derived, acyclic, long chain compounds as antimycobacterial agents.[6] In the context of our interest in this area, we required highly functionalized terminal alkenic alcohols that could be obtained by literature methods[4,5] from 2,3-epoxy alcohols[7] via 2,3-epoxy-1-iodides. Therefore, when the epoxy alcohol **1a**, derived from an enantiopure α,β-unsaturated sugar aldehyde[8] was subjected to iodination[9] as per the conditions given in Scheme 1, iodide **2a** was obtained in moderate yield. Our initial attempt to brominate[10] **1a** afforded a mixture of several products, which were difficult to separate even by repeated column chromatography. After optimization of the iodination of **1a**, the series **1b**–**e** was submitted to iodination under similar conditions (Scheme 1) to yield the respective iodides **2b**–**e**. All the iodination reactions proceeded quickly to produce iodides in good yields (Table 1). The moderate yields of **2a** and **2d**, obtained from **1a** and **1d**, respectively, were attributed to participation of the free 5-OH in the reaction.

The next challenge was to reduce selectively the epoxy C–O bond in lieu of the C–C bond of the 2,3-epoxy-1-iodides to obtain terminal alkenic alcohols. To achieve

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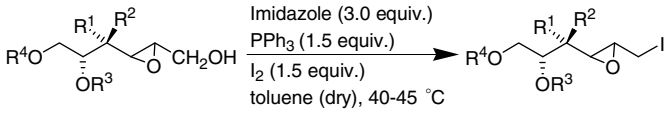


1a R^1=OBn, R^2=R^3=H, R^4=Bn
1b R^1=OBn, R^2=H, R^3=R^4=Bn
1c R^1=OBn, R^2=H, R^3=Ac, R^4=Bn
1d R^1=R^3=H, R^2=OBn, R^4=Bn
1e R^1=H, R^2=OBn, R^3=R^4=Bn

2a R^1=OBn, R^2=R^3=H, R^4=Bn
2b R^1=OBn, R^2=H, R^3=R^4=Bn
2c R^1=OBn, R^2=H, R^3=Ac, R^4=Bn
2d R^1=R^3=H, R^2=OBn, R^4=Bn
2e R^1=H, R^2=OBn, R^3=R^4=Bn

Scheme 1. Iodination of epoxy alcohols.

Table 1. Iodination of epoxy alcohols

Substrate	dr[a]	Time (h)	Product	Yield[b] (%)
1a	29:71	1.5	**2a**	48
1b	60:40	1.1	**2b**	70
1c	32:68	2.0	**2c**	60
1d	58:42	2.0	**2d**	45
1e	28:72	1.3	**2e**	68

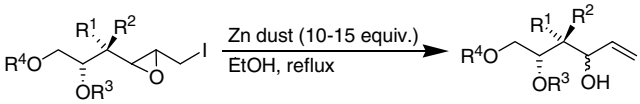
[a] Determined by ^{1}H NMR of crude material.
[b] Isolated yields.

this we tried various reagents such as $NaBH_4/InCl_3$, triethylsilane and activated magnesium metal under different reaction conditions but none of the reagents worked well except $NaBH_4/InCl_3$[5b] which furnished the desired terminal alkenic alcohol **3b** from **2b** in moderate yield (46%).

We came across Vasella's pioneering work,[11] and the extended report by Weidmann,[12] which dealt with reductive dealkoxyhalogenation of 6-deoxy-6-halopyranose and 5-deoxy-5-halofuranose derivatives with metal reagents to form acyclic olefinic sugar derivatives. A close examination of these halosugar derivatives revealed some similarities with our substrates. Both substrates contained cyclic ether functionality with the only difference being their ring sizes. Several references of synthetic applications of zinc-induced reductive ring openings are available in the literature.[13]

A combination of purified zinc dust and sodium iodide or *n*-BuLi/THF at −23 °C involving radical chemistry are also effective for the conversion of 2,3-epoxy halides to allylic alcohols under an argon atmosphere.[14] As it is well known that iodides are more reactive,[15] we tried first with commercial zinc dust as activated zinc dust was reported to form unwanted products in some cases.[13i] The reductive cleavage of 2,3-epoxy-1-iodide **2b** was attempted in a protic solvent as the final product here that we needed was the alcohol. Our preliminary experiments for reductive cleavage of **2b** with commercial as well as purified zinc dust in ethanol at ambient temperatures were unsuccessful even under an inert atmosphere.

However, at reflux in ethanol we found 100% conversion of the reactant **2b** in 3 h (TLC) when commercial zinc dust was used. The spectral analysis (^{1}H and ^{13}C NMR) of chromatographically pure compound obtained from this reaction (Scheme 2) indicated a mixture of inseparable diastereomers **3b** in 92% yield. Encouraged by this result, the same protocol was applied to the remaining substrates (Table 2). Here, it is worth mentioning that the results were identical irrespective of the quality and batch of zinc dust used.[16] To our delight the result was the same even on a gram scale.[17]



2a R^1=OBn, R^2=R^3=H, R^4=Bn
2b R^1=OBn, R^2=H, R^3=R^4=Bn
2c R^1=OBn, R^2=H, R^3=Ac, R^4=Bn
2d R^1=R^3=H, R^2=OBn, R^4=Bn
2e R^1=H, R^2=OBn, R^3=R^4=Bn

3a R^1=OBn, R^2=R^3=H, R^4=Bn
3b R^1=OBn, R^2=H, R^3=R^4=Bn
3c R^1=OBn, R^2=H, R^3=Ac, R^4=Bn
3d R^1=R^3=H, R^2=OBn, R^4=Bn
3e R^1=H, R^2=OBn, R^3=R^4=Bn

Scheme 2. Selective reduction of 2,3-epoxy-1-iodides.

Table 2. Selective reduction of 2,3-epoxy-1-iodides

Substrate	Time (h)	Product	dr[a]	Yield[c] (%)
2a	3	**3a**	29:71	87
2b	3	**3b**	60:40	92
2c	1	**3c**	33:67	85
2d	3	**3d**	56:44	86
2e	3	**3e**	nd[b]	90

[a] Determined by ^{1}H NMR of crude spectra.
[b] Not detectable, but we presume the ratio to be same as that of **1e**.
[c] Isolated yields.

From these results it appears that the reaction proceeded through an organometallic intermediate **b** followed by opening of the epoxy ring to form the alkoxide **c** which abstracts proton from the solvent furnishing the terminal alkenic alcohol **d** as shown in Figure 1.

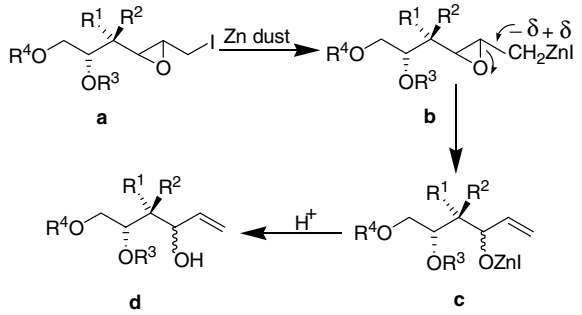
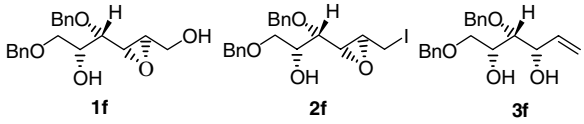


Figure 1.

Finally, the whole process was also repeated using stereochemically pure epoxy alcohol **1f** (de >99%), prepared by Sharpless epoxidation[18] of its allylic alcohol in the presence of L-(+)-DET. The stereochemically pure 2,3-epoxy alcohol **1f**, on iodination gave the epoxy iodide **2f** in 50% yield. This on further reduction with commercial zinc dust gave the diastereomerically pure terminal alkenic alcohol **3f**[19] in 86% yield. The structures of all new compounds synthesized were in accordance with their spectral data.



In summary, zinc dust can be used for reductive opening of sugar derived 2,3-epoxy-1-iodides, without any activation/external iodide source, to furnish highly functionalized acyclic long chain terminal alkenic alcohols.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.043.

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16. Different batches of zinc dust from Spectrochem Pvt. Ltd (India) were used (from 1 month to 2 years old).
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19. General procedure for reductive opening of 2,3-epoxy-1-iodides: To 500 mg (1.10 mmol) of 2,3-epoxy-1-iodide **2f** distilled ethanol (20 ml) was added and allowed to be stirred under reflux. Zinc dust (10 equiv.) was added and the stirring was continued on till completion of the reaction. Once the reaction was judged complete (TLC) the reaction mixture was allowed to cool to room temperature. After cooling, the reaction mixture was filtered through a Celite bed and washed thrice with DCM. The filtrate obtained was concentrated and passed through a silica gel column to isolate the pure terminal alkenic alcohol **3f**.
Compound **3f**: 4,6-Di-*O*-benzyl-1,2-dideoxy-D-*xylo*-hex-1-enitol: Oil, eluent for column chromatography, 7:43 EtOAc–Hex v/v, R_f 0.56 (3:7 EtOAc/hexane), $[\alpha]_D^{20}$ −7.6 (*c* 0.197, $CHCl_3$); IR (neat, cm^{-1}): 3434 (O–H str), 3018 (=C–H str), 1638, 1545, 1496, 1453 (C=C str), 1217, 1071 (C–O str); ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.27 (m, 10H, ArH), 5.93 (ddd, $J_{2,1E} = 17.1$ Hz, $J_{2,1Z} = 10.5$ Hz, $J_{2,3} = 5.3$ Hz, 1H, H-2), 5.38 (dt, $J_{1E,2} = 17.2$ Hz and $J = 1.5$ Hz, 1H, H-1E), 5.23 (dt, $J_{1Z,2} = 10.5$ Hz and $J = 1.4$ Hz, 1H, H-1Z), 4.74–4.50 (m, 4H, $2 \times OCH_2Ph$), 4.49–4.43 (m, 1H, H-5), 4.08 (m, 1H, H-3), 3.62–3.46 (m, 3H, H-6, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 137.8 (ArqC), 137.7 (C-2), 128.8, 128.5, 128.2, (ArC), 116.8 (C-1), 80.0 (C-4), 73.8 (C-3), 73.4, 73.0 ($2 \times OCH_2Ph$), 71.4 (C-5), 70.5 (C-6); FAB MS calcd for $C_{20}H_{24}O_4$ *m*/*z* 328; found 329 $[M+1]^{+\cdot}$, 237 $[M-CH_2Ph]^{+\cdot}$, 228, 203, 181. Elemental analysis calcd for $C_{20}H_{24}O_4 \cdot 0.5H_2O$; calcd: C, 71.19; H, 7.46, found: C, 70.79; H, 7.68.