Titanocene Induced Deoxygenation of Di-epoxides - A Convenient Regioselective Preparation of 1,3-Diols

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(Received May 8, 1997; CL-970345)

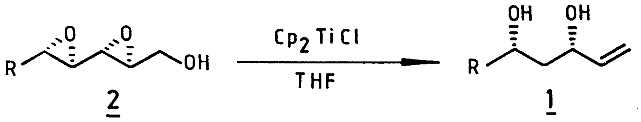
Titanocene induced regioselective opening of 2,4-di-epoxy alcohols to 1-ene-3,5-diols is described. Diepoxy alcohols were treated with 3 eq. of Cp_2TiCl in dry THF to obtain 1-ene-3,5 diols with conservation of stereochemistry at C-3 and C-5 was observed.

In our continuing efforts towards the quest for new synthetic methods employing Cp_2TiCl,[2,3] we have developed an efficient method for the syntheses of 1,3-diols by reductive elimination of di-epoxides. 1,3-Diols (1) are unique constituents of several natural products,[4,5,6] and are considered to be key intermediates[7] for the synthesis of biologically active important natural products viz. antibiotics, macrolides etc.

Earlier methods[7] for the synthesis of these diols made appropriate use of either selective reduction of carbonyls or the use of Wittig rearrangement of alkoxy ethers. Reports have also appeared on synthesis of these by making use of chiron approach.

We report herein a new facile methodology for the regioselective synthesis of 1,3-diols 1 from di-epoxy alcohols. Di-epoxy alcohols 2 were treated with 3 equivalents of Cp_2TiCl_2[8,9] and 1.5 equivalents of Zn and $ZnCl_2$ in dry THF to obtain the 1-ene-3,5diols (scheme-1).

Scheme 1.

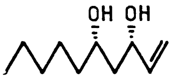
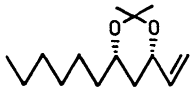
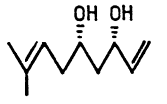
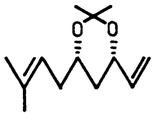
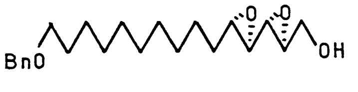
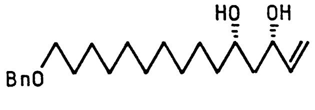
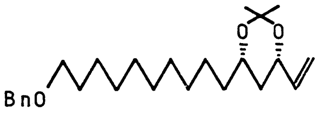
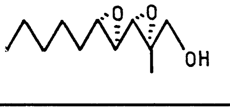
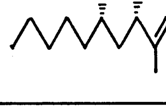
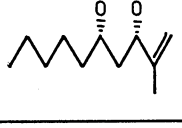


To establish generality and functional group compatibility in this reaction, different types of di-epoxides were prepared and subjected to the deoxygenation using Cp_2TiCl and obtained the corresponding 1.3 diols in good to excellent yields. The mechanism of this conversion is not completely understood to us, it may need further investigation. The results are listed in the table which clearly show not only the generality, versatility, regioselectivity and efficacy of the process but also conservation of the chirality of the di-epoxides at C-3, C-5, in 1,3-diols as indicated by the resulting data of their acetonides vis-a-vis to reported data (Table).

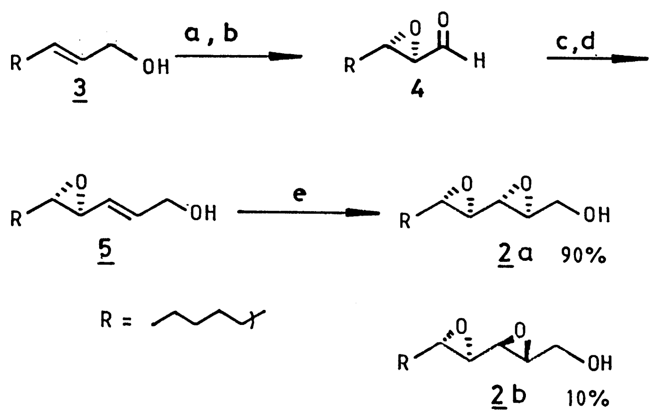
The di-epoxides were obtained from the requisite allyl alcohols. The allyl alcohol 3 on epoxidation using Sharpless asymmetric conditions, coupled with a modified Collin's oxidation gave 4. A two carbon homologation via Wittig olefination and followed by reduction using DIBAL-H at -78 °C gave the epoxyallyl alcohol 5.[3] A second epoxidation using Sharpless asymmetric conditions afforded the desired di-epoxide 2[7e] with good selectivity 90:10 (scheme-2).

In conclusion, our protocol demonstrates an efficient

Table

Entry	Substrate	Product	Yield %	Acetonide	$[\alpha]_D$
1			78		-47.3
2			71		-28.5
3			73		—
4			68		-15.9

Scheme 2.



Reagents and Conditions : a) TIP, (+) DET, TBHP, 4 Å MS, -26^0 C, DCM b) CrO_3, Pyridine, Celite, 4 Å MS, 0-5^0 C, DCM c) $Ph_3P{=}CH{-}COOEt$, C_6H_6, r.t. d) DIBAL–H, -78^0 C, DCM e) TIP, (+) DET, TBHP, 4 Å MS, -26^{0}C, DCM

method for the synthesis of chiral and multifunctional 1,3-diols containing a terminal olefin which are valuable and versatile intermediates in natural product synthesis, as the olefin can be manipulated to further desired transformations.

Typical experimental procedure : To a red solution of titanocene (0.65 g, 2.7 mmols) in dry THF (5 ml) containing freshly fused $ZnCl_2$ (0.18 g, 1.32 mmols) was added activated (through usual procedure) Zn powder (0.10 g, 1.32 mmols) and stirred for 0.5 min. To the resulting green solution was added 2a (100 mg, 0.515 mmols) in dry THF (3 ml) through canula. After 5 min the reaction mixture was treated with 5% HCl (5 ml) and extracted thoroughly with ether, washed successively with water, 10% $NaHCO_3$, and brine. The organic layer dried over Na_2SO_4, concentrated under reduced pressure and subsequent purification by column chromatography afforded 1-ene-3,5-diol (1a) in 78% yield.

One of the authors (Srinivas Dale) is thankful to the CSIR, New Delhi for the financial support in the form of CSIR fellowship.

References and Notes

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10 (a) ^{1}H NMR of compound 2a 0.8 (t, J=5.2 Hz, 3 H, $-CH_2-CH_3$), 1.1-1.4 (m, 10 H), 1.6-2.0 (m, 2 H), 2.6 (d, J=6.9 Hz, 1 H), 2.86 (t, J=6.8 Hz, 1 H), 2.98 (t, J=6.8 Hz, 1 H), 3.08 (t, J=5.4 Hz, 1 H), 3.62-3.94 (2m, 2H,$-\underline{CH}_2-OH$). (b) Acetonide of 1 0.9 (t, J=5.3, 3 H,$-CH_2-\underline{CH}_3$), 1.15-1.34 (m, 10 H), 1.4 (s, 3H, acetonide), 1.45 (s, 3 H, acetonide), 1.6-1.8 (m, 2 H), 3.7-3.9 (m, 1 H), 4.24-4.38 (m, 1 H), 5.1 (d, J=8.8 Hz, 1 H), 5.25 (d, J=6.6 Hz, 1 H), 5.7-5.95 (m, 1 H). All new compounds are characterised by spectral data and HRMS.